



Australian Government

Department of Health and Ageing  
Therapeutic Goods Administration

# Australian Public Assessment Report for Tramadol hydrochloride / Paracetamol

Proprietary Product Name: Zaldiar

Sponsor: Grunenthal Pty Ltd

**September 2012**

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <[www.tga.gov.au](http://www.tga.gov.au)>.

## About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

### Copyright

© Commonwealth of Australia 2012

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <[tga.copyright@tga.gov.au](mailto:tga.copyright@tga.gov.au)>.

# Contents

<b>Introduction to product submission</b>	<b>2</b>
Submission details	2
Product background	3
Regulatory status	4
Product Information	5
<b>II. Quality findings</b>	<b>5</b>
<b>III. Nonclinical findings</b>	<b>6</b>
Introduction	6
Pharmacology	6
Pharmacokinetics	7
Toxicology	19
Nonclinical summary	26
Conclusions	27
<b>IV. Clinical findings</b>	<b>27</b>
Introduction	27
Pharmacokinetics	30
Introduction	30
Pharmacodynamics	39
Efficacy	39
Safety	104
Clinical summary and conclusions	117
Conclusions	119
<b>V. Pharmacovigilance findings</b>	<b>119</b>
<b>VI. Overall conclusion and risk/benefit assessment</b>	<b>119</b>
Quality	119
Nonclinical	119
Clinical	120
Risk Management Plan	124
Risk-benefit analysis	125
Outcome	136
<b>Attachment 1. Product Information</b>	<b>136</b>

## Introduction to product submission

### Submission details

<i>Type of Submission</i>	New Fixed Combination
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	5 March 2012
<i>Active ingredient(s):</i>	Tramadol hydrochloride Paracetamol
<i>Product Name(s):</i>	Zaldiar
<i>Sponsor's Name and Address:</i>	Grunenthal Pty Ltd, 616 St Kilda Rd Melbourne, VIC 3004
<i>Dose form(s):</i>	Film-coated tablets and effervescent tablets
<i>Strength(s):</i>	Tramadol hydrochloride 37.5 mg Paracetamol 325 mg
<i>Container(s):</i>	Blister packs (film-coated tablets) and Aluminium (Al) Al/Al strip packs (effervescent tablets)
<i>Pack size(s):</i>	2, 20, 50 and 100 tablets
<i>Approved Therapeutic use:</i>	Zaldiar is indicated for the treatment of moderate pain.
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	Dosage needs to be individually adjusted. The proposed maximum daily dose of Zaldiar is 8 tablets providing 300 mg tramadol and 2600 mg paracetamol.
<i>ARTG Number (s)</i>	179677 and 179 678

## Product background

This AusPAR describes the application to register a new fixed combination of tramadol and paracetamol, Zaldiar for the proposed indication:

*Zaldiar is indicated for the symptomatic treatment of moderate to severe pain.*

*The use of Zaldiar should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see Pharmacology).*

Tramadol was first registered in 1998 and is available in oral and parenteral dose forms. It is a centrally-acting synthetic analgesic of the aminocyclohexanol group with opioid-like effects. It is not chemically related to opiates. It is thought to act by binding to  $\mu$ -opioid receptors and by inhibition of re-uptake of noradrenaline and serotonin. It is a mixture of two stereoisomers. Tramadol also has an active metabolite (M1) formed by *O*-desmethyltramadol.

Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P450. Patients who metabolise drugs poorly via CYP2D6 may obtain reduced benefit from tramadol due to their reduced formation of M1.

Tramadol is indicated for the relief of moderate to severe pain in adults and adolescents aged from 12 years. The lowest strength oral tablet/capsule contains 50 mg tramadol compared with 37.5 mg in the proposed Zaldair film-coated tablets and effervescent tablets. The oral dosing recommendations for tramadol include that for the treatment of moderate pain 50 - 100 mg administered two or three times daily may be sufficient. Tramadol 50 mg may be adequate as the initial dose for moderate pain.

Paracetamol is a pain reliever and a fever reducer. The exact mechanism of action is not known. It is available in non prescription products for oral administration. Paracetamol is indicated for use in infants, children and adults. The usual adult dose of paracetamol is 2 x 500 mg every 4 hs to a maximum of 4 g daily. It is proposed that 325 mg paracetamol be included in each Zaldiar tablet, giving 650 mg paracetamol per dose from Zaldiar.

The proposed maximum daily dose of Zaldiar is 8 tablets providing 300 mg tramadol and 2600 mg paracetamol. For currently registered products containing tramadol, the maximum recommended dose is 400 mg daily. The maximum recommended total daily dose of paracetamol for adults is 4 g daily (8 x 500 mg tablets/ capsules). Thus, the proposed maximum daily doses of both tramadol and paracetamol from Zaldiar are lower than the current maximum daily dose recommendations for each of these constituent actives taken individually. The proposed dosing interval for Zaldiar of 6 hs is longer than the recommended dosing interval of 4-6 hs for both tramadol and paracetamol.

The major reason for development of this combination is that as the 2 actives are well-established analgesics with complementary onsets and duration of action there should be an improved analgesic profile compared with either active given alone. In addition, safety is expected to improve due to the lower total dose of each of the actives compared with either active given at its currently recommended maximum daily dose. The effervescent tablet was developed as an alternative for patients unable to swallow tablets or capsules.

There are two guidelines relevant to this submission and the most relevant recommendations from each guideline are summarised below:

### 1. *Guideline on Clinical Development of Fixed Combination Medicinal Products*<sup>1</sup>

Each dose combination should be carefully justified and clinically relevant

- Combinations, in principle, may not be considered rational if the duration of action of the substances differs significantly.

<sup>1</sup> CPMP/EWP/240/95 Rev. 1 <http://www.tga.gov.au/pdf/euguide/ewp024095enfin.pdf>

- Each substance of the fixed combination must have a documented therapeutic contribution within the combination.
- The combination contains known active substances and it is a substitution indication (that is, use in patients adequately controlled with the individual products given concurrently, at the same dose level as in the combination, but as separate tablets) or the new fixed combination contains known active ingredients that have not been used in combination before. In these cases bioequivalence should be demonstrated between the free combination of the recognised reference formulations of the individual monocomponents and the marketing formulation (fixed combination).
- The development of a fixed combination should follow specific disease related guidelines in the choice study design (severity of the disease at baseline, primary and secondary efficacy endpoints, study duration, comparators).
- The dosage of each substance within the fixed combination must be such that the combination is safe and effective for a significant target population and the benefit/risk assessment of the fixed combination is equal or exceeds that of each substance taken alone.

2. *Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain<sup>2</sup>*

- This guideline is intended to provide general guidance for the clinical development of new medicinal products for the treatment of pain.
- Well-planned dose ranging studies should be carried out before the confirmatory clinical trials.
- Due to a high and variable placebo-response rate, placebo-controlled designs with appropriate use of rescue medication are recommended for trials not aiming to show superior efficacy to an active comparator.
- The duration of the study should be related to the proposed indications.
- Tachyphylaxis and tolerance need to be investigated for chronic treatment unless an appropriate justification is given.
- For fixed combination products the benefits of the association should be clearly demonstrated in clinical trials on an efficacy and/ or safety basis.
- Studies of pain due to surgical removal of impacted teeth are given as examples of studies for moderate to severe acute pain. Studies in patients with low back pain are given as examples of mild to moderate chronic pain.

Most of the studies in this submission were conducted prior to 2001. Data were subsequently added to the initial package between 2004 and 2006 (data from subsequent “Type 2” variations in Europe) and in 2010 (from Study ZAL-06).

### **Regulatory status**

Zaldiar has marketing authorisations in many countries including the USA (2001), Canada (2205), UK (2003), Switzerland (2002) and European Union (EU) countries.

In the USA the indications is

*Short-term (five days or less) management of acute pain.*

In Canada the indication includes

*Management of moderate to moderately severe pain in adults*

---

<sup>2</sup> CPMP/EWP/612/00 <http://www.tga.gov.au/pdf/euguide/ewp061200final.pdf>

and notes that the product has not been systematically evaluated beyond 12 weeks in controlled clinical trials. Therefore, the physician who elects to use it for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. It is not recommended for minor pain that may be treated adequately through lesser means.

## Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

## II. Quality findings

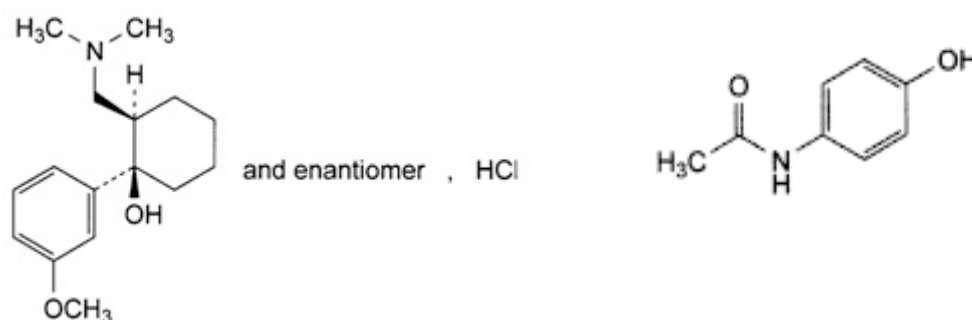
Tramadol hydrochloride is currently registered by a number of sponsors in Australia in the form of 100, 150 and 200 mg immediate release tablets and 100, 150, 200 and 300 mg modified release tablets. It is also registered in the form of capsules and injection.

Paracetamol is a very common over the counter (OTC) medicine, usually given at a dose of 1 g.

The present submission seeks registration of the first fixed dose combination of these active ingredients.

The structures of tramadol hydrochloride and paracetamol are shown in Figure 1.

**Figure 1. Chemical structures**



Tramadol hydrochloride is freely soluble in water, while paracetamol is sparingly soluble. Both drug substances are the subject of pharmacopoeial monographs.

Both drug products are conventional formulations and neither tablet is scored.

The submitted bioavailability studies satisfactorily established the following:

1. Tramadol and paracetamol are well absorbed from the film-coated tablet. Both drug substances in the combination tablet are bioequivalent to corresponding single agent solid oral dose forms and to oral solutions of the active ingredients.
2. Multi-dose co-administration of tramadol and paracetamol in the fed state does not affect the bioavailability of paracetamol but the bioavailability of tramadol is reduced by about 15%.
3. Single dose co-administration of tramadol and paracetamol in the fasted state does not affect the bioavailability of either drug substance.
4. The rate of absorption of both drug substances is reduced by food but the extent of drug absorption is not affected.
5. The effervescent and film-coated tablets are bioequivalent.

## III. Nonclinical findings

### Introduction

This was a hybrid literature-based submission. The published nonclinical literature deals mainly with tramadol and paracetamol as individual agents. Nonclinical data related to tramadol and the combination product have been submitted as sponsor study reports.

Nonclinical studies of fixed combinations of approved compounds are required to identify any interactions between the two agents which may have effects on the pharmacology, pharmacokinetics or toxicology of the combination which were not previously identified for the individual agents. The nonclinical data related to the combination product were limited to a pharmacodynamic study, pharmacokinetic absorption studies in rats and dogs, metabolism studies in liver microsomes from rats, dogs and humans, single and repeat dose toxicity studies in rats and dogs and reproductive toxicity studies in rats. The nonclinical bridging submission was considered adequate to characterise the potential additive or antagonistic effects of combination dosing of tramadol and paracetamol with respect to pharmacokinetics and toxicology and to identify any toxicity unique to the combination. While a nonclinical evaluation of tramadol has been carried out previously, a significant body of new data and published references were submitted with this application and these were evaluated in the context of the role of tramadol in the combination product.

### Pharmacology

#### Primary pharmacology

The pharmacodynamic properties of tramadol and paracetamol as individual analgesics are well established. The pharmacology of tramadol had been documented and evaluated previously and paracetamol has a long history of use as a non prescription analgesic for mild to moderate pain. The rationale for the combination is based on distinct and complementary mechanisms of action. Paracetamol has a rapid onset of action and is thought to exert its analgesic and antipyretic effects primarily via inhibition of cyclo-oxygenase 2 (COX-2) and modulation of the endogenous cannabinoid system. Tramadol acts centrally via  $\mu$ -opioid receptors and also inhibits noradrenaline and serotonin uptake; the effects are slower onset than paracetamol but more sustained.

Tramadol is a mixture of enantiomers which act in a complementary and synergistic manner improving the analgesic efficacy and tolerability profile of the racemate. Tramadol is metabolised to active metabolites, the enantiomers of which also exhibit differential effects. The primary metabolite M1 has a much higher affinity for the  $\mu$ -opioid receptor than tramadol suggesting that it is primarily responsible for the opioid analgesic effect. Variability in the efficacy of tramadol is partly due to polymorphisms in CYP2D6 resulting in significant variations in plasma concentrations of M1.

Clinical and nonclinical studies have demonstrated synergistic analgesic activity of tramadol with paracetamol. The addition of paracetamol allows lower doses of tramadol to be used with consequent fewer side effects but without loss of analgesic response. Recent clinical data showed that 37.5 mg tramadol/325 mg paracetamol combination tablets provided comparable analgesic efficacy with a better safety profile than 50 mg tramadol<sup>3</sup> and 37.5 mg tramadol/325

---

<sup>3</sup> Rawal N, Macquaire V, Catalá E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial. *J Pain Res.* 2011 Apr 8;4:103-10.



mg paracetamol provided superior efficacy to 1000 mg paracetamol monotherapy capsules in patients with postoperative pain<sup>4</sup>. A nonclinical study in mice to evaluate the antinociceptive efficacy over a range of fixed dose ratios demonstrated synergistic analgesic effects of tramadol and paracetamol. Additive effects have been demonstrated in hyperalgesia and antinociception in rats. No further nonclinical efficacy data are considered necessary.

### Secondary pharmacodynamics and safety pharmacology

Tramadol is a potent analgesic but has the potential to induce tolerance and dependence and produces a range of unwanted opioid-associated effects including reduced co-ordination, tremor, mydriasis, respiratory depression and delays in gastrointestinal (GI) transit. Tramadol causes nausea and vomiting in some individuals and the incidence and severity may be associated with genetic variants of CYP2D6 and the  $\mu$ -opioid receptor gene (OPRM1)  $\mu$ -opioid receptor.

Paracetamol has a lower analgesic efficacy than tramadol but more rapid onset and has no dependence potential. Paracetamol overdose causes hepatotoxicity (due to depletion of glutathione for detoxification) and associated toxicity in a range of other tissues and may be fatal. However, there are few secondary effects at therapeutic doses.

**Serotonin Syndrome:** The secondary antidepressant effects of tramadol are associated with an increased risk of the development of Serotonin Syndrome when used in combination with serotonin enhancing drugs such as selective-serotonin reuptake inhibitor (SSRIs) and monoamine oxidase inhibitors (MAOIs). Numerous case reports implicate tramadol as causative in Serotonin Syndrome including adverse drug reactions reported to the TGA<sup>5</sup>. Retrospective analysis of an Australian veteran cohort showed a significant level of prescribed potentially life threatening serotonergic medicine combinations involving an overlap of an SSRI and tramadol<sup>6</sup>. The risk of Serotonin Syndrome is considered in the draft PI (*Interactions with Other Medicines* section).

Studies in a rat kindling model suggest that tramadol is associated with an increased risk of seizures in susceptible individuals. The increased risk of seizures with tramadol in patients with epilepsy is addressed in the draft PI (*Contraindication and Precautions* section).

## Pharmacokinetics

### Paracetamol

The clinical pharmacokinetics of paracetamol has been well characterised and no nonclinical data were submitted. Following oral (PO) administration, paracetamol is rapidly absorbed and evenly distributed through the tissues with bioavailability from 60-90%. Paracetamol is metabolised in the liver to sulphate and glucuronide conjugates. A small proportion is converted to a highly reactive and toxic metabolite NAPQ1 which is rapidly inactivated by glutathione and excreted in the urine. Large doses of paracetamol cause acute hepatic necrosis due to depletion of glutathione and subsequent toxic interactions of NAPQ1 with cellular components. The

---

<sup>4</sup> Spagnoli AM, Rizzo MI, Palmieri A, Sorvillo V, Quadrini L, Scuderi N. A single blind controlled comparison of tramadol/paracetamol combination and paracetamol in hand and foot surgery. A prospective study. *In Vivo*. 2011 Mar-Apr;25(2):291-5.

<sup>5</sup> Fox MA, Jensen CL, Murphy DL. Tramadol and another atypical opioid meperidine have exaggerated serotonin syndrome behavioural effects, but decreased analgesic effects, in genetically deficient serotonin transporter (SERT) mice. *Int J Neuropsychopharmacol*. 2009 Sep;12(8):1055-65.

<sup>6</sup> Ringland *et al.*, 2008, TGA Medicine Safety Update No.6; 2010; <http://www.tga.gov.au/hp/msu-2010-06.htm>

plasma half-life in humans is about 2 h, longer in men than women and is increased with alcohol consumption and oral contraceptive use.

## Tramadol

The clinical pharmacokinetics of tramadol have been well characterised. Tramadol is well absorbed with a bioavailability of *ca* 70% and extensively metabolised after PO administration. Tramadol is metabolised in the liver to active metabolites, primarily by *O*- and *N*-demethylation to M1 and M2. Tramadol is excreted by renal (90%) and faecal (10%) routes. The elimination half-lives of tramadol and M1 are about 5-6 h and 8 h, respectively.

New nonclinical studies described the absorption kinetics of tramadol in rats and monkeys. Male and female rats were administered 10 or 50 mg/kg tramadol PO as a single dose or daily doses for 14 days. Blood samples were collected from 0.5-12 h (10 mg/kg group) and at 0.5-24 h (50 mg/kg group) for determination of plasma concentrations of tramadol and M1. The time to peak plasma concentration ( $T_{max}$ ) was 0.5 h for both tramadol and M1 except for day 14 multiple dose 50 mg/kg males when  $T_{max}$  was 0.8 h for both tramadol and M1. Females exhibited 3-4x higher concentrations of tramadol and 1.2-2x higher concentrations of M1 than males. Exposure to tramadol and M1 was dose-related. Systemic exposure (peak plasma concentration ( $C_{max}$ ) and area under the plasma concentration time curve (AUC)) to tramadol increased 28-105% after repeat dosing for 14 days except for the AUC at 50 mg/mL which was constant. Systemic exposure to M1 decreased by 24-56% after multiple dosing.

Monkeys (2/sex) were treated with 10 mg/kg tramadol PO as a single dose on Days 1 and 28 and twice daily doses for the intervening 26 days; blood was collected from 0.5-24 h on Days 1 and 28 for determination of plasma concentrations of tramadol and M1. Plasma concentrations of tramadol were highly variable between animals with the  $C_{max}$  ranging from 39.2 ng/mL at 4 h to 231 ng/mL at 0.5 h after a single dose. After repeat dosing, systemic exposure ( $C_{max}$  and AUC) to tramadol increased by 33-34% and systemic exposure to M1 decreased by 54-62%. The half-life was tramadol: 2-3 h; M1: 3-4 h.

In summary, the data showed that repeat dosing with tramadol in rats (10, 50 mg/kg/day) and monkeys (10 mg/kg/day) caused increased tramadol and decreased M1 exposure suggesting accumulation of tramadol via saturation of early metabolic pathways and induction of pathways downstream from M1.

## Combination studies

Nonclinical data compared the absorption kinetics of tramadol and paracetamol individually or in combination with single or repeat dosing in rats and dogs.

### Rats

Studies in rats treated with 45 mg/kg/day tramadol and 390 mg/kg/day paracetamol showed that repeat dosing with tramadol alone increased tramadol exposure 2-3.4x but M1 exposure was unchanged suggesting accumulation and saturation of the M1 metabolic pathway; this effect was reduced with combination dosing. Repeat dosing for 3 months with paracetamol alone increased paracetamol exposure suggesting accumulation and saturation of metabolic pathways. The only apparent effect of co-administration of a single dose was increased (-) tramadol in males suggesting a gender-related, stereo-specific metabolic effect.

Combination dosing for 21 days led to decreased exposure to tramadol and M1 (60-70%) and paracetamol (30%) compared to separate dosing, suggesting induction of metabolic pathways. Similar but reduced effects of combination dosing were seen after 3 months with a paradoxical increase in (-)tramadol in males. Exposure in females to (+)(-)tramadol and (+)M1 was 2-9.5x higher than in male rats after individual, combination, single and repeat (3 months) dosing, except for (-)tramadol after combination dosing which was equivalent in females and males.

Parasrampur *et al.* (2007)<sup>7</sup> showed that stereoselectivity in tramadol metabolism was not present with intravenous (IV) dosing suggesting an effect of first pass metabolism in the liver and possibly the GI tract.

### ***Dogs***

Tramadol exposure decreased after repeat dosing with 22.5 or 30 mg/kg/day tramadol for 1 week, 1 month or 3 months compared to a single dose, in 3 separate studies, confirming previous reports of enzyme induction in dogs. M1 was below the detection limit in most samples and data were not informative. Paracetamol exposure was similar after single and repeat dosing at 195 or 260 mg/kg/day.

Some studies showed interactions between paracetamol on tramadol with combination dosing and there appeared to be gender-related differences, however results were variable between animals. Paracetamol exposure was increased when co-administered with tramadol in a single dose but not with subsequent dosing. Co-administration with paracetamol appeared to reduce the plasma concentration of (+)tramadol with single or repeat dosing, suggesting stereospecific metabolic effects.

---

<sup>7</sup> Parasrampur R, Vuppugalla R, Elliott K, Mehvar R. Route-dependent stereoselective pharmacokinetics of tramadol and its active O-demethylated metabolite in rats. *Chirality*. 2007 Mar;19(3):190-6.

**Table 1. Range-Finding Study DM96302 in rats.**

45 mg/kg/day tramadol 390 mg/kg/day paracetamol	Individual dosing	Combination dosing	Ratio
<b>SINGLE DOSE</b>			
<b>AUC<sub>0-infinity</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	2020	2024	1.0
<b>(-)tramadol</b>	679	751	0.9
<b>(+)M1</b>	972	713	1.4
<b>(-)M1</b>	926	850	1.1
<b>paracetamol*</b>	331	333	1.0
<b>REPEAT DOSING (21 DAYS)</b>			
<b>AUC<sub>0-24h</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	3979	1684	2.4
<b>(-)tramadol</b>	2327	993	2.3
<b>(+)M1</b>	897	244	3.7
<b>(-)M1</b>	993	325	3.1
<b>paracetamol*</b>	269	181	1.5
<b>RATIO (SINGLE/REPEAT DOSING)</b>			
<b>(+)tramadol</b>	0.5	1.2	
<b>(-)tramadol</b>	0.3	0.8	
<b>(+)M1</b>	1.1	2.9	
<b>(-)M1</b>	0.9	2.6	
<b>paracetamol*</b>	1.2	1.8	

Exposure to paracetamol, (+)tramadol, (-)tramadol, (+)M1, (-)M1 following single and repeat oral doses of paracetamol and racemic tramadol separately and as a combination

Sampling at 0, 0.5, 1, 2 & 4 h after the first and twenty-first day of dosing.

*n*=2/sex/group

**Table 2. Study DM96319 in rats.**

45 mg/kg/day tramadol 390 mg/kg/day paracetamol	Individual dosing	Combination dosing	Ratio
<b>SINGLE DOSE (DAY 1) males/ females (ratio f/m)</b>			
<b>AUC<sub>0-infinity</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	1174/5627 (4.8)	1593/5426 (3.4)	0.7/1.0
<b>(-)tramadol</b>	647/6162 (9.5)	2828/5639 (2.0)	0.2/1.1
<b>(+)M1</b>	544/2868 (5.3)	598/3185 (5.3)	0.9/0.9
<b>(-)M1</b>	1172/1483 (1.3)	1086/1105 (1.0)	1.1/1.3
<b>paracetamol*</b>	470	591	0.8
<b>REPEAT DOSING (3 MONTHS) males/ females (ratio f/m)</b>			
<b>AUC<sub>0-24h</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	2507/10378 (4.1)	2445/7595 (3.1)	1.0/1.4
<b>(-)tramadol</b>	1472/8203 (5.6)	5045/4669 (0.9)	0.3/1.8
<b>(+)M1</b>	746/3749 (5.0)	512/2575 (5.0)	1.5/1.5
<b>(-)M1</b>	1514/1953 (1.3)	1063/1187 (1.1)	1.4/1.6
<b>paracetamol*</b>	868	669	1.3
<b>RATIO (SINGLE/REPEAT DOSING)</b>			
<b>(+)tramadol</b>	0.5/0.5	0.6/0.7	
<b>(-)tramadol</b>	0.4/0.8	0.6/1.2	
<b>(+)M1</b>	0.7/0.8	1.2/1.2	
<b>(-)M1</b>	0.8/0.8	1.0/0.9	
<b>paracetamol</b>	0.5	0.9	

Exposure to paracetamol, (+)tramadol, (-) tramadol, (+)M1 & (-)M1 following single & repeat oral doses of paracetamol and racemic tramadol separately & as a combination.

Sampling at 0, 0.5, 1, 2 & 4 h after the first and ninety-first day of dosing.

n=3/sex/group

**Table 3. Dose-Finding Study DM95359 in dogs.**

30 mg/kg tramadol 260 mg/kg paracetamol Twice daily	Individual dosing	Combination dosing	Ratio
<b>SINGLE DOSE (DAY 1)</b>			
<b>AUC<sub>0-infinity</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	1868±1476	1495±635	1.2
<b>(-)tramadol</b>	1822±1510	1560±539	1.2
<b>paracetamol*</b>	365±78	625±82	0.6
<b>REPEAT DOSING (DAY 27)</b>			
<b>AUC<sub>0-24h</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	269±121	240±66	1.1
<b>(-)tramadol</b>	305±167	253±94	1.2
<b>paracetamol*</b>	418±26	370±51	1.1
<b>RATIO (SINGLE/REPEAT DOSING)</b>			
<b>(+)tramadol</b>	6.9	6.2	
<b>(-)tramadol</b>	6.0	6.2	
<b>paracetamol</b>	0.9	1.7	

Exposure to paracetamol, (+)tramadol & (-)tramadol (AUC<sub>0-infinity</sub>, AUC<sub>0-24h</sub>) following single and repeat oral doses of paracetamol and racemic tramadol separately & as a combination in dogs.

M1 was undetectable in most samples.

Sampling at 0, 0.5, 1, 2, 4, 6, 6.5, 7.5, 9.5 & 24 h after first and twenty-seventh day of dosing.

n=2/sex/group

**Table 4. Study DM96320 in dogs.**

22.5 mg/kg/day tramadol 195 mg/kg/day paracetamol Dosed twice daily	Individual dosing	Combination dosing	Ratio
<b>SINGLE DOSE (DAY 1)</b>			
<b>AUC<sub>0-10.5h</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	1231	943	1.3
<b>(-)tramadol</b>	2401	2397	1.0
<b>paracetamol*</b>	247	366	0.7
<b>REPEAT DOSING (DAY 89)</b>			
<b>AUC<sub>0-10.5h</sub> (ng.h/mL) (µg.h/mL)*</b>			
<b>(+)tramadol</b>	198	106	1.9
<b>(-)tramadol</b>	1383	1305	1.1
<b>paracetamol*</b>	248	264	0.9
<b>RATIO (SINGLE/REPEAT DOSING)</b>			
<b>(+)tramadol</b>	6.2	8.9	
<b>(-)tramadol</b>	1.7	1.8	
<b>paracetamol</b>	1.0	1.4	

Exposure to paracetamol, (+)tramadol and (-)tramadol (AUC<sub>0-10.5h</sub>) following single and repeat oral doses of paracetamol and racemic tramadol separately and as a combination in dogs.

M1 was undetectable in most samples.

Sampling at 0, 0.5, 1, 2, 4, 6, 7.5 & 10.5 h after the first and eighty-ninth doses.

n=4/sex/group

**Table 5. Study No. DM99371 in dogs.**

30 mg/kg/day tramadol 260 mg/kg/day paracetamol Twice daily	Individual dosing AUC <sub>0-24h</sub> (ng.h/mL) (µg.h/mL)*	Combination dosing AUC <sub>0-24h</sub> (ng.h/mL) (µg.h/mL)*	Ratio
<b>SINGLE DOSE (DAY 1) males/ females (ratio f/m)</b>			
<b>tramadol</b>	301/585 (1.9)	402/172 (0.4)	0.7/3.4
<b>paracetamol*</b>	202/214 (1.1)	268/306 (1.1)	0.8/0.7
<b>REPEAT DOSING (DAY 8) males/ females (ratio f/m)</b>			
<b>tramadol</b>	128/365 (2.9)	230/225 (1.0)	0.6/1.6
<b>paracetamol*</b>	192/320 (1.7)	197/239 (1.2)	1.0/1.3
<b>REPEAT DOSING (DAY 28) males/ females (ratio f/m)</b>			
<b>tramadol</b>	224/148 (0.7)	439/959 (2.2)	0.5/0.2
<b>paracetamol*</b>	246/301 (1.2)	171/434 (2.5)	1.4/0.7
<b>RATIO (DAY 1/DAY 8) males/ females</b>			
<b>tramadol</b>	2.4/1.6	1.7/0.8	
<b>paracetamol</b>	1.0/0.8	1.4/1.3	
<b>RATIO (DAY 1/DAY 28) males/ females</b>			
<b>tramadol</b>	1.3/4.0	0.9/0.2	
<b>paracetamol</b>	0.8/0.7	1.6/0.7	

Exposure to paracetamol and tramadol following single and repeat oral doses of paracetamol and tramadol separately & as a combination in dogs.

Administered twice daily, 6 h apart.

Sampling at 0, 0.5, 1, 2, 4, 6, 6.5, 7.5, 9.5 & 24 h postdose on Days 1, 8 and 28 of dosing.

n=4/sex/group.

A comprehensive assessment of the metabolism of paracetamol and its glucuronide, sulphate, glutathione, cysteine and mercapturate metabolites and tramadol and metabolites M1, M2, M3, M4, M5 and M1 glucuronide was undertaken in dogs. Pharmacokinetic parameters were determined for all analytes. No effects of combination dosing on tramadol metabolites were evident and M1 was below the limit of detection in most samples. On Day 1, co-administration with tramadol slightly increased the AUC<sub>0-24h</sub> of paracetamol and its cysteine and mercapturate metabolites while decreasing the glucuronide and sulphate metabolites. The AUC<sub>0-24h</sub> of tramadol was lower with repeat dosing indicating induction of its own metabolism but this effect was reduced with co-administration with paracetamol.



**Table 6. A comparison of exposure to paracetamol and its conjugates following single and repeat oral doses of 260 mg/kg/day paracetamol and 30 mg/kg/day tramadol individually and as a combination in dogs (Study No. DM99371).**

RATIO AUC <sub>0-24h</sub> Combination/ Individual dosing	Paracetamol		Cysteine conjugate	Mercapturate conjugate	Glucuronide conjugate	Sulphate conjugate	Glutathione conjugate
	Single dose	M	1.3	1.6	1.5	0.7	0.4
F		1.4	1.4	1.2	0.9	0.8	1.5
Repeat dosing Day 8	M	1.0	0.5	0.6	1.0	1.1	1.7
	F	1.3	0.8	1.3	2.2	1.1	1.6
Repeat dosing Day 28	M	1.4	0.7	0.9	1.2	0.9	0.5
	F	0.7	1.1	1.3	1.0	1.4	0.9

In summary:

- Active tramadol metabolite M1 was detectable in comparable amounts to tramadol in rats but was at low or undetectable levels in dogs;
- Tramadol accumulated after repeat dosing in rats but induced its own metabolism in dogs;
- Paracetamol accumulated after 3 month repeat dosing in rats;
- Exposure to (+)tramadol and (+)(-)M1 was decreased by repeat co-administration with paracetamol in rats;
- Exposure to (-)tramadol was increased by single or repeat co-administration with paracetamol in male but not female rats;
- Co-administration with paracetamol has gender-related and stereo-specific effects on tramadol exposure in dogs;
- Exposure to paracetamol was increased by co-administration with tramadol in a single dose in dogs;
- Exposure to (+)(-)tramadol and (+)M1 was higher in female than male rats with or without paracetamol co-administration.

## CYP450 Metabolism

### *Paracetamol*

Oxidation via CYP450 enzymes comprises less than 15% of total paracetamol metabolism; however, the toxic metabolite NAPQI is formed partly via this pathway. Production of NAPQI is due to the activity of CYP2E1, CYP1A2, CYP3A4 and CYP2D6.

### *Tramadol*

Multiple CYP isoforms are involved in tramadol metabolism but primarily CYP2D6 for M1 and CYP2B6 and CYP3A4 for M2. *In vitro* studies of CYP450 metabolism in human microsomes showed that metabolism of tramadol to M1, M2 and M6 was reduced in CYP2D6-deficient microsomes, with CYP3A4 inhibition confirming the role of these isoforms in tramadol

metabolism. Metabolism was stereoselective: (+)tramadol was more selective for *N*-demethylation to M2 via CYP3A4/5; (-)tramadol was more selective for *O*-demethylation to M1 via CYP2D6 and for 4-hydroxylation partly via CYP3A4/5. Drug interaction studies in human microsomes suggest that tramadol metabolism via CYP2D6-mediated *O*-demethylation, CYP3A4-mediated *N*-demethylation, CYP3A4/5-mediated 4-hydroxylation and formation of secondary metabolite *N,O*-didesmethyltramadol may be significantly inhibited by amitriptyline, fluoxetine and norfluoxetine, but not by cyclobenzaprine at therapeutic doses.

Significant inhibition by tramadol enantiomers was not observed for CYP2A6, CYP1A2, CYP2C9, CYP3A4, CYP2C19 or CYP2E1. Dose-related inhibition by tramadol was observed for CYP2D6 but was only significant at 40  $\mu$ M, a concentration more than 10x the plasma concentration of tramadol achieved at therapeutic doses. There was no inhibition of quinidine metabolism (via CYP3A4/5) by tramadol at concentrations up to 40  $\mu$ M.

### **Combination**

In studies of the potential metabolic interaction of paracetamol and tramadol in liver microsomes, paracetamol inhibited tramadol metabolism to M1 and M2 by  $\geq 50\%$  in rats, dogs and humans but only at doses  $\geq 10$  mM which is at least 2 orders of magnitude higher than the concentration of paracetamol reached with therapeutic dosing. Tramadol up to 40  $\mu$ M did not inhibit the formation of paracetamol-glutathione conjugates.

#### *CYP2D6 polymorphism effects*

Demethylation by CYP2D6 to M1 is a major metabolic pathway of tramadol. M1 is an active metabolite with a high affinity for the  $\mu$ -opioid receptor and is responsible for a proportion of the therapeutic efficacy of tramadol. CYP2D6 is also involved in metabolism of paracetamol to NADPI. Therefore genetic polymorphisms<sup>8</sup> of CYP2D6 may theoretically affect the efficacy and adverse event profile of paracetamol/tramadol combination products.

Tramadol appears to be a better analgesic in CYP2D6 extensive metabolisers than Poor Metabolisers, likely due to reduced active metabolite M1 formation in Poor Metabolisers, however analgesia is still provided by monoaminergic pathways<sup>9</sup>. Patients devoid of CYP2D6 activity need higher doses of tramadol to achieve comparable efficacy<sup>10</sup>, and patients with high CYP2D6 activity are more susceptible to adverse events<sup>11</sup>. In a study of postoperative analgesia in 174 patients treated with IV tramadol (3 mg/kg), CYP2D6 genotypes conferring low enzyme activity (and low plasma M1 concentration) were associated with non-response to treatment<sup>10</sup>. In a study in Malaysian patients, homozygosity of the CYP2D6\*10 allele correlated with plasma

---

<sup>8</sup> CYP2D6 is expressed polymorphically, with 93% of Caucasians being phenotypically extensive metabolisers and the remainder being Poor Metabolisers of CYP2D6 probe substrates. The CYP2D6 pathway is low capacity, exhibits saturable kinetics and is highly polymorphic; 7-10% of Caucasians have a non-functional enzyme; reduced activity enzymes are common in Asian populations (40-50%); and ultra rapid metabolising variants are found in increased proportions in Mediterranean (7-12%) and North African (21-29%) populations.

<sup>9</sup> Poulsen L, Arendt-Nielsen L, Brøsen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther.* 1996 Dec;**60**(6):636-44.

<sup>10</sup> Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A and Stuber F. Concentrations of tramadol and *O*-desmethyltramadol enantiomers in different CYP2D6 genotypes. *Clinical Pharmacology and Therapeutics* 2007;**82**(1):41-7.

<sup>11</sup> Kim E, Choi C-B, Kang C and Bae S-C. Adverse events in analgesic treatment with tramadol associated with CYP2D6 extensive-metaboliser and OPRM1 high-expression variants. *Ann Rheum Dis* 2010;**69**(10):1889-90.

tramadol concentration<sup>12</sup> and was associated with reduced tramadol analgesia in a Chinese population in which 28% were homozygous<sup>13</sup>.

Polymorphisms of CYP2D6 may contribute to different rates of NAPQI production and have an impact on susceptibility to hepatotoxicity with paracetamol overdose.

In a study of 154 Korean patients with knee osteoarthritis taking 37.5 mg tramadol/325 mg paracetamol up to 3 times/day for  $\leq 14$  days, CYP2D6 polymorphisms conferring increased enzyme activity were associated with increased risk of nausea and vomiting<sup>11</sup>. CYP2D6 increased activity alleles would be expected to cause higher exposure to M1 as well as faster metabolism of paracetamol however paradoxical effects of CYP2D6 polymorphisms have been described<sup>14</sup>. The clinical effects of tramadol via M1 are substantially dependent on CYP2D6 activity and the metabolism of paracetamol (to its toxic metabolite NAPQ1) is partly affected by CYP2D6 activity. In addition, the effects of paracetamol on tramadol metabolism to M1 are likely to be mediated by CYP2D6. No nonclinical data are available on the potential clinical effects of CYP2D6 polymorphisms on tramadol/paracetamol metabolism. The potential clinical consequences of Zaldiar treatment in CYP2D6 extensive versus Poor Metabolisers will need to be assessed from the clinical data.

## Relative exposure

### *Tramadol*

The submitted data were published by Matthiesen *et al.* (1998)<sup>15</sup>, and the derived pharmacokinetic parameters of tramadol in dogs, rats, mice and man associated with toxicology studies are shown in Table 7. In animals, tramadol is metabolised more rapidly than in humans with a half-life of circa 1, 1.5 and 3 h in mice, dogs and rats, respectively, compared to 6 h in humans. In rats, there was evidence of increased exposure but reduced half-life ( $t_{1/2}$ ) after repeat dosing as well as significant gender differences with exposure ( $C_{max}$ , AUC) at least 3x higher in females than males after single and multiple dosing. In dogs but not mice, multiple dosing results in greatly reduced exposure.

A comparison of exposure after a single dose of tramadol suggests that a dose of 30 mg/kg in rats, circa 100 mg/kg in mice and 20 mg/kg in dogs provides exposure greater than or equal to a dose of 1.5 mg/kg in humans.

---

<sup>12</sup> Gan SH, Ismail R, Wan Adnan WA, Wan Z. Correlation of tramadol pharmacokinetics and CYP2D6\*10 genotype in Malaysian subjects. *J Pharm Biomed Anal.* 2002 Sep **5**;30(2):189-195.

<sup>13</sup> Wang G, Zhang H, He F, Fang X. Effect of the CYP2D6\*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. *Eur J Clin Pharmacol.* 2006 Nov;**62**(11):927-31.

<sup>14</sup> Bogni A, Monshouwer M, Moscone A, Hidestrand M, Ingelman-Sundberg M, Hartung T, Coecke S. Substrate specific metabolism by polymorphic cytochrome P450 2D6 alleles. *Toxicol In Vitro.* 2005 Aug;**19**(5):621-9.

<sup>15</sup> Matthiesen T, Wöhrmann T, Coogan TP, Uragg H. The experimental toxicology of tramadol: an overview. *Toxicol Lett.* 1998 Mar 16;**95**(1):63-71.

**Table 7. Summary of main pharmacokinetic parameters after administration of tramadol in dogs, rats mice and man (Matthiesen et al.,1998<sup>15</sup>)**

Species	Dose	Duration	C <sub>max</sub> (ng/mL)		t <sub>1/2</sub> (h)		AUC (ng.h/mL)	
			males	females	males	females	males	females
<b>Dog</b>	20 mg/kg	Single dose	1380		1.4-1.5		2505 - 6587	
		Multi dose - 1 week	555		1.5		842	
<b>Mouse</b>	30 mg/kg	Single dose	593		1.1		725	
		Multi dose - 4 weeks	611		0.7		707	
			males	females	males	females	males	females
<b>Rat</b>	30 mg/kg	Single dose						
		(+)enantiomer	192	712	3.0	3.9	519	2677
		(-)enantiomer	73	224	5.8	4.2	153	888
		Multi dose - 2 weeks						
		(+)enantiomer	343	906	2.5	3.0	840	2942
		(-)enantiomer	158	596	2.7	2.9	307	1364
<b>Human</b>	1.5 mg/kg*	Single dose						
		Tramadol (total)	274		5.9		2177	
		(+)enantiomer	147		6.0		1258	
		(-)enantiomer	125		5.2		908	

\*Equivalent to the proposed loading dose of 75 mg tramadol in a 50 kg person.

The most appropriate animal studies for a comparison of time-weighted plasma exposure over a prolonged period are the 3 month repeat dose studies with the combination in rats and dogs. These data are tabulated below (Table 8).

The exposure margins achieved in the 3 month rat and dog studies for the tramadol isomers, M1 isomers and paracetamol were quite modest, about 1.5 for tramadol and M1 and 2-5 for paracetamol. It is also noted that the maximum recommended human dose (MRHDs) of tramadol and paracetamol in the combination product are only 75% and 65% of the respective MRHDs of the individual agents.

**Table 8. Exposure ratios based on high dose plasma AUC for the 3 month combination studies in rats and dogs**

Species, study, high doses* of tramadol/paracetamol	Analyte	AUC <sub>0-24h</sub> (ng.h/mL) (M/F or M+F)	Exposure ratio <sup>^</sup> (M/F or M+F)
<b>Rat</b> (DS96002, DM96319): 45/390 mg/kg/day PO for 3 months	(+)-tramadol	2445/7595	0.7/2.0
	(-)-tramadol	5045/4669	1.6/1.5
	(+)-M1	512/2575	0.6/3.2
	(-)-M1	1063/1187	1.4/1.5
	Paracetamol	669 <sup>\$</sup>	5.5
<b>Dog</b> (DS96303, DM96320): 22.5/195 mg/kg/day PO for 3 months	(+)-tramadol	106	0.03
	(-)-tramadol	1305	0.4
	Paracetamol	265 <sup>\$</sup>	2.2
<b>Human</b> (EDMS-USRA-2697771, DM96361): 300/2600 <sup>#</sup> mg/day PO (MRHD) for 7 days	(+)-tramadol	3733	NA
	(-)-tramadol	3096	
	(+)-M1	816	
	(-)-M1	782	
	Paracetamol	121.6 <sup>\$</sup>	

\* The high doses in the animal studies. <sup>^</sup> AUC<sub>animal</sub>/AUC<sub>human</sub>      <sup>\$</sup> µg.h/mL      NA, not applicable

<sup>#</sup> The human study used doses of 375/3250 mg/day; tabulated AUC values have been linearly corrected for the MRHD in the current submission (300/2600 mg/day) by multiplying values obtained at 375/3250 mg/day in this study by 0.8

## Toxicology

### General toxicity

#### Single dose toxicity

The submitted data for tramadol alone showed that the maximum non lethal PO dose was 200 mg/kg in mice and <200 mg/kg in rats. Mortality was 90-100% at doses of 300-400 mg/kg. (+)Tramadol was substantially more toxic than (-)tramadol and clinical signs at doses ≥200 mg/kg included increased restlessness, decreased spontaneous activity, decreased pain reaction, cramps/tonicity, exophthalmia, Straub tail, rapid or gasping breathing, tremor, salivation and convulsions. Clinical signs resolved with 4-6 h in survivors. Kidney and bladder discolouration/haemorrhage were observed at necropsy with severity of effects of (+)tramadol > tramadol > (-)tramadol.

With combination dosing, no treatment related findings were observed in rats at a dose of 150 mg/kg tramadol and 300 mg/kg paracetamol. In a separate study, increasing paracetamol dosing to 100/867.1 mg/kg tramadol/paracetamol led to mild clinical findings including decreased activity, decreased faeces production, increased salivation and increased nasal/ocular discharge but no mortality. At doses ≥ 215/1864 mg/kg tramadol/paracetamol, dose-dependent decreased body weight and opioid-related clinical signs were observed including prostration, exophthalmia, Straub tail, rales, decreased respiration rate and tremor as

well as discoloured urine and urine and faeces stained coat, which may indicate liver and/or kidney toxicity of paracetamol. Effects were greater in females than males, consistent with kinetic findings of greater female exposure to tramadol and M1. Mortality was associated with fluid in the stomach, distended bladder and lung discolouration. Kinetic data showed similar exposures (AUC) to tramadol and M1 isomers and paracetamol with individual or combination treatment (apart from higher (-)-tramadol exposure with combination treatment in males).

In dogs, there was no mortality with dosing up to 60/520.2 mg/kg tramadol/paracetamol. At this dose, animals showed clonic convulsions, dyspnoea and increased muscle tone. At doses  $\geq 40/346.8$  mg/kg tramadol/paracetamol animals showed coarse tremors, ataxia, cyanosis, eye discharge, red conjunctiva, oedema of neck, face, mouth and eye, ptosis and decreased food consumption and drug emesis. At doses  $\geq 20/173.4$  mg/kg tramadol/paracetamol animals showed decreased activity, fine tremors and increased vocalisation and licking. There were no treatment-related necropsy findings. Kinetic data showed slightly lower tramadol exposure, and higher paracetamol exposure, with combination treatment.

It can be concluded from the acute toxicity studies that the clinical signs after combination dosing are consistent with individual dosing with tramadol; renal and bladder effects may be paracetamol-related. More pronounced effects in female rats and greater toxicity of (+)tramadol is consistent with the higher exposure to tramadol in females and higher plasma levels of (+)tramadol compared to (-)tramadol demonstrated in pharmacokinetic studies. The maximum non lethal dose was 100/867.1 mg/kg tramadol/paracetamol in rats and in the dog study there was no mortality at doses up to 60/520.2 mg/kg.

The recommended initial clinical dose of Zaldiar is 75/650 mg tramadol hydrochloride/paracetamol (1.5/13 mg/kg in a 50 kg person). A single tramadol dose of 30 mg/kg in rats and 20 mg/kg in dogs results in similar or greater exposure than a dose of 1.5 mg/kg in humans.

### ***Repeat dose toxicity***

Rats and dogs treated with tramadol at doses up to 30 mg/kg/day for 18 months and up to 40 mg/kg/day for 12 months, respectively, showed no treatment related effects with the exception of slightly reduced body weight and mydriasis in dogs.

#### *Rats*

Individual and combination dosing with tramadol (7.5 - 45 mg/kg/day) and paracetamol (65 - 390 mg/kg/day) in rats resulted in alopecia, erythema and scabbing at all doses with transient reductions in body weight at 4 weeks. High dose (HD) females (45/390 mg/kg) exhibited increased salivation after 3 months. HD paracetamol (390 mg/kg) either alone or in combination with HD tramadol (45 mg/kg) was associated with a decreased number of red blood cells with increased cell volume and haemoglobin content in males after 4 weeks and 3 months; decreased alkaline phosphatase (ALP) in males after 4 weeks; decreased alanine transaminase (ALT) and aspartate transaminases (AST), increased ALP, increased serum potassium and increased urine volume in females; and increased kidney and liver weights and decreased adrenal weights in males after 3 months. The kinetic data showed that exposure to tramadol, M1 and paracetamol was reduced with combination compared to separate dosing and exposure to (+)tramadol and (+)M1 in females is 3-5x higher than in males (no gender comparisons were provided for paracetamol exposure).

#### *Dogs*

In the 4 week range-finding study in dogs, 2/2 females died after 5 days of dosing at 40/346.8 mg/kg/day and 1/2 females died after 8 days of dosing at 0/346.8 mg/kg/day, implicating HD paracetamol as causative. This is consistent with kinetic data which shows higher exposure to paracetamol in female compared to male dogs with both individual and combination dosing. In the 3 month study, lower doses were used. One male in the highest dose group (22.5/195 mg/kg/day) was humanely sacrificed due to severe toxicity including 36% decreased body

weight, jaundice, anorexia, decreased activity, fine tremors and oedema of the head, neck and mouth. Body weights were also decreased in surviving HD animals with 2/7 exhibiting similar clinical signs as well as hunched posture, ataxia, emesis, lack of faeces, pallor, urine-stained coat and blood in urine. Dogs treated at 7.5/65 mg/kg/day showed minor sporadic increased salivation, decreased faeces and unkempt coat. HD paracetamol was associated with discoloured faeces and unkempt coat and HD tramadol was associated with decreased faeces and increased salivation. There were no electrocardiogram (ECG) findings. At doses of 22.5/195 and 0/195 mg/kg/day, data indicated decreased red blood cells and haemoglobin; increased reticulocytes, platelets and Heinz bodies; increased plasma ALT, ALP, gamma glutamyl transferase, triglycerides and bilirubin; increased bilirubin, urobilinogen and nitrites in the urine associated with decreased pH; and increased kidney, liver and heart weights; gross and histopathological changes in liver, gall bladder, kidney, thymus, bone marrow, spleen, duodenum, testicles and lung. There was no clear pattern of altered exposure to tramadol and M1 isomers and paracetamol with combination compared to individual treatment.

It can be concluded from the chronic toxicity studies that in rats, mild renal and hepatic toxicity was associated with paracetamol dosing at  $\geq 390$  mg/kg/day, and in dogs severe renal, hepatic toxicity and multiple organ and tissue damage was associated with paracetamol at doses  $\geq 195$  mg/kg/day, regardless of co administration of tramadol. Opioid-related clinical signs associated with tramadol treatment were unchanged by co treatment with paracetamol. The No Observable Adverse Effect Level (NOAEL) was 7.5/65 mg/kg/day in dogs and not determined in rats.

Compared with the exposures to tramadol and M1 isomers and paracetamol at the MRHD of Zaldiar (6/52 mg/kg/day tramadol/paracetamol in a 50 kg person), the animal exposures at the HD were about 1.5x (tramadol, M1) and 2-5x (paracetamol), and well below clinical exposures at the NOAEL in dogs.

#### *Hepatic toxicity*

The hepatic toxicity of paracetamol overdose in humans is well known. Ecobichon et al., (1989) 16 reported that hepatotoxicity in animals is only observed in those species capable of the rapid formation of the reactive metabolites accompanied by the depletion of glutathione (mouse, hamster) and that little hepatic injury is observed in species excreting small amounts of intoxication pathway products (rat, rabbit, guinea pig). In other studies, susceptibility to paracetamol hepatotoxicity was lower in rats than in hamsters, mice, dogs and humans and induction of oxidative metabolism of CYP450 enzymes by 3-methylcholanthrene increased paracetamol toxicity 17, 18. Temporal variations in susceptibility to paracetamol hepatotoxicity in mice (8 am administration was not toxic, 8 pm administration was toxic) have been associated with circadian variations in glutathione levels (for detoxification of NAPQ1) and metabolic enzyme activity 19. Data in mice have demonstrated increased hepatotoxicity of paracetamol in pregnancy associated with greater glutathione depletion.

The submitted data in rats and dogs clearly demonstrate hepatic toxicity of paracetamol in dogs and rats with little effect of co administration of tramadol which is consistent with the kinetic

---

<sup>16</sup> Ecobichon DJ, Hidvegi S, Comeau AM, Varma DR. Acetaminophen metabolism in vivo by pregnant, fetal, and neonatal guinea pigs. *J Biochem Toxicol.* 1989 Winter;4(4):235-40.

<sup>17</sup> Hart SJ, Calder IC, Tange JD. The metabolism and toxicity of paracetamol in Sprague-Dawley and Wistar rats. *Eur J Drug Metab Pharmacokinet.* 1982;7(3):203-22.

<sup>18</sup> Jollow DJ, Thorgeirsson SS, Potter WZ, Hashimoto M, Mitchell JR. Acetaminophen-induced hepatic necrosis. VI. Metabolic disposition of toxic and nontoxic doses of acetaminophen. *Pharmacology.* 1974;12(4-5):251-71.

<sup>19</sup> Kim YC, Lee SJ. Temporal variation in hepatotoxicity and metabolism of acetaminophen in mice. *Toxicology.* 1998 Jun 26;128(1):53-61.



data indicating no effect of tramadol on paracetamol exposure<sup>20</sup>. In a published study of twice weekly dosing of female Wistar rats with 4.25 g/kg paracetamol (equivalent to 10% Lethal Dose (LD10)) for 18 weeks, death resulted within 24 h in 1/15 animals and death with progressive weight loss in 5/15 animals<sup>21</sup>. Surviving animals showed varying degrees of centrilobular liver cell necrosis; hepatotoxicity was reduced after long term treatment due to induced enzyme activity.

Strain differences in susceptibility to paracetamol induced hepatotoxicity have been demonstrated in rats and mice and differences in susceptibility in humans may be due to several factors. An association between inflammatory phenotype (T helper cell (Th)1/Th2 cytokine balance<sup>22</sup>) and paracetamol-induced liver injury has been demonstrated<sup>23</sup>. Acute or chronic ethanol use may increase paracetamol-induced hepatotoxicity by inducing CYP2E1 and chronic alcohol use can deplete liver glutathione stores. Drugs that induce CYP2E1 and CYP1A2 may potentially increase the risk for paracetamol-induced hepatotoxicity. *In vitro* studies in human liver microsomes suggested that co medication with CYP3A4 inducers such as phenobarbitone, phenytoin, carbamazepine or rifampicin or CYP2E1 inducer isoniazid (itself a hepatotoxin) may increase paracetamol hepatotoxicity<sup>24</sup>. However, human data suggest that patients with drug-induced hepatic enzymes are not at increased risk of paracetamol-mediated hepatotoxicity when used at therapeutic doses<sup>25</sup>.

#### *Renal toxicity*

Paracetamol overdose may cause renal toxicity in humans and animals. Acute renal failure at therapeutic doses has been described in alcoholics and a chronic nephrotoxic effect of paracetamol is suggested by case-control studies; however, the mechanisms are not fully elucidated. The nephrotoxic potential of paracetamol may be associated with induction of apoptosis via Bcl-xL<sup>26</sup>, or effects on prostaglandin synthase, N-deacetylase, cytochrome P450 and glutathione S-transferase<sup>27,28</sup>. Published studies in rats show an age related increase in susceptibility to paracetamol-induced nephrotoxicity; greater plasma concentrations of paracetamol and conjugated metabolites suggest a pharmacokinetic basis to this finding<sup>29</sup>.

---

<sup>20</sup> Tramadol increased paracetamol exposure/toxicity in dogs on Day 1 of treatment, but not with repeat dosing.

<sup>21</sup> Poulsen HE, Thomsen P. Long-term administration of toxic doses of paracetamol (acetaminophen) to rats. *Liver*. 1988 Jun;**8**(3):151-6.

<sup>22</sup> Homeostatic control of the immune system by secretion of different cytokines by the Th1 and Th2 cells. The concentration dependent binding of the various cytokines to specific receptors determines the balance (or imbalance leading to disease).

<sup>23</sup> Masubuchi Y, Sugiyama S, Horie T. Th1/Th2 cytokine balance as a determinant of acetaminophen-induced liver injury. *Chem Biol Interact*. 2009 May 15;**179**(2-3):273-9.

<sup>24</sup> Thummel KE, Lee CA, Kunze KL, Nelson SD, Slattery JT. Oxidation of acetaminophen to N-acetyl-p-aminobenzoquinone imine by human CYP3A4. *Biochem Pharmacol*. 1993 Apr 22;**45**(8):1563-9.

<sup>25</sup> Forrest JA, Clements JA, Prescott LF. Clinical pharmacokinetics of paracetamol. *Clin Pharmacokinet*. 1982 Mar-Apr;**7**(2):93-107.

<sup>26</sup> Bcl-xL is a transmembrane molecule in the mitochondria. It is involved in the signal transduction pathway of the FAS-L. It is one of several anti-apoptotic proteins which are members of the Bcl-2 family of proteins.

<sup>27</sup> Lorz C, Justo P, Sanz AB, Egido J, Ortíz A. Role of Bcl-xL in paracetamol-induced tubular epithelial cell death. *Kidney Int*. 2005 Feb;**67**(2):592-601.

<sup>28</sup> Bessems JG, Vermeulen NP. Paracetamol (acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. *Crit Rev Toxicol*. 2001 Jan;**31**(1):55-138.

<sup>29</sup> Tarloff JB, Goldstein RS, Mico BA, Hook JB. Role of pharmacokinetics and metabolism in the enhanced susceptibility of middle-aged male Sprague-Dawley rats to acetaminophen nephrotoxicity. *Drug Metab Dispos*. 1989 Mar-Apr;**17**(2):139-46.



The submitted toxicology data implicated paracetamol in renal toxicity with abnormalities in urine parameters and histopathological findings in chronic studies in dogs. In acute studies, high doses of tramadol were associated with kidney and bladder discolouration/haemorrhage in rats.

#### *Cardiovascular effects*

The submitted data showed that chronic dosing of paracetamol at 195 mg/kg/day with or without co administration of 22.5 mg/kg/day tramadol in dogs caused discolouration of the atria, right ventricular and vena cava dilation but no effects on ECG parameters.

#### *Gastrointestinal effects*

Paracetamol is regarded as having a superior GI safety profile to non-steroidal anti-inflammatory drugs (NSAIDs) due to the lack of peripheral action on prostaglandins. High doses of paracetamol may induce upper GI symptoms but the risk of ulcers and bleeding is low.

Opioid receptors in the GI tract mediate the effects of opioid analgesics. The submitted data demonstrated opioid-related GI effects including reduced/absent faeces (constipation), decreased food consumption (anorexia) and emesis at doses of  $\geq 22.5/195$  mg/kg/day tramadol/paracetamol for 3 months in dogs. These effects, with the exception of anorexia, were not reported with tramadol alone at doses up to 40 mg/kg/day for 12 months suggesting a possible synergistic effect of co administration of paracetamol.

***In summary***, the toxicity profile of the combination product observed in rats and dogs in repeat dose studies of up to 3 months was consistent with those observed for the individual agents. In dogs, a pharmacokinetic interaction led to initially increased paracetamol exposure, with resultant hepatotoxicity; this effect was less apparent with continued treatment due to induction of tramadol metabolism over time in this species. This kinetic interaction was not observed in rats (or humans).

### **Genotoxicity and carcinogenicity**

No genotoxicity or carcinogenicity data were submitted for the paracetamol/tramadol combination; however, previously evaluated data, new data and literature references for the individual components were provided. TGA adopted European Union (EU) guidelines state that for fixed dose combinations of non genotoxic non carcinogenic drugs, genotoxicity and carcinogenicity studies with the combination are not needed<sup>30</sup>.

#### ***Genotoxicity***

##### *Paracetamol*

A review of the genotoxicity of paracetamol by Bergman *et al.* (1996)<sup>31</sup> concluded that there was clear evidence that high concentrations of paracetamol cause chromosomal damage *in vitro* and *in vivo* in mammalian cells and that the data indicated three possible mechanisms:

- i. inhibition of ribonucleotide reductase resulting in disrupted DNA repair and replication;
- ii. DNA damage caused by NAPQ1 after glutathione depletion (CYP450-mediated); and
- iii. increases in cytosolic and intranuclear calcium ( $Ca^{2+}$ ) resulting in endonuclease activation and DNA fragmentation.

---

<sup>30</sup> EMEA/CHMP/SWP/258498/2005 Guideline On The Non-Clinical Development Of Fixed Combinations Of Medicinal Products. <http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf>

<sup>31</sup> Bergman K, Müller L, Teigen SW. Series: current issues in mutagenesis and carcinogenesis, No. 65. The genotoxicity and carcinogenicity of paracetamol: a regulatory (re)view. *Mutat Res.* 1996 Feb 1;349(2):263-88.

*In vitro* genotoxic effects of paracetamol are highly dependent on concentration and duration of exposure and are only observed at hepatotoxic doses in 6-12 h incubations; such extended exposures are not expected *in vivo* as the half-life ( $t_{1/2}$ ) of paracetamol is 2-3 h. Safety factors of 3-10 (*in vitro*) and 7 (*in vivo*) were derived from rat micronucleus studies<sup>31</sup>.

#### *Tramadol*

Based on the submitted *in vitro* and *in vivo* studies, there was no evidence for a genotoxicity liability of tramadol; all assays were negative, apart from a positive result in the mouse lymphoma assay at  $\geq 100 \mu\text{g/mL}$  in the presence of metabolic activation.

The weight-of-evidence indicates a non genotoxic profile for tramadol.

### **Carcinogenicity**

#### *Paracetamol*

No carcinogenicity data were submitted for paracetamol. A comprehensive review by Bergman *et al.* (1996)<sup>31</sup> concluded that paracetamol may be carcinogenic at very high doses, causing liver tumours in mice and bladder tumours and neoplastic liver changes in rats, but has low carcinogenic potential at non hepatotoxic doses.

#### *Tramadol*

The 24 month carcinogenicity study in rats showed no treatment related neoplastic changes. The 30 month study in mice treated with 7.5, 15 or 30 mg/kg showed a dose-related increased incidence of hepatocellular adenomas at all doses and a slightly increased incidence of Harderian gland tumours at the HD only in males; and a non-dose-related increased incidence of pulmonary adenomas at all doses and small dose-related related increased incidence of histiocytic sarcomas at the mid dose (MD) and HD in females. These tumours are common in aged mice and the values were within historical controls levels. The data from the Grünenthal laboratories were published in a peer-reviewed journal<sup>15</sup>, and it was concluded by those authors that the findings did not reveal a carcinogenic effect of the test substance.

In the previous evaluation, concerns were raised regarding the adequacy of exposure levels. Toxicokinetic data showed that a single oral dose of 30 mg/kg tramadol generated an AUC of 725 ng.h/mL in mice and 672 ng.h/mL (males) to 3565 ng.h/mL (females) in rats compared to 2177 ng.h/mL for a 75 mg/50 kg dose in human males<sup>15</sup>). Following further investigations in mice and rats of plasma profiles of tramadol, M1 and M1-conjugates, Matthiesen *et al.* (1998)<sup>15</sup> concluded that animals in the carcinogenicity studies were adequately exposed. It is also noted that exposure at the recommended doses of the combination product (300 mg/day tramadol and 2600 mg/day paracetamol) is lower than exposure at the maximal recommended dose of each agent individually (400 mg/day tramadol and 4000 mg/day paracetamol).

### **Reproductive toxicity**

All of the submitted reproductive toxicity studies involved tramadol alone except one developmental toxicity study with the combination product in rats. Some of the tramadol data had been evaluated previously.

#### **Toxicokinetics**

Toxicokinetic data in pregnant rabbits (gestational day (GD) 6/7) demonstrated dose dependent exposure to tramadol from 10-175 mg/kg in a single dose. Plasma concentrations of M1 and M1 conjugates were dose dependent up to 75 mg/kg and then relatively constant suggesting saturation of metabolic pathways. After repeat dosing (GD 7-19) there was an accumulation of tramadol at 50 and 125 mg/kg/day and then a plateau at 175 mg/kg/day; M1 concentration was reduced at higher doses suggesting enhanced clearance. Plasma concentrations of (+)tramadol and (+)M1 were 2-3x higher than the (-) enantiomers. Co

administration with paracetamol reduced the accumulation of tramadol after repeat dosing suggesting enzyme induction.

A single dose of 50 mg/kg tramadol in pregnant rabbits at GD 7 showed a  $C_{max}$  at 1 h of 396 ng/mL which was in the range of the  $C_{max}$  in non pregnant humans of a dose of 1.5 mg/kg of 274 ng/mL.

#### *Paracetamol*

No data were submitted for the reproductive toxicity of paracetamol alone. Based on published information<sup>32,33</sup>, there was no evidence for teratogenicity in a continuous breeding study in male and female mice treated with paracetamol in the diet at doses up to 1430 mg/kg/day. Reported effects included fewer litters and pups/litter (1430 mg/kg/day), reduced postnatal pup weight gain (357-1430 mg/kg/day), reduced F<sub>2</sub> pup birth weight (1430 mg/kg/day), and increased percentage of abnormal epididymal sperm in continuously-exposed F<sub>1</sub> males (1430 mg/kg/day). The 1430 mg/kg/day dose corresponds to about 2.5x the paracetamol dose at the MRHD of Zaldiar (52 mg/kg/day), on a body surface area basis; the NOAEL dose (715 mg/kg/day) is circa 1.3x the paracetamol dose at the MRHD of Zaldiar.

#### *Tramadol, Combination dosing*

The fertility of rats was not significantly affected by oral treatment with tramadol (males: 10 or 50 mg/kg/day, 60 days prior to mating; females; 25-75 mg/kg/day, 2 weeks before and 3 weeks after conception).

In female rats, treatment with tramadol 25-75 mg/kg/day PO from GD 7-17 resulted in slightly lower fetal and placental weights and an increased incidence of delayed ossification in pups, possibly due to maternal toxicity but there was no evidence of embryotoxicity or teratogenicity. Similar effects were seen in rats with combination dosing (GD 6-17) up to 50/434 mg/kg/day PO tramadol/paracetamol.

In female rabbits treated with tramadol 25-75 mg/kg/day PO from GD 7-19, there was no evidence of embryotoxicity or teratogenicity; post-implantation losses were increased in the 25 and 50 mg/kg/day dose groups only, with retarded ossification in HD pups only. A similar unremarkable profile was reported in rabbits similarly treated up to 175 mg/kg/day PO (GD 7-19), with concomitant clinical toxicity at 125 and 175 mg/kg/day. Although a parallel kinetic study in rabbits at doses of 75, 100 and 150 mg/kg/day PO (GD 6-18) reported increased pre (MD, HD) and post (low dose (LD), HD) implantation losses (but no malformations), doe numbers were small (2-3/group), dose relationship was not convincing, and these findings were not confirmed in the main studies with larger groups. Tramadol and M1 exposures at the high doses exceeded corresponding  $C_{max}$  values at the MRHD of Zaldiar.

Treatment of female rats from GD 15 to lactation day (LD) 22 with tramadol 10, 25 and 50 mg/kg/day PO was associated with increased post implantation loss and reduced pup viability at the MD and HD, although effects were not dose related. A further similar study (8, 20, 40, 80 mg/kg/day PO, GD 15 - LD 21) found maternal toxicity and reduced maternal care, increased stillbirths, reduced pup weight gain and viability at the high(er) dose(s); offspring NOAEL was 40 mg/kg/day.

Overall, the data from rats and rabbits show that tramadol does not appear to show direct (embryofetal) reproductive toxicity, although maternotoxicity and its consequences were evident at higher doses in both species.

---

<sup>32</sup>IARC (International Agency for Research on Cancer) monograph

<sup>33</sup>Reel JR, Lawton AD, Lamb JC 4th. Reproductive toxicity evaluation of acetaminophen in Swiss CD-1 mice using a continuous breeding protocol. *Fundam Appl Toxicol.* 1992 Feb;18(2):233-9.

## Nonclinical summary

- Efficacy studies in rodents supported clinical data demonstrating supra additive analgesic and anti-hyperalgesic effects of combination dosing with tramadol and paracetamol. No secondary effects particular to the combination were identified. As for all tramadol-containing products, there is a potential risk of Serotonin Syndrome when used in combination with other serotonin-enhancing medicines.
- Pharmacokinetic studies in rats and dogs showed a complex interaction of responses to combination dosing. The activity of tramadol may be partly dependent on the active metabolite M1 and the (+) and (-) enantiomers exhibit differential metabolism and target specificity. Briefly: rats had greater exposure to (+)-tramadol than (-)-tramadol in both sexes but female levels exceeded male levels, indicating both stereo-selective and gender-selective metabolism. With repeat dosing, paracetamol temporarily attenuated the known increase in tramadol AUC values, suggestive of induction of tramadol metabolism by paracetamol. Dogs had greater exposure to (-)-tramadol than (+)-tramadol and exhibit auto-induction of tramadol metabolism ( $\pm$  paracetamol). With single co administration in dogs, tramadol elevated paracetamol concentrations but this effect did not persist with repeated co administration and was not observed in rats or humans. No metabolic inhibitory activity between paracetamol and tramadol was detected in liver microsomes at therapeutic concentrations. Tramadol metabolism primarily involves CYP2D6, CYP2B6 and CYP3A4/5; paracetamol metabolism involves CYP2E1, CYP1A2, CYP3A4 and CYP2D6. The potential clinical effects of CYP2D6 polymorphisms should be assessed from the clinical data.
- Combination repeat dose PO toxicity studies were conducted in rats and dogs for 4 weeks and 3 months. The effects of combination treatment were generally similar to the well-established toxicological profiles of the individual agents. An exception was noted in dogs, where a kinetic interaction produced an initial elevation of paracetamol concentrations and consequent hepatotoxicity; the effect did not persist due to autoinduction of tramadol metabolism in this species. This was considered a species specific effect not seen in rat or human studies and not clinically relevant. No additional toxicity risks associated with combination compared to separate administration were identified.
- No genotoxicity or carcinogenicity data were submitted for the combination. Previous assessments have noted paracetamol genotoxicity after long exposures at hepatotoxic doses (unlikely with normal therapeutic use) and liver and bladder tumours have been reported at very high, cytotoxic doses of paracetamol. Taking into account the evidence of a threshold effect, it is considered that paracetamol is non genotoxic and non carcinogenic at therapeutic doses. Tramadol (100  $\mu\text{g}/\text{mL}$ ) was genotoxic in the mouse lymphoma assay in the presence of metabolic activation but negative in all other tests. Carcinogenicity studies showed a dose-related increase in hepatocellular adenoma in males and a non-dose-related increased incidence of pulmonary adenomas in female mice (common tumours in aged mice). The genotoxic and carcinogenic liabilities of paracetamol and tramadol individually are considered to be low at therapeutic doses and a similar conclusion for the combination is reasonable.
- Reproductive toxicity studies with the combination were limited to one embryofetal development study in rats. Observations were similar to corresponding tramadol-alone studies. The reproductive toxicity profiles of tramadol and paracetamol individually were generally unremarkable, with adverse embryofetal/offspring effects likely secondary to maternotoxicity. There was no evidence of teratogenicity in mice, rats or rabbits.

## Conclusions

The nonclinical efficacy data demonstrate synergistic effects of combination dosing, supporting the therapeutic aim of providing effective clinical analgesia with lower exposure to tramadol and paracetamol.

The nonclinical pharmacology, pharmacokinetics and toxicology of tramadol and paracetamol individually are well established from extensive prior investigations and published literature, and the focus of the present submission was on potential untoward effects of treatment with the combination. Pharmacokinetic interactions were observed in the animal studies, the most noteworthy being increased paracetamol concentrations (and hepatotoxicity) with single co administration in dogs, although this did not persist with repeated dosing and appeared to be specific to this species. The interactive kinetic data have interpretative value for the corresponding toxicity findings in these species, with little/no direct relevance to the clinical situation. Tramadol metabolism is mainly via CYP2D6, which plays a minor role in paracetamol metabolism, and metabolic interactions between the two are not anticipated at therapeutic concentrations. It is unclear whether this also applies in 2D6 Poor Metabolisers and assessment of the clinical data may consider this issue.

No additional toxicity risks were identified with combination dosing beyond well known renal and hepatic toxicity of high paracetamol doses and opioid related clinical effects of high dose tramadol. Although genotoxicity/carcinogenicity were not investigated with the combination, previous studies with the individual compounds have concluded that these liabilities are low. Reproductive toxicity in rats with the combination was consistent with tramadol-alone studies and no teratogenicity was observed. The potential risk of Serotonin Syndrome has been included in the draft PI document and the adequacy of the warning statements will be assessed by the clinical evaluator.

The calculated animal/human systemic exposure margins at the highest tested doses in combination studies in rats and dogs were modest, and less than anticipated clinical exposure at No Effect doses. However, the toxicity profiles of tramadol and paracetamol individually are well known and both medicines have had extensive periods of widespread clinical usage. It is also noted that the maximal doses of tramadol (300 mg) and paracetamol (2600 mg) in the proposed maximal Zaldiar daily dose are lower than the maximal recommended daily doses of each medicine alone (400 and 4000 mg, respectively) and pharmacokinetic data confirm that lower doses result in lower exposure.

In conclusion, there are no objections on nonclinical grounds to the registration of Zaldiar as proposed by the sponsor.

## IV. Clinical findings

### Introduction

The current data submission included:

- a complete application to register a film-coated tablet (FCT)
- an abridged application to register an effervescent tablet

Acetaminophen' has been abbreviated to APAP in this report; 'tramadol' has been abbreviated to T; and the combination 'tramadol/acetaminophen' has been abbreviated to T/A and will refer to the FCT unless otherwise specified. Both T and its principal metabolite, M1, have activity.

Comment: As proposed during submission planning, the abridged application for the effervescent tablet consists of a single pharmacokinetic (PK) bioequivalence (BE) study, to be evaluated in conjunction with the application for the FCT, with demonstration of BE of the two

tablets deemed by the sponsor to be sufficient evidence to infer that efficacy and safety of the formulations are also equivalent (sponsor's Clinical Overview).

According to the Therapeutic Goods Administration (TGA) guidelines for the development of fixed combination medicinal products<sup>34</sup>, a bibliographical data analysis may be submitted "when the fixed combination corresponds closely to combinations that are already in widespread use" (p7) in order to reduce the amount of clinical efficacy trials to be performed; and "an abridged safety database from available experience may be considered" (p8) "for pure substitution indications in case of fixed dose combination containing active substances with a wide therapeutic experience in the claimed indication at the proposed dosing schedule" (p8). Although "substitution" in the Guideline refers to replacement of individual components with the same dosages as a fixed dose combination medication, the evaluator considered that in this situation, the substitution of one fixed dose combination formulation with a different formulation but the same dose combination could fulfil the same criteria. Additionally, the effervescent tablet corresponds closely to the FCT which has been in "widespread use" with post marketing data from 2 million patients since 2002. Hence, the use of an abridged application could be justified.

However, the evaluator has also identified three specific safety issues relevant to the effervescent formulation of the tablet that may be of concern, namely: effervescent tablets can contain high sodium and/or potassium ion concentrations and may not be suitable for use in the elderly or in patients with renal insufficiency<sup>35</sup>, there may be a potential for abuse with the effervescent tablet not seen with the FCT and there is a lack of efficacy/safety data with the FCT in patients aged 12-16 years. These points are discussed further in the evaluator's overall *Conclusions on Clinical Safety* below.

### ***Aspects of development***

Pain can be nociceptive (due to continual tissue trauma) or neuropathic (due to aberrant somatosensory processing). It affects millions and is often undertreated. Acute pain is a normal response to tissue damage and usually resolves as tissues heal, while chronic pain persists longer than the expected healing time or is associated with malignant or non-malignant disease. Appropriate treatment of pain can lead to a faster and more complete recovery.

The most widely recognised pain management guideline is the 3-step WHO Analgesic Ladder for treatment of acute or persistent nociceptive pain (such as cancer):

1. Non-opioid analgesic (acetylsalicylic acid, other non-steroidal anti-inflammatory drug [NSAID], APAP),
2. Opioid for mild to moderate pain (codeine [COD]), alone or with non-opioid analgesic,
3. Opioid for moderate to severe pain (hydrocodone, morphine).

The stepwise concept of combining analgesic agents with complementary modes of action and time-kinetic profiles, is a useful guide to treatment of other pain states. A single combined analgesic with flexible dosing would improve the treatment of pain by: simplifying drug delivery, improving compliance and improving safety (if the combination could achieve the same level of efficacy of the individual medications at lower component doses).

### ***Rationale for T/A combination FCT***

APAP is a non-opioid, Step 1 analgesic with a rapid-onset, short-acting PK/pharmacodynamic (PD) profile (starting analgesic activity 0.5 h, peak activity 1-1.5 h,  $t_{1/2}$  2 h). In therapeutic doses, APAP does not cause acid-base changes, gastric irritation, erosion or bleeding; does not affect platelets or bleeding time; and does not affect the cardiovascular or respiratory systems, or

---

<sup>34</sup>Guideline on clinical development of fixed combination medicinal products, EMEA/CHMP/EWP/240/95 Rev. 1

<sup>35</sup> Reflection Paper: Formulations of Choice for the Paediatric Population, EMEA/CHMP/PEG/194810/2005, p9

renal function. It is often taken as needed (prn) for minor pain and the maximum dose is 4 g/day.

T is a non-opioid, centrally-acting, Step 2 analgesic with a slower onset, longer-acting PK/PD profile (peak activity 2-3 h,  $t_{1/2}$  and duration of analgesia ~6 h), used to treat nociceptive and neuropathic pain. T causes less sedation, constipation and respiratory depression than equianalgesic doses of opioid analgesics; and does not cause the serious gastrointestinal (GI) adverse effects or renal toxicity of NSAIDs. The usual dose is 50-100 mg, every 4-6 h, maximum dose 400 mg/day for moderate to severe pain but the slower onset of action decreases its usefulness in the treatment of acute pain.

Combining the two medications makes sense as:

- Both analgesics are well-established ( $\geq 10$  years) but have not been previously combined for therapeutic purposes.
- The rapid onset of APAP and prolonged effect of T are expected to give complementary analgesic activity and an improved analgesic profile compared to either component.
- The combination drug would be a Step 2 analgesic suitable for the relief of:
  - Moderate to severe acute pain.
  - Chronic pain which may be relatively constant, requiring by-the-clock dosing; or may vary in severity and intensity over time, requiring prn treatment.
- Expected decreased doses of each component drug would decrease adverse events (AEs) and improve patient tolerability, thereby improving the safety profile.
- The decreased number of tablets required is expected to increase compliance.

#### ***Rationale for T/A combination effervescent tablet***

The effervescent tablet provides an alternative for patients unable to swallow tablets or capsules. Other effervescent analgesic medications have been well accepted by patients.

#### ***Special populations:***

*Paediatrics* Although T is available in paediatric formulations overseas, the TGA has not approved the use of T in children due to insufficient efficacy and safety data and there is no plan to register T in a paediatric formulation in Australia.

*Hepatic impairment, renal impairment, elderly* A population PK study, DM98313 in 84 healthy volunteers (50 male/34 female), and another, Study DM98311 in 236 patients with chronic pain (94 male/142 female; both summarised in *Pharmacokinetics* below), investigated the effects of various covariates (gender, age, race, weight, creatinine clearance ( $CL_{CR}$ ), smoking, CYP2D6, concomitant administration of oestrogen) on the PKs of A and T. None of the analysed studies included patients with hepatic impairment or severe renal impairment and only 19 of the patients analysed in DM98311 were  $>75$  years of age.

#### ***Data submitted***

For Zaldiar FCTs the clinical data also included complete, full reports of:

- 4 pharmacology studies, involving 92 healthy subjects (52 male, 40 female; TRAM-PHI-001; TRAMAP-PHI-001 [T-P-001], TRAMAP-PHI-002 [T-P-002], TRAMAP-PHI-003 [T-P-003])
- 2 population PK studies (DM98313, DM98111)
- 29 efficacy/safety studies, involving 8373 patients (3209 male, 5164 female; CA, CB; TRAMAP-ANAG-002 [T-A-002], TRAMAP-ANAG-003 [T-A-003], TRAMAP-ANAG-004 [T-A-004], TRAMAP-ANAG-005 [T-A-005], TRAMAP-ANAG-006 [T-A-006], TRAMAP-ANAG-006-OL [T-A-006-OL], TRAMAP-ANAG-007 [T-A-007], TRAMAP-ANAG-008 [T-A-008], TRAMAP-



ANAG-009 [T-A-009], TRAMAP-ANAG-010 [T-A-010] (pivotal), TRAMAP-ANAG-011 [T-A-011], TRAMAP-ANAG-012 [T-A-012] (pivotal), TRAMAP-ANAG-013 [T-A-013] (pivotal), TRAMAP-ANAG-015 [T-A-015]; CAPSS-104 [C-104], CAPSS-105 [C-105], CAPSS-112 [C-112], CAPSS-113 [C-113], CAPSS-114 [C-114], CAPSS-115 [C-115], CAPSS-128 [C-128], CAPSS-216 [C-216], CAPSS-241 [C-241]; PRI/TRP-CAN-1, GRTF-ZALI, SP-ZAL-III-02, ZAL-06)

And additional supportive data:

- meta-analysis of single-dose T/A in acute post-operative pain, and update
- meta-analysis of T and T/A in chronic pain
- 1999 integrated summary of effectiveness of T/A
- 1999 integrated summary of safety of T/A, and update
- 2001 integrated summary of safety of T/A, and update
- 13 reports of post-marketing experience with T/A, 2001-2010
- 7 studies of T (CAPSS-051 [C-051], tkb, tkm, tl2, tps bp, tps fm, tps oa)
- 2 reports regarding T (1999 Safety Summary; 2002 Summary of Abuse Risk)

For Zaldiar effervescent tablets the clinical data also included a complete, full report of:

1 pharmacology study, involving 32 healthy subjects (32 males; HPZALDEFF/01)

The studies were generally of high quality (although T-A-011 was terminated early due to data integrity problems) and the submission was well presented.

All the studies were performed in accordance with the Declaration of Helsinki, and in compliance with Good Clinical Practice (GCP).

T-A-015, C-105, C-112, C-113, C-114, C-115, C-128, C-216, and PRI/TRP-CAN-1, also contain the statement, "Known instances of non-conformance were documented and are not considered to have impacted the overall conclusions of this study.", regarding 'GCP' and/or 'the Declaration of Helsinki' and/or 'the obtaining of informed consent'.

Comment: Could the sponsor clarify what the 'known instances of non-conformance' consist of?

## Pharmacokinetics

TRAM-PHI-001 was a bioavailability (BA) study of T and APAP given as a single final market image (FMI) T/A 37.5/325 mg FCT; while T-P-003 examined the effect of food on the PKs of T/A. Two population PK studies, DM98313 and DM98311, investigated the effects of demographic covariates on the PKs of T and A to evaluate the need for any dosage adjustment in special populations. T-P-002 was a single dose drug interaction study and T-P-001 was a multiple dose drug interaction study of T and APAP given alone or in combination.

HPZALDEFF/01 was a BE study of FMI T/A effervescent tablets and FCTs.

## Introduction

All five PK studies were single centre, open label (OL), Phase I studies in healthy subjects:

*TRAM-PHI-001* was a study to evaluate the PKs/BA of T and APAP in 12 male subjects who received a single dose of one FMI T/A 37.5/325 mg combination tablet.

The PK parameters calculated were:  $C_{max}$ ,  $T_{max}$ , AUC, apparent clearance (CL/F), elimination rate constant ( $k_e$ ) and  $t_{1/2}$ .



*T-P-003* was a randomised, two-way cross over study to evaluate the effect of food on the BA of T and APAP in 24 subjects (12 male, 12 female), who received a single dose of 3x T/A 37.5/325 mg combination tablets in both fed and fasted states, with 7 days washout between.

The PK parameters calculated were: AUC,  $C_{max}$ ,  $T_{max}$ ,  $t_{1/2}$ , CL/F and  $k_e$ .

*T-P-002* was a randomised, three-way cross-over study to evaluate the effect of a T/A combination on the PKs of T and APAP in 24 subjects (12 male, 12 female), who received three single dose treatments in the fasted state (3x T/A 37.5/325 mg combination tablets; 3x T 37.5 mg capsules; 3x APAP 325 mg tablets) with  $\geq 1$  week (wk) washout periods between.

The PK parameters calculated were:  $C_{max}$ ,  $T_{max}$ , AUC, CL/F,  $k_e$  and  $t_{1/2}$ .

*T-P-001* was a randomised, two-way cross-over study to evaluate the effect of a T/A combination on the PKs of T and APAP at steady state in 32 subjects (16 male, 16 female). The first 16 subjects (8 male, 8 female) were assigned to Group I and randomly received APAP 325 mg (Treatment A) or T/A 37.5/325 mg (Treatment C), every 6 h (q6h) for 7 days, followed immediately by the alternate treatment, q6h for 7 days. The next 16 subjects (8 male, 8 female) were assigned to Group II and randomly received T 37.5 mg (Treatment B) or T/A 37.5/325 mg (Treatment C), q6h for 7 days, followed immediately by the alternate treatment, q6h for 7 days. Randomisation was stratified by gender within Group I and Group II.

The PK parameters calculated were:  $C_{max1}$ ,  $T_{max1}$ , trough plasma concentration ( $C_{min1}$ ), (after 7:00 am dose);  $C_{max2}$ ,  $t_{max2}$ ,  $C_{min2}$ , (after 1:00 pm dose); area under the plasma concentration time curve between 0 and 12 h ( $AUC_{(0-12h)}$ ), CL/F,  $k_e$  and  $t_{1/2}$ .

*HPZALDEFF/01* was a randomised, two-way cross-over study to demonstrate BE (for  $C_{max}$  and  $AUC_{0-t}$  of T and M1; and  $AUC_{0-t}$  of APAP) of test T/A 37.5/325 mg effervescent formulation compared to reference T/A 37.5/325 mg FCT formulation and to compare safety and tolerability (including local tolerability of oral mucosa) of the two formulations in 32 male subjects, who received two single dose treatments (T/A 37.5/325 mg effervescent tablet dissolved in 200 mL water; T/A 37.5/325 mg FCT taken with 200 mL water) with a  $\geq 5$  day washout period between treatments.

The PK parameters calculated were:  $C_{max}$ ,  $AUC_{0-t}$ , AUC,  $t_{max}$ ,  $t_{1/2,z}$  and mean residence time (MRT).

The two population PK studies were performed in order to determine whether any demographic covariates might significantly affect the PKs of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP when T and APAP were given as a combination:

*DM98313* was a NONMEM<sup>36</sup> population analysis of 4 Phase I PK studies (TRAM-PHI-001; T-P-001, T-P-002, T-P-003) in 84 healthy subjects (50 male, 34 female) who received T/A.

PK parameters, oral clearance (CL) and volume of distribution ( $V_d$ ) were determined from plasma data for APAP, T, and M1 and analysed for effects of demographic covariates: gender, race, body weight, creatinine clearance ( $CL_{CR}$ ), smoking and CYP2D6 genotyping.

*DM98311* was a NONMEM population analysis of a randomised, double blind (DB), parallel group, active controlled, multi centre, Phase III, efficacy/safety study (T-A-006) in 236 patients with chronic pain of benign origin (94 male, 142 female) who received T/A.

PK parameters, CL and volume of distribution ( $V_d$ ) were determined from plasma data for APAP, T and M1 and analysed for effects of demographic covariates: gender, age, weight,  $CL_{CR}$ , race and concomitant oestrogen medication.

---

<sup>36</sup> NONMEM (NONlinear Mixed-Effect Modeling) is a specialised software for the analysis of pharmacokinetic and pharmacodynamic data.

## Methods

### *Analytical methods*

In TRAM-PHI-001, T-P-003, T-P-002, and T-P-001; plasma samples were assayed for (+)- and (-)- enantiomers of both T and M1 (using validated GC methods), and for APAP (using validated HPLC methods).

In HPZALDEFF/01, plasma samples were assayed for T, M1, and APAP (using a validated LC-MS/MS method).

### *Pharmacokinetic data analysis*

*TRAM-PHI-001:* A screening visit was conducted  $\leq 2$  weeks prior to study entry when subjects received a single oral dose of x1 T/A 37.5/325 mg combination tablet, following a 10 h fast. Blood samples were taken for assay pre and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h post dose.

*T-P-003:* A screening visit was conducted  $\leq 2$  weeks prior to subjects receiving a single oral dose of x3 T/A 37.5/325 mg combination tablets following either a 10 h fast (Treatment A) or a high-fat breakfast (Treatment B), with cross-over to the other treatment 7 days later. Randomisation to treatment group was stratified by gender. Blood samples were taken for assay pre and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, and 36 h post treatment.

*T-P-002:* A screening visit was conducted  $\leq 2$  weeks prior to subjects randomly receiving three single dose treatments (3x T/A 37.5/325 mg combination tablets [Treatment A], 3x T 37.5 mg capsules [Treatment B], 3x APAP 325 mg tablets [Treatment C]) with  $\geq 1$  week washout periods between. Blood samples were taken for assay pre and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 30, and 36 h post treatment; while urine was collected for analysis pre and 0-12, 12-24, and 24-36 h post treatment.

*T-P-001:* A screening visit was conducted  $\leq 2$  weeks prior to subjects randomly receiving APAP 325 mg (Treatment A) or T/A 37.5/325 mg (Treatment C) q6h for 7 days followed immediately by the alternate treatment q6h for 7 days (Group I); or T 37.5 mg (Treatment B) or T/A 37.5/325 mg (Treatment C) q6h for 7 days followed immediately by the alternate treatment q6h for 7 days (Group II). Note that the doses of all medication were titrated over 2 days to minimise any nausea and vomiting that might be associated with T. Blood samples were taken for assay before the 1:00 am dose on Day 1; before the 7:00 am dose on Days 4-6 and 11-13; before the 7:00 am dose and 0.5, 1, 1.5, 2, 3, 4, 6, 6.5, 7, 7.5, 8, 9, 10, 12 h post dose on Day 7; before the 7:00am dose and 0.5, 1, 1.5, 2, 3, 4, 6, 6.5, 7, 7.5, 8, 9, 10, 12, 14, 24, 32, and 40 h post dose on Day 14; while urine was collected for analysis before the 1:00am dose on Day 1 and 0-12 h after the 7:00am dose on Days 7 and 14.

*HPZALDEFF/01:* A screening visit was conducted  $\leq 14$  days prior to subjects randomly receiving two single dose treatments (1x T/A 37.5/325 mg effervescent tablet dissolved in 200 mL water [Test], 1x T/A 37.5/325 mg FCT taken with 200 mL water [Reference]) with a  $\geq 5$  day washout period between treatments. Blood samples were taken for assay pre and 0.083, 0.166, 0.333, 0.5, 0.75, 1, 1.50, 2, 3, 4, 6, 8, 12, 16, 24, 30 and 36 h post treatment.

*DM98313:* A NONMEM analysis used data from the T/A treatment groups from 4 PK studies in healthy volunteers to determine the contribution of covariates (dichotomous: gender, race, smoker, CYP2D6 genotype; or continuous:  $CL_{CR}$ , body weight) on apparent CL and apparent  $V_d$ . Complete PK profiles were available for each subject from the studies: TRAM-PHI-001 (14 blood samples per subject, 0-24 h), T-P-002 (14 blood samples per subject, 0-36 h), T-P-001 (First period: 15 blood samples per subject at steady state, 0-12 h; Second period: 19 blood samples per subject at steady state, 0-40 h), T-P-003 (14 blood samples per subject, 0-36 h; data collected under fed conditions was not included in the analysis).

*DM98311*: A NONMEM analysis used data from the T/A treatment group from an efficacy/safety study in patients with chronic pain of benign origin to determine the contribution of covariates (dichotomous: gender, race, age, concomitant oestrogen medication; or continuous: body weight,  $CL_{CR}$ ) on  $CL$ ,  $V_d$ , first-order rate constant for absorption ( $k_a$ ), and a lag parameter ( $T_{lag}$ ) to describe delay in absorption for T. PK data were available from every patient in the Study T-A-006 (blood samples were collected on Days 15 and 29 of DB phase and at end of Months 2 and 3 of OL extension phase).

### **Statistical analysis**

In TRAM-PHI-001, summary statistics were calculated for PK data and the results compared to T and APAP data from previous studies.

Analysis of variance (ANOVA) models were used to construct 90% confidence intervals (CIs) for ratios of AUC for time 0 to infinity ( $_{(0-\text{inf})}$ ),  $AUC_{(0-\ast)}$ , and  $C_{\text{max}}$  in T-P-003 and T-P-002; ratios of  $AUC_{(0-12\text{ h})}$ ,  $C_{\text{max}1}$ ,  $C_{\text{max}2}$ ,  $C_{\text{min}1}$ ,  $C_{\text{min}2}$  in T-P-001; and ratios of  $AUC_{0-t}$ , AUC and  $C_{\text{max}}$  in HPZALDEFF/01.

## **Absorption**

### **Bioavailability**

#### *TRAM-PHI-001*

Twelve subjects enrolled in and completed the study: 100% male; 75% Hispanic, 17% White, 8% Black; mean age 28 years, range 20-40 years.

PK parameters for a single oral dose of one T/A 37.5/325 mg combination tablet after a fast are summarised as follows: the peak plasma concentrations of 64.3 ng/mL for (+)-T and 55.5 ng/mL for (-)-T were reached at 1.8 h. Mean elimination half-life for both was ~5 h and the mean  $CL$  was 588 mL/min for (+)-T and 736 mL/min for (-)-T. Peak plasma concentrations of 10.9 ng/mL for (+)-M1 and 12.8 ng/mL for (-)-M1 were reached at 2.1-2.2 h. Mean elimination half-life was 7.8 h for (+)-M1 and 6.2 h for (-)-M1 and the mean  $CL$  was 2245 mL/min for (+)-M1 and 2504 mL/min for (-)-M1. A peak plasma concentration of 4.2 ng/mL for APAP was reached at 0.9 h. The mean elimination half-life was 2.5 h and the mean  $CL$  was 365 mL/min.

The parameters,  $C_{\text{max}}$ ,  $t_{\text{max}}$  and AUC for the combination tablet were compared to dose normalised data for T and APAP from previous studies. The times to peak plasma concentration for (+)-T, (-)-T, and APAP were greater for the combination tablet (1.8 h, 1.8 h and 0.9 h respectively) than for the oral T or APAP solution (1.7 h, 1.4 h and 0.3 h respectively), consistent with the need for a tablet to breakdown and dissolve prior to absorption. Mean AUC values were comparable for (+)-T, (-)-T, (+)-M1, (-)-M1, and APAP. Thus, although rate of absorption was slower with the combination tablet, BA of T and APAP was similar for the combination tablet and the individual components.

### **Bioequivalence**

#### *HPZALDEFF/01*

Thirty-two male subjects were enrolled and of these all but one (31) completed the study: 100% male, 100% Caucasian; mean age was 31.3 years with a range of 20-45 years.

PK parameters and comparisons for T/A 37.5/325 mg effervescent tablets and FCTs: for all comparisons of  $C_{\text{max}}$  and  $AUC_{0-t}$  for T and  $AUC_{0-t}$  for APAP, point estimates ranged from 0.95 to 1.02, and 90% CIs were all within the pre determined interval for BE of (0.8, 1.25) for effervescent and film-coated T/A tablets. For comparisons of  $C_{\text{max}}$  for APAP and  $C_{\text{max}}$  and  $AUC_{0-t}$  for M1, point estimates also ranged from 0.96 to 1.03 and 90% CIs were all within the interval for BE of (0.8, 1.25). The formulations were therefore BE.

## ***Influence of food***

### *T-P-003*

Twenty-four subjects were enrolled and all but one (23) of these subjects completed the study: 50% male, 50% female; 83% White, 8% Asian, 8% Other; mean age was 28.3 years with a range of 19-39 years.

PK parameters for a single oral dose of three T/A 37.5/325 mg combination tablets after a high fat meal and after fasting are summarised below.

For both (+)-T and (-)-T: the mean AUC was only 5.1-6.4% higher and the mean  $C_{max}$  was unchanged (148 ng/mL for (+)-T, 131-132 ng/mL for (-)-T), when T/A was taken after a meal compared to when fasting; although time to reach peak plasma concentration was greater after a meal (2.5 h) compared to after fasting (1.9 h); 90% CIs for ratios (fed:fasting) of  $C_{max}$ ,  $AUC_{(0-\infty)}$  and  $AUC_{(0-inf)}$  were within the interval 80-125%. Elimination half-life was unchanged regardless of fed or fasted conditions (5.9 h for (+)-T, 5.3-5.4 h for (-)-T).

For (+)-M1 and (-)-M1: mean AUC was only 2.3-6.4% higher for (+)-M1 and essentially unchanged (0.5-0.9%) for (-)-M1, and mean  $C_{max}$  values were only 2.9% greater for (+)-M1 and unchanged for (-)-M1, when T/A was taken after a meal compared to when fasting. Time to reach peak plasma concentration, after a meal compared to fasting, was increased for (+)-M1 (3.2h versus [vs] 2.6h), but comparable for (-)-M1 (2.6h versus 2.5h); 90% CIs for ratios (fed:fasting) of  $C_{max}$ ,  $AUC_{(0-\infty)}$  and  $AUC_{(0-inf)}$  were within the interval 80-125%. Elimination half-life after a meal compared to fasting was decreased for (+)-M1 (6.2 h versus 6.8 h), but comparable for (-)-M1 (6.3 h versus 6.4 h).

For APAP: mean AUC was only 4.3-5.2% lower but the mean  $C_{max}$  was lower (11.0 ng/mL versus 13.1 ng/mL) and time to reach peak plasma concentration was greater (1.9 h versus 1.1 h), when T/A was taken after a meal compared to when fasting; 90% CIs for ratios (fed:fasting) of  $AUC_{(0-\infty)}$  and  $AUC_{(0-inf)}$  were within the interval 80-125%, whereas the ratio for  $C_{max}$  was outside the interval. Elimination half-life was unchanged regardless of fed or fasted conditions (2.6 h).

None of the changes were considered clinically significant. Thus, although rate of absorption of T and A from the combination tablet was prolonged in fed compared to fasting conditions, bioavailability was comparable for both conditions.

## **Pharmacokinetics in special populations**

### *DM98313*

Eighty-four subjects were included in the analysis: 50 male and 34 female; 43 White, 41 Non-white (16 Black, 21 Hispanic, 4 Other); 11 Smokers; 8 Poor Metabolisers (6 identified by CYP2D6 genotyping, 2 by (+)-M1/(-)-M1 ratio); mean age was 28.8 years and the range was 19-40 years; mean body weight was 70.2 kg with a range of 49-94 kg; mean  $CL_{CR}$  was 114.6 mL/min with a range of 75-150 mL/min.

A small but clinically non significant gender effect was seen on clearance of (+)-T and (-)-T. No gender effect was seen on CL of (+)-M1, (-)-M1 or APAP; or on  $V_d$  of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP.

Body weight (which was ~14% lower in females than in males) had a significant effect on CL and  $V_d$  of APAP but not on (+)-T and (-)-T (possibly due to the narrow range of distribution of body weight seen in healthy subjects typical of Phase I studies).

$CL_{CR}$  had a significant effect on CL of (+)-M1 and (-)-M1 (reflecting the importance of renal excretion in the elimination of M1); but not on (+)-T, (-)-T, or APAP (reflecting elimination mainly by extensive metabolism and possibly due to the narrow range of distribution of  $CL_{CR}$  seen in healthy subjects typical of Phase I studies).

A small but clinically non significant race effect was seen on CL of (+)-M1 and (-)-M1 (CL of M1 in non White subjects was ~20% higher than in White subjects). No race effect was seen on CL of (+)-T, (-)-T, or APAP, or on the  $V_d$  of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP.

CYP2D6 Poor Metabolisers had slightly decreased CL of T and a 70% increase in CL of M1 (consistent with a 40% decrease in formation of M1 from T in Poor Metabolisers).

Smokers and non smokers showed no differences in CL and  $V_d$  of T, M1, or APAP.

Overall, no covariates showed differences requiring a dose adjustment of T or APAP when given as a combination; however these results cannot be extrapolated for body weight or creatinine outside the narrow ranges encountered in healthy subjects typical of Phase I studies.

#### *DM98311*

Two hundred and thirty-six patients were included in the analysis: 94 male and 142 female; 211 White, 25 Non-white (18 Black, 7 Other); 162 <65 years old, 55 65-75 years old, 19 >75 years old; the mean body weight was 84.4 kg (range 45-173); the mean  $CL_{CR}$  was 93.8 mL/min (range 32-260 mL/min).

Body weight had a significant effect on the CL of APAP but not on (+)-T, (-)-T, (+)-M1, or (-)-M1.

$CL_{CR}$  had a significant effect on CL of (+)-M1 and (-)-M1 (reflecting the importance of renal excretion in the elimination of M1) but not on (+)-T, (-)-T, or APAP (reflecting elimination mainly by extensive metabolism).

No significant gender effect was seen on CL or  $V_d$  of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP.

No significant race effect was seen on CL or  $V_d$  of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP.

Age was significant in describing  $V_d$  of (+)-M1 (reflecting the lower  $CL_{CR}$  seen in elderly patients). Age had no significant effect on  $V_d$  of (+)-T, (-)-T, (-)-M1, or APAP and no significant effect on CL of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP.

No effect was seen of concomitant oestrogen medication on CL or  $V_d$  of (+)-T, (-)-T, (+)-M1, (-)-M1, or APAP.

Overall, no covariates showed differences requiring a dose adjustment of T or APAP when given as a combination.

### **Pharmacokinetic interactions with other medicinal products or substances**

#### *T-P-002*

Twenty-four subjects were enrolled and of these 4 discontinued treatment prematurely (3 after the second dose and one after the first dose). Twenty subjects completed the study: 50% male, 50% female; 79% White, 4% Black, 4% Asian, 13% Other; the mean age was 27 years (range 19-40 years).

PK parameters for (+)-T, (-)-T, (+)-M1, (-)-M1 and APAP, are summarised below.

For (+)-T, the ratios of means (90% CIs) for  $C_{max}$ ,  $AUC_{(0-*)}$ , and  $AUC_{(0-inf)}$  were 100.7 (94.3, 107.5), 93.1 (86.7, 100.1), and 94.3 (88.3, 100.6) respectively; and for (-)-T, the ratios of means (90% CIs) were 101.1 (94.3, 108.3), 96.8 (90.9, 103.0) and 97.0 (91.2, 103.2) respectively, for T/A combination tablets compared to T capsules. The treatments were therefore bioequivalent (BE) for (+)-T and (-)-T as the 90% CIs were all contained within the interval (80, 125).

CL of (+)-T was 661 mL/min after T/A and 631 mL/min after T alone, while CL of (-)-T was 809 mL/min after T/A, and 797 mL/min after T alone. Time to peak plasma concentrations for both (+)-T and (-)-T was ~2 h; the mean elimination half-life of (+)-T was ~6 h, ~5.5 h for (-)-T; for T given alone or in combination with APAP.

For (+)-M1, the ratios of means (90% CIs) for  $C_{max}$ ,  $AUC_{(0-*)}$  and  $AUC_{(0-inf)}$  were 105.4 (97.1, 114.4), 100.3 (91.6, 109.8) and 104.5 (99.4, 109.8) respectively; and for (-)-M1, the ratios of the means (90% CIs) were 103.4 (96.3, 111.1), 103.0 (98.1, 108.3) and 103.4 (99.4, 107.6) respectively; for T/A combination tablets compared to T capsules. The treatments were therefore BE for (+)-M1 and (-)-M1 as the 90% CIs were all contained within the interval (80, 125).

CL of (+)-M1 was 2172 mL/min after T/A and 2299 mL/min after T alone, and similar for (-)-M1 (1983 mL/min) after T/A and T alone (2059 mL/min). Time to peak plasma concentration for both (+)-M1 and (-)-M1 was ~3 h; and the mean elimination half-life of both (+)-M1 and (-)-M1 was ~6.5 h for T given alone or in combination with APAP.

For APAP, the ratios of means (90% CIs) for  $C_{max}$ ,  $AUC_{(0-*)}$  and  $AUC_{(0-inf)}$  were 92.4 (84.9, 100.6), 98.8 (93.9, 103.9) and 98.7 (93.9, 103.7) respectively; for T/A combination tablets compared to APAP tablets. The treatments were therefore BE for APAP as the 90% CIs were all contained within the interval (80, 125).

CL of APAP was the same after T/A (337 mL/min) and APAP alone (332 mL/min). The time for the the plasma concentration of APAP to peak was ~1 h; and mean elimination half-life was ~3 h; for APAP given alone or in combination with T.

Thus, the PKs of T and APAP were not affected in any significant way when the drugs were given in combination.

#### *T-P-001*

Thirty-two subjects enrolled, 5 of these discontinued from treatment and 27 completed the study: 50% male, 50% female; 53% Black, 22% White, 25% Other; the mean age 29.9 years (range 19-40 years.)

PK parameters for (+)-T, (-)-T, (+)-M1, (-)-M1 and APAP are summarised below.

For (+)-T, the ratios of means (90% CIs) for  $C_{max1}$ ,  $C_{max2}$ ,  $C_{min1}$ ,  $C_{min2}$  and  $AUC_{(0-12)}$  were 86.6 (78.2, 95.9), 85.3 (75.4, 96.4), 78.7 (69.0, 89.8), 78.5 (68.7, 89.8) and 84.3 (77.7, 91.4) respectively; and for (-)-T the ratios of means (90% CIs) were 89.8 (81.3, 99.2), 89.1 (79.1, 100.3), 81.5 (71.4, 93.0), 82.2 (72.7, 92.8) and 87.7 (81.2, 94.7) respectively; for T/A compared to T. Thus, for (+)-T the peak plasma values and  $AUC_{(0-12)}$  were 14-16% lower and trough plasma values were 22% lower; and for (-)-T, the peak plasma values and  $AUC_{(0-12)}$  were 11-13% lower and trough plasma values were 18-19% lower when T was given with APAP compared to when it was given alone. BE was demonstrated for (-)-T for  $C_{max1}$  and  $AUC_{(0-12)}$  as the 90% CIs were contained within the interval (80, 125); but 90% CIs for  $C_{max2}$ ,  $C_{min1}$  and  $C_{min2}$ , for (-)-T and all (+)-T BA parameters were outside the interval (80, 125).

CL of (+)-T was 660 mL/min after T/A and 555 mL/min after T alone, while CL of (-)-T was 826 mL/min after T/A, and 718 mL/min after T alone. Time to peak plasma concentrations for both (+)-T and (-)-T after the 7:00 am dose was longer for the combination (2.7 h) than for T alone (2.4 h). However, after the 1:00 pm dose it was shorter for the combination (1.6 h) than for T alone (2.1-2.3 h). Elimination half-lives for both (+)-T and (-)-T were longer with the combination (8.9 h and 8.6 h respectively) than with T alone (8.0 h and 7.0 h respectively).

For (+)-M1, the ratios of means (90% CIs) for  $C_{max1}$ ,  $C_{max2}$ ,  $C_{min1}$ ,  $C_{min2}$  and  $AUC_{(0-12)}$  were 85.8 (72.7, 101.3), 85.5 (71.4, 102.5), 80.9 (67.7, 96.7), 86.2 (75.2, 98.8) and 86.4 (75.1, 99.5) respectively; and for (-)-M1, the ratios of means (90% CIs) were 73.6 (62.5, 86.7), 76.9 (66.4, 90.0), 70.0 (57.5, 85.3), 70.1 (58.9, 83.5) and 74.5 (64.9, 85.6) respectively; for T/A compared to T. Thus, for (+)-M1 the peak plasma values and  $AUC_{(0-12)}$  were 14-15% lower and trough plasma values were 14-20% lower; and for (-)-M1 the peak plasma values and  $AUC_{(0-12)}$  were 24-27% lower and the trough plasma values were 30% lower when T was given with APAP compared to when it was given alone. BE was not demonstrated as the 90% CIs of all the BA parameters for (+)- and (-)-M1 were outside the interval (80, 125).



CL of (+)-M1 was 3289 mL/min after T/A, and 2837 mL/min after T alone, while CL of (-)-M1 was 3141 mL/min after T/A and 2371 mL/min after T alone.  $T_{max}$  values for both (+)-M1 and (-)-M1 after the 7:00 am dose were comparable for the combination (3.1-3.3 h) and for T alone (2.9-3.0 h). However, after the 1:00 pm dose they were shorter for the combination (1.2-1.5 h) than for T alone (2.5 h). Elimination half-lives for both (+)-M1 and (-)-M1 at steady state were longer with the combination (11.6 h and 9.1 h respectively) than with T alone (9.2 h and 7.5 h respectively).

For APAP, the ratios of means (90% CIs) for  $C_{max1}$ ,  $C_{max2}$ ,  $C_{min1}$ ,  $C_{min2}$  and  $AUC_{(0-12)}$  were 102.3 (94.1, 111.3), 104.8 (98.6, 111.4), 103.8 (89.5, 120.4), 111.8 (99.0, 126.2) and 101.5 (97.3, 105.9) respectively for T/A compared to APAP. Thus, the peak plasma values and  $AUC_{(0-12)}$  were 1-5% higher and trough plasma values were only 3-12% higher when APAP was given with T compared to when it was given alone. BE was demonstrated for  $C_{max1}$ ,  $C_{max2}$ ,  $C_{min1}$  and  $AUC_{(0-12)}$  as the 90% CIs were within the interval (80, 125). This was not the case for  $C_{min2}$ .

CL of APAP was unaffected by T (373 mL/min after T/A, 382 mL/min after APAP alone).  $T_{max}$  values for APAP were not significantly affected by combination with T after both the 7:00 am dose (2.1 h for combination, 1.7 h for APAP alone) and the 1:00 pm dose (1.4 h for combination, 1.2 h for APAP alone). The elimination half-life of APAP at steady state was unaffected by combination with T (2.4-2.5 h).

Hence, although differences were seen for some BA parameters (for (+)-T, (-)-T, (+)-M1 and (-)-M1) the differences were not considered clinically significant as the magnitudes of difference for (+)-T and (-)-T were only 9-16% for  $C_{max1}$ ,  $C_{max2}$  and  $AUC_{(0-12h)}$  and 19-21% for  $C_{min1}$  and  $C_{min2}$ . There were no clinically significant differences seen for APAP when given as a combination with T or when given alone at steady state.

#### ***Evaluator's overall comments on pharmacokinetic interactions***

No interaction studies were performed for the combination T/A tablet with concomitant medications.

As there were no significant effects on the PKs of T or A when administered as a combination in single or multiple doses and the PKs of the individual medications are well characterised, the sponsor considered that potential drug-drug interactions can be predicted from knowledge of the individual medications (sponsor's Clinical Overview). The evaluator agreed with this reasoning.

#### ***Evaluator's overall conclusions on pharmacokinetics***

The individual medications T and APAP are well known and their PKs are well characterised.

Since T/A can be classified as a "new fixed combination [that] contains known active ingredients that have not been used in combination before"<sup>37</sup>, the TGA guidelines for fixed combination medications deem that a full PK profile is not required. Instead, it is sufficient to evaluate the extent of PK effect of each component medication on the other, based on "previous knowledge or on experimental evidence" (p6). The FMI T/A tablet was used in the clinical studies so it was only necessary to demonstrate BE for the FMI effervescent tablet and the FCT.

The sponsor has fulfilled the TGA requirements for PK studies for the FCT through the provision of:

- a BA study of the FMI T/A tablet,
- two interaction studies of T and APAP using single and multiple dose T/A,
- previous knowledge of the PKs of the component medications T and APAP.

<sup>37</sup> Guideline on clinical development of fixed combination medicinal products, EMEA/CHMP/EWP/240/95 Rev. 1, p6

The sponsor has also provided a study of the effect of food on the PKs of T/A and has conducted two population PK studies investigating the use of T/A in special populations.

A single BE study of the FMI T/A effervescent tablet and the FMI T/A FCT used in the majority of the clinical studies was also provided.

**Conclusions regarding PKs of T/A FCT:**

- In TRAM-PHI-001 for T/A compared to dose normalised data of oral solutions of T and APAP from previous studies, rates of absorption of T and APAP were both slower but the BA of T and APAP were similar.
- In T-P-002 the single dose PKs of T were not significantly affected by APAP and the single dose PKs of APAP were not significantly affected by T.
- In T-P-001, the steady-state PKs of T were decreased by APAP but the decreases were not considered clinically relevant and the steady-state PKs of APAP were not significantly affected by T.
- In T-P-003 food had no clinically relevant effect on the BA of T and APAP when given as T/A.
- Since the PKs of T and APAP are not clinically affected by each other, the well characterised PKs of the individual medications can be used as a guide to PK behaviour of the combination medication.

**In special populations:**

- In DM98313, gender, race, body weight,  $CL_{CR}$ , smoking and CYP2D6 genotype had no clinically relevant effect on the PKs of T and APAP that would require a dose adjustment of the T/A combination tablet. Due to a narrow range of values for body weight and  $CL_{CR}$  (as might be expected with healthy, Phase I study subjects) these results cannot be extrapolated further.
- In DM98311, gender, race, age, concomitant oestrogen medication, body weight and  $CL_{CR}$  had no clinically relevant effect on the PKs of T and APAP that would require a dose adjustment of the T/A combination tablet.
- Although the population PK studies found no dose adjustment was required with age, and the results were consistent with data for T alone and APAP alone from previous studies, only 19 patients over the age of 75 years were included in the studies. The sponsor therefore considers that whilst no dose adjustment is required for T/A in patients up to the age of 75 years, for patients >75 years the minimum (min) dosing interval should be at least 6 h.

Comment: The statement that ‘the minimum dosing interval should be at least 6 h’ for patients over 75 years is obsolete since it states in the draft PI under *Dosage and Administration* that “the dosing interval should not be less than six hs”. This statement may refer to the fact that in some of the clinical studies the dosing interval was 4-6 h; it may refer to the fact that the PI for T suggests a dosing interval of 4-6 h; or it may be that the sponsor intended to recommend a longer min dosing interval. This needs to be clarified.

- Although  $CL_{CR}$  had a significant effect on the clearance of M1, it had no effect on the CL of T or APA and had no clinically relevant effect overall, no patients with severe renal impairment were included in either study. A previous study of T alone found that impaired renal function was associated with a decreased rate and extent of excretion of T and M1; and previous studies of APAP alone found that the PKs of APAP were unaffected in moderate renal impairment and there was no evidence of accumulation of glutathione derived metabolites of APAP. The sponsor therefore recommended that an estimate of  $CL_{CR}$  be obtained in all patients with renal impairment: for moderate renal impairment ( $CL_{CR}<30$



mL/min) the dosing interval for T/A should be increased to 'not greater than x2 tablets q12h<sup>38</sup>'; and for severe renal impairment ( $CL_{CR} < 10$  mL/min) T/A is not recommended at all.

- Neither study included patients with hepatic impairment. A previous study of T alone found that the metabolism of T and M1 decreased in patients with advanced cirrhosis of the liver; and previous studies of APAP in patients with varying levels of hepatic impairment found no effect on the PKs of APAP. T/A is therefore not recommended in patients with severe hepatic insufficiency; and in moderate hepatic insufficiency, prolonging the dosage interval should be considered.

#### ***Conclusions regarding PKs of T/A effervescent tablet:***

- In HPZALDEFF/01 the effervescent T/A tablet and the film-coated T/A tablet were bioequivalent.

### **Pharmacodynamics**

There were no pharmacodynamic studies of T/A for evaluation.

### **Efficacy**

#### **Introduction**

Three randomised, double blind (DB), single dose studies in patients with moderate to severe pain after oral surgery (T-A-010, T-A-012, T-A-013) were pivotal in demonstrating the analgesic efficacy of T/A compared to its components.

A dose ranging trial (T-A-007) and two pilot studies (CA, CB), together with knowledge of the combination in animal studies, clinical knowledge of the individual components and the known lack of PK interaction between the components, determined the final dose ratio used in the T/A combination tablet, with the usual dose of 2 tablets in dental pain trials allowing for the flexibility of taking a single tablet in chronic pain situations where severity and need for analgesia may vary. The dosing interval of q4h-q6h used in the clinical trials was based on recommended dosing for the individual components.

Other efficacy studies presented in the 2001 application were 4 single dose studies in patients with acute pain (T-A-002, T-A-003, T-A-004, T-A-005) which helped the sponsor to determine the most appropriate sample size and pain model for the pivotal studies (another single-dose study, T-A-011, was terminated early due to data integrity problems and its efficacy data was not analysed); and 4 multiple dose studies in patients with chronic pain (T-A-008, T-A-009, T-A-006, T-A-015), 2 of which provided long-term data (T-A-006-OL, T-A-015). Additional efficacy data up until 2010 came from further studies including 6 multiple dose studies in patients with chronic pain (C-104, C-112, C-113, C-114, PRI/TRP-CAN-1, SP-ZAL-III-02); and 2 single dose (C-128, C-241) and 5 multiple dose (C-105, C-115, C-216, GRTF-ZAL1, ZAL-06) studies in patients with acute pain. All the efficacy studies are summarised in Table 9 below.

---

<sup>38</sup> q12h=every 12 h.

**Table 9. Summary of clinical efficacy studies. Table continued across 15 pages.**

Study ID	No. of centres Locations	Design	Study posology	Study objective	Subjects by arm: Entered (Completed)	Duration	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
<b>Main (pivotal) studies</b>									
T-A-010	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>• T/A 75/650 mg, or</li> <li>• T 75 mg, or</li> <li>• APAP 650 mg, or</li> <li>• IBU 400 mg, or</li> <li>• PBO</li> </ul>	To evaluate efficacy and safety of T/A 75/650 mg in subjects with pain from oral surgical procedure, and to demonstrate contribution of each component to analgesic effect	T/A 75/650: 80 (66 [82.5%]) T 75: 80 (50 [62.5%]) APAP 650: 80 (67 [83.8%]) IBU 400: 80 (60 [75.0%]) PBO: 80 (44 [55.0%])	Single dose	151 (38%) / 249 (62%) (21.5y [16-46y])	<ul style="list-style-type: none"> <li>• ≥16y</li> <li>• male or female</li> <li>• moderate or severe pain (VAS score ≥5) after oral surgical procedure (extraction of 2 ipsilateral, or &gt;2, impacted third molars requiring bone removal)</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR; 0-4h, 4-8h, 0-8h</li> <li>• SPID; 0-4h, 4-8h, 0-8h</li> <li>• SPRID; 0-4h, 4-8h, 0-8h</li> </ul>
T-A-012	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>• T/A 75/650 mg, or</li> <li>• T 75 mg, or</li> <li>• APAP 650 mg, or</li> </ul>	To evaluate efficacy and safety of T/A 75/650 mg in subjects with pain from oral surgical procedure and to demonstrate contribution of each component to analgesic effect	T/A 75/650: 80 (70 [87.5%]) T 75: 80 (53 [66.3%]) APAP 650: 80 (74 [92.5%]) IBU 400: 80 (61 [76.3%]) PBO: 80 (39 [48.8%])	Single dose	179 (45%) / 221 (55%) (21.7y [16-46y])	<ul style="list-style-type: none"> <li>• ≥16y</li> <li>• male or female</li> <li>• moderate or severe pain (VAS score ≥5) after oral surgical procedure (extraction of 2 ipsilateral, or &gt;2, impacted third molars requiring bone removal)</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR; 0-4h, 4-8h, 0-8h</li> <li>• SPID; 0-4h, 4-8h, 0-8h</li> <li>• SPRID; 0-4h, 4-8h, 0-8h</li> </ul>

Study ID	No. of centres Locations	Design	Study posology	Study objective	Subjects by arm: Entered (Completed)	Duration	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
			<ul style="list-style-type: none"> <li>• IBU 400 mg, or</li> <li>• PBO</li> </ul>					removal)	
T-A-013	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>• T/A 75/650 mg, or</li> <li>• T 75 mg, or</li> <li>• APAP 650 mg, or</li> <li>• IBU 400 mg, or</li> <li>• PBO</li> </ul>	To evaluate efficacy and safety of T/A 75/650 mg in subjects with pain from oral surgical procedure, and to demonstrate contribution of each component to analgesic effect	T/A 75/650: 80 (75 [93.8%]) T 75: 80 (54 [67.5%]) APAP 650: 80 (70 [87.5%]) IBU 400: 80 (74 [92.5%]) PBO: 80 (35 [43.8%])	Single dose	147 (37%) / 253 (63%) (21.1y [16-46y])	<ul style="list-style-type: none"> <li>• ≥16y</li> <li>• male or female</li> <li>• moderate or severe pain (NRS score ≥5) after oral surgical procedure (extraction of 2 ipsilateral, or &gt;2, impacted third molars requiring bone removal)</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR; 0-4h, 4-8h, 0-8h</li> <li>• SPID; 0-4h, 4-8h, 0-8h</li> <li>• NSPID; 0-4h, 4-8h, 0-8h</li> <li>• SPRID; 0-4h, 4-8h, 0-8h</li> <li>• NSPRID; 0-4h, 4-8h, 0-8h</li> </ul>
<b>Other Studies</b>									
T-A-007	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, Phase IIb	<ul style="list-style-type: none"> <li>• T 25 mg, or</li> <li>• T 50 mg, or</li> <li>• APAP 650 mg,</li> </ul>	To evaluate and compare analgesic efficacy and safety of single doses of APAP 650 mg, T/A	T/A 50/650: 50 (50 [100%]) T/A 25/650: 50 (50 [100%]) APAP 650: 50 (49 [98.0%])	Single dose	125 (42%) / 175 (58%) (22.3y [16-62y])	<ul style="list-style-type: none"> <li>• ≥16y</li> <li>• male or female</li> <li>• moderate or severe pain after oral surgical procedure (extraction of ≥1</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR; 1-4h, 5-8h, 1-8h</li> <li>• SPID; 1-4h, 5-8h, 1-8h</li> <li>• SPRID; 1-4h, 5-8h, 1-8h</li> </ul>

Study ID	No. of centres Locations	Design	Study posology	Study objective	Subjects by arm: Entered (Completed)	Duration	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
		study	<ul style="list-style-type: none"> <li>or</li> <li>· T/A 25/650 mg, or</li> <li>· T/A 50/650 mg, or</li> <li>· PBO</li> </ul>	25/650 mg, T/A 50/650 mg, T 25 mg, T 50 mg, and PBO, over 8h when given to subjects with at least moderate post-operative dental pain from mandibular third molar extraction	T 50: 50 (48 [96.0%]) T 25: 50 (50 [100%]) PBO: 50 (50 [100%])			impacted mandibular third molar requiring bone removal)	
CA	1 centre (1 in USA)	R, DB, OP, Phase II study	<ul style="list-style-type: none"> <li>· T/A 100/500 mg, or</li> <li>· T 100 mg, or</li> <li>· APAP 500 mg, or</li> <li>· PBO</li> </ul>	To determine efficacy and safety of T and APAP, alone or in combination, and PBO in subjects with pain following oral surgery	T/A 100/500: 53 (48 [90.6%]) T 100: 54 (49 [90.7%]) APAP 500: 55 (55 [100%]) PBO: 53 (50 [94.3%])	Single dose	102 (55.5%) / 113 (44.5%) (24.0-25.2y [16-49y])	<ul style="list-style-type: none"> <li>· 16-65y</li> <li>· male or female</li> <li>· moderate or severe pain after extraction of ≥1 impacted third molar</li> </ul>	<ul style="list-style-type: none"> <li>· TOTPAR; 0-4h, 4-8h, 0-8h</li> <li>· SPID; 0-4h, 4-8h, 0-8h</li> <li>· SPRID; 0-4h, 4-8h, 0-8h</li> </ul>
CB	1 centre (1 in Venezuela)	DB, parallel-group, Phase II study	<ul style="list-style-type: none"> <li>· T 25 mg + APAP 500 mg, or</li> <li>· T 25</li> </ul>	To evaluate analgesic efficacy of T 25 mg, APAP 500 mg, T 25 mg + APAP 500 mg, and PBO, in	T 25 + APAP 500: 40 (31 [77.5%]) T 25: 40 (28 [70.0%]) APAP 500: 40 (27 [67.5%])	Single dose	0 (0%) / 160 (100%) (26y [18-39y])	<ul style="list-style-type: none"> <li>· 18-55y</li> <li>· female</li> <li>· moderate or severe pain from Caesarian section</li> </ul>	<ul style="list-style-type: none"> <li>· TOTPAR; 0-3h, 3-6h, 0-6h</li> <li>· SPID; 0-3h, 3-6h, 0-6h</li> <li>· SPRID; 0-3h, 3-6h, 0-</li> </ul>

Study ID	No. of centres Locations	Design	Study posology	Study objective	Subjects by arm: Entered (Completed)	Duration	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
			mg, or <ul style="list-style-type: none"> <li>APAP 500 mg, or</li> <li>PBO</li> </ul>	subjects with pain following Caesarian section	PBO: 40 (27 [67.5%])			<ul style="list-style-type: none"> <li>willing not to breast feed for 48h after drug administration</li> </ul>	<ul style="list-style-type: none"> <li>6h</li> <li>PEAKPID</li> <li>time to remedication</li> </ul>
T-A-002	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>T/A 75/650 mg, or</li> <li>T 75 mg, or</li> <li>APAP 650 mg, or</li> <li>IBU 400 mg, or</li> <li>PBO</li> </ul>	To evaluate efficacy and safety of T/A 75/650 mg in subjects with pain from oral surgical procedure and to demonstrate contribution of each component to analgesic effect of combination	T/A 75/650: 50 (50 [100%]) T 75: 50 (50 [100%]) APAP 650: 50 (50 [100%]) IBU 400: 50 (50 [100%]) PBO: 50 (49 [98.0%])	Single dose	111 (44%) / 139 (56%) (23.9y [16-48y])	<ul style="list-style-type: none"> <li>≥16y</li> <li>male or female</li> <li>moderate or severe pain after oral surgical procedure (extraction of ≥1 impacted mandibular third molar requiring bone removal)</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR; 1-4h, 5-8h, 1-8h</li> <li>SPID; 1-4h, 5-8h, 1-8h</li> <li>SPRID; 1-4h, 5-8h, 1-8h</li> </ul>
T-A-003	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>T/A 75/650 mg, or</li> <li>T 75 mg, or</li> <li>APAP 650 mg, or</li> </ul>	To evaluate efficacy and safety of T/A 75/650 mg in subjects with pain from oral surgical procedure and to demonstrate contribution of	T/A 75/650: 50 (49 [98.0%]) T 75: 50 (49 [98.0%]) APAP 650: 50 (50 [100%]) IBU 400: 50 (49 [98.0%]) PBO: 50 (49 [98.0%])	Single dose	130 (52%) / 120 (48%) (18.8y [16-33y])	<ul style="list-style-type: none"> <li>≥16y</li> <li>male or female</li> <li>moderate or severe pain after oral surgical procedure (extraction of ≥1 impacted third molar)</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR; 1-4h, 5-8h, 1-8h</li> <li>SPID; 1-4h, 5-8h, 1-8h</li> <li>SPRID; 1-4h, 5-8h, 1-8h</li> </ul>

Study ID	No. of centres Locations	Design	Study posology	Study objective	Subjects by arm: Entered (Completed)	Duration	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
			<ul style="list-style-type: none"> <li>IBU 400 mg, or</li> <li>PBO</li> </ul>	each component to analgesic effect of combination	[98.0%]				
T-A-004	2 centres (2 in Puerto Rico)	R, DB, parallel-group, PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>T/A 112.5/975 mg, or</li> <li>T 112.5 mg, or</li> <li>APAP 975 mg, or</li> <li>PBO</li> </ul>	To evaluate efficacy and safety of T/A 112.5/975 mg in subjects with pain from gynecologic surgical procedure and to demonstrate contribution of each component to analgesic effect of combination	T/A 112.5/975: 51 (51 [100%]) T 112.5: 49 (48 [98.0%]) APAP 975: 50 (46 [92.0%]) PBO: 50 (48 [96.0%])	Single dose	0 (0%) / 200 (100%) (26.5y [18-49y])	<ul style="list-style-type: none"> <li>≥18y</li> <li>female (not pregnant or nursing within 48h after medication)</li> <li>moderate or severe pain after major abdominal gynecologic surgical procedure other than laparoscopy</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR; 1-4h, 5-8h, 1-8h</li> <li>SPID; 1-4h, 5-8h, 1-8h</li> <li>SPRID; 1-4h, 5-8h, 1-8h</li> </ul>
T-A-005	1 centre (1 in USA)	R, DB, parallel-group, PC, factorial, Phase III study	<ul style="list-style-type: none"> <li>T/A 112.5/975 mg, or</li> <li>T 112.5 mg, or</li> <li>APAP 975 mg, or</li> <li>PBO</li> </ul>	To evaluate efficacy and safety of T/A 112.5/975 mg in subjects with pain from orthopedic surgical procedure and to demonstrate contribution of each component to analgesic effect	T/A 112.5/975: 50 (50 [100%]) T 112.5: 50 (48 [96.0%]) APAP 975: 50 (48 [96.0%]) PBO: 50 (47 [94.0%])	Single dose	116 (58%) / 84 (42%) (45.4y [20-83y])	<ul style="list-style-type: none"> <li>≥18y</li> <li>male or female</li> <li>moderate or severe pain after orthopedic surgical procedure</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR; 1-4h, 5-8h, 1-8h</li> <li>SPID; 1-4h, 5-8h, 1-8h</li> <li>SPRID; 1-4h, 5-8h, 1-8h</li> </ul>

Study ID	No. of centres Locations	Design	Study posology	Study objective	Subjects by arm: Entered (Completed)	Duration	Gender: M/F (Age)	Diagnosis & main inclusion criteria	Primary endpoint
T-A-011	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, Factorial Phase III study	<ul style="list-style-type: none"> <li>• T/A 75/650 mg, or</li> <li>• T 75 mg, or</li> <li>• APAP 650 mg, or</li> <li>• IBU 400 mg, or</li> <li>• PBO</li> </ul>	To evaluate safety and efficacy of T/A 75/650 mg in subjects with pain from oral surgical procedure and to demonstrate contribution of each component to analgesic effect of combination	T/A 75/650: 31 (26 [83.9%]) T 75: 32 (19 [59.4%]) APAP 650: 32 (26 [81.3%]) IBU 400: 31 (23 [74.2%]) PBO: 30 (19 [63.3%])	Single dose	56 (36%) / 100 (64%) (23.6y [16-53y])	<ul style="list-style-type: none"> <li>• ≥16y</li> <li>• male or female</li> <li>• moderate or severe pain after oral surgical procedure (extraction of 2 ipsilateral, or ≥2, impacted third molars requiring bone removal)</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR</li> <li>• SPID</li> <li>• PID</li> <li>• PAR</li> <li>• overall assessment of medication</li> <li>• rate of re-medication</li> <li>• time to re-medication</li> </ul>
T-A-008	54 centres (54 in USA)	Multi-centre, R, DB, parallel-group, AC, Phase III study	<p>OL run-in phase (1wk):</p> <ul style="list-style-type: none"> <li>• T/A 37.5/325 mg prn, min x1 qid, max 8/day</li> </ul> <p>DB phase (8wks):</p> <ul style="list-style-type: none"> <li>• T/A 37.5/325 mg x1-2 q4h-q6h, max</li> </ul>	To compare relative potency of T/A 37.5/325 mg to IBU 200 mg in subjects with osteoarthritis of hip or knee and to provide information on average dosing requirements of such treatment	T/A: 119 (91 [76.5%]) IBU: 125 (106 [84.8%])	11wks	99 (41%) / 145 (59%) (63.2y [35-89y])	<ul style="list-style-type: none"> <li>• ≥45y</li> <li>• male or female</li> <li>• moderate to severe pain from osteoarthritis of hip or knee documented on x-ray within two years</li> <li>• taking stable daily dose of oral pain medication</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR; 1-6h</li> <li>• SPID; 1-6h</li> <li>• SPRID; 1-6h</li> </ul>

			<p>10/day (8/day if &gt;75y) (if analgesia inadequate, extra PBO capsule prn, max 6/day), or</p> <ul style="list-style-type: none"> <li>IBU 200 mg x1-2 q4h-q6h, max 10/day (8/day if &gt;75y) (if analgesia inadequate, extra IBU 200 mg capsule prn, max 6/day)</li> </ul>						
T-A-009	28 centres (28 in USA)	Multi-centre, R, DB, parallel-group, AC, Phase III study	<p>OL run-in phase (1wk):</p> <ul style="list-style-type: none"> <li>T/A 37.5/325 mg prn, max 8/day</li> </ul> <p>DB phase (8wks):</p> <ul style="list-style-type: none"> <li>T/A 37.5/325 mg x1-2 q4h-</li> </ul>	To compare relative potency of T/A 37.5/325 mg to IBU 200 mg in subjects with low back pain of non-malignant origin and to provide information on average dosing requirements of	T/A: 151 (115 [76.2%]) IBU: 151 (114 [75.5%])	11wks	153 (51%) / 149 (49%) (54.9y [20-86y])	<ul style="list-style-type: none"> <li>≥18y</li> <li>male or female</li> <li>history of low back pain from conditions such as spondylolisthesis, osteoarthritis, spinal stenosis, spondylosis, degenerative disc disease, etc, for</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR; 1-6h</li> <li>SPID; 1-6h</li> <li>SPRID; 1-6h</li> </ul>



			<p>q6h, min x1 qid, max 10/day (8/day if &gt;75y) (if analgesia inadequate, extra PBO capsule prn, max 6/day), or</p> <ul style="list-style-type: none"> <li>IBU 200 mg x1-2 q4h-q6h, min x1 qid, max 10/day (8/day if &gt;75y) (if analgesia inadequate, extra IBU 200 mg capsule prn, max 6/day)</li> </ul>	such treatment				<p>≥6months</p> <ul style="list-style-type: none"> <li>moderate or severe pain prior to taking first dose of study medication</li> <li>taking stable daily dose of oral pain medication</li> </ul>	
T-A-006	58 centres (58 in USA)	Multi-centre, R, DB, parallel-group, AC, Phase III study	<p>DB phase (4wks):</p> <ul style="list-style-type: none"> <li>T/A 37.5/325 mg x1-2 q4h-q6h, max 10/day (max 8/day if &gt;75y), or</li> </ul>	To compare relative potency and safety of T/A 37.5/325 mg to A/COD 300/30 mg in subjects with chronic pain of benign origin	T/A: 309 (248 [80.3%]) A/COD: 153 (121 [79.1%])	5wks	176 (38%) / 286 (62%) (57.6y [22-91y])	<ul style="list-style-type: none"> <li>≥18y</li> <li>male or female</li> <li>history of chronic pain from osteoarthritis of any joint or joints, or low back pain from a non-malignant condition,</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR; 1-6h</li> <li>SPID; 1-6h</li> <li>SPRID; 1-6h</li> </ul>

			<ul style="list-style-type: none"> <li>• A/COD 300/30 mg x1-2 q4h-q6h, max 10/day (max 8/day if &gt;75y)</li> </ul>					for ≥6 months	
T-A-006-OL	58 centres (58 in USA)	Multi-centre, R, DB, parallel-group, AC, Phase III study: OL extension phase	<p>OL phase (24months):</p> <ul style="list-style-type: none"> <li>• T/A 37.5/325 mg x1-3 q4h-q6h, prn, max 10/day (8/day if &gt;75y) (if analgesia inadequate, extra IBU 400 mg q4h-q6h prn, max 6/day)</li> </ul>	To compare relative potency and safety of T/A 37.5/325 mg to A/COD 300/30 mg in subjects with chronic pain of benign origin	T/A: 403 (154 [38%])	24months	154 (38%) / 249 (62%) (57.5y [22-91y])	<ul style="list-style-type: none"> <li>• ≥18y</li> <li>• male or female</li> <li>• history of chronic pain from osteoarthritis of any joint or joints, or low back pain from a non-malignant condition, for ≥6 months</li> </ul>	<ul style="list-style-type: none"> <li>• predose pain</li> <li>• max pain relief during 6h observation period on Day 1 of each 7-day diary</li> <li>• subject's assessment after each 6h evaluation period</li> <li>• subject's and investigator's overall assessment at end of OL period</li> <li>• daily dosage of study drug</li> <li>• proportion of subjects using supplemental analgesic medication</li> </ul>
T-A-015	47 centres (47 in USA)	Multi-centre, OL, Phase III study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg x1-3 q4h-q6h, prn, max 10/day</li> </ul>	To evaluate safety and efficacy of T/A 37.5/325 mg in subjects with chronic pain of	T/A: 369 (191 [51.8%])	6months	133 (36%) / 236 (64%) (58.4y [20-90y])	<ul style="list-style-type: none"> <li>• ≥18y</li> <li>• male or female</li> <li>• history of chronic pain from</li> </ul>	<ul style="list-style-type: none"> <li>• average daily dose of study drug and supplemental drug by month</li> <li>• subject's assessment of</li> </ul>

			(8/day if >75y) (if analgesia inadequate, extra Motrin IB, prn, max 6/day)	benign origin				osteoarthritis of any joint or joints, or low back pain from a non-malignant condition, for ≥6 months	medication per visit <ul style="list-style-type: none"> <li>subject's and investigator's overall assessment of study drug at EOS</li> </ul>
C-104	35 centres (35 in USA)	Multi-centre, OP, R, DB, parallel-group, PC, Phase III study	<ul style="list-style-type: none"> <li>T/A 37.5/325 mg: titrate over 10days to x1 qid or max tolerated dose; then: x1-2 up to qid, min 2/day, max 8/day, up to Day 91, or</li> <li>PBO: same schedule</li> </ul>	To demonstrate analgesic efficacy and safety of T/A 37.5/325 mg in symptomatic treatment of pain of osteoarthritis	T/A: 162 (79 [48.8%]) PBO: 159 (79 [49.7%])	16wks	114 (35.8%) / 204 (64.2%) (61.3y [35-87y])	<ul style="list-style-type: none"> <li>40-75y</li> <li>male or female</li> <li>symptomatic osteoarthritis of knee (target joint) ≥1y as evidenced by pain and osteophytes confirmed on x-ray within last year</li> <li>taking stable daily dose of NSAID ≥3months</li> <li>PVA score &lt;80mm at Screening prior to entering medication washout phase</li> <li>PVA score &gt;40mm (at least moderate pain) and ≥20mm greater than initial screening PVA score at end of washout phase</li> </ul>	<ul style="list-style-type: none"> <li>comparison of PVA scores at Final Visit between two treatment groups</li> </ul>
C-112	29 centres (29 in USA)	Multi-centre,	<ul style="list-style-type: none"> <li>T/A</li> </ul>	To evaluate	T/A: 162 (91 [56.2%])	16wks	117 (36.8%) / 201 (63.2%)	<ul style="list-style-type: none"> <li>25-75y</li> </ul>	<ul style="list-style-type: none"> <li>final PVA score</li> </ul>

		OP, R, DB, parallel-group, PC, Phase III study	37.5/325 mg: titrate over 10days to x1 qid or max tolerated dose; then: x1-2 up to qid, min 2/day, max 8/day, up to Day 91, or  • PBO: same schedule	analgesic efficacy of T/A 37.5/325 mg in treatment of chronic lower back pain	PBO: 160 (74 [46.3%])		(53.9y [22-75y])	<ul style="list-style-type: none"> <li>• male or female</li> <li>• ambulatory</li> <li>• had chronic lower back pain, with or without pain radiation, severe enough to have required daily medication for ≥3months prior to Screening</li> <li>• completed Screening/wash-out procedures and had PVA score ≥40mm at end of wash out phase</li> </ul>	
C-113	27 centres (27 in USA)	Multi-centre, OP, R, DB, parallel-group, PC, Phase III study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg: titrate over 10days to x1 qid or max tolerated dose; then: x1-2 up to qid, min 2/day, max 8/day, up to Day 91, or</li> <li>• PBO: same schedule</li> </ul>	To evaluate analgesic efficacy of T/A 37.5/325 mg in treatment of pain of fibromyalgia	T/A: 158 (81 [51.3%]) PBO: 157 (59 [37.6%])	16wks	19 (6.1%) / 294 (93.9%) (49.7y [19-75y])	<ul style="list-style-type: none"> <li>• 18-75y</li> <li>• male or female</li> <li>• met American College of Rheumatology 1990 Criteria for Classification of Fibromyalgia (had widespread pain [pain in three quadrants and in axial skeleton] ≥3months; had pain on digital palpation in ≥11/18 tender-point</li> </ul>	<ul style="list-style-type: none"> <li>• time to discontinuation due to lack of efficacy</li> </ul>

								sites) <ul style="list-style-type: none"> <li>• completed Screening/wash-out procedures and had PVA score <math>\geq 40</math>mm at end of wash out phase</li> </ul>	
C-114	28 centres (28 in USA)	Multi-centre, OP, R, DB, parallel-group, PC, Phase III study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg: titrate over 10 days to x1 qid or max tolerated dose; then: x1-2 up to qid, min 2/day, max 8/day, up to Day 91, or</li> <li>• PBO: same schedule</li> </ul>	To demonstrate analgesic efficacy and safety of T/A 37.5/325 mg in treatment of pain of osteoarthritis in subjects receiving a iCOX2	T/A: 153 (112 [73.2%]) PBO: 154 (115 [74.7%])	16wks	97 (31.7%) / 209 (68.3%) (61.0y [35-80y])	<ul style="list-style-type: none"> <li>• 40-75y</li> <li>• male or female</li> <li>• had symptomatic osteoarthritis of knee or hip (target joint) <math>\geq 1</math>y as evidenced by pain and osteophytes confirmed by x-ray within last two years</li> <li>• taking stable daily dose of iCOX2 [<math>\geq 200</math> mg/day celecoxib, or <math>\geq 25</math> mg/day rofecoxib] <math>\geq 2</math>wks prior to study (if unable to tolerate 25 mg/day rofecoxib, a subject could enter study if taking 12.5 mg/day rofecoxib <math>\geq 5</math>days prior to Day 1 of study)</li> <li>• completed Screening procedures and had</li> </ul>	<ul style="list-style-type: none"> <li>• final PVA score</li> </ul>

								PVA score >50mm at Visit 2	
PRI / TRP-CAN-1	29 centres (29 in USA)	Multi-centre, OP, R, DB, parallel-group, PC, Phase IIIb study	<ul style="list-style-type: none"> <li>T/A 37.5/325 mg: titrate over 10days to x1 qid or max tolerated dose; then: x1-2 up to qid, min 3/day, max 8/day, up to Day 91, or</li> <li>PBO: same schedule</li> </ul>	To demonstrate analgesic efficacy and safety of T/A 37.5/325 mg in treatment of chronic lower back pain	-T/A: 167 (81 [48.5%]) -PBO: 171 (110 [64.3%])	16wks	126 (37.5%) / 210 (62.5%) (57.5y [25-82y])	<ul style="list-style-type: none"> <li>25-80y</li> <li>male or female</li> <li>ambulatory</li> <li>had chronic lower back pain, with or without pain radiation, which required daily medication ≥3months prior to Screening/wash-out phase</li> <li>had PVA score ≥40mm prior to randomization</li> </ul>	<ul style="list-style-type: none"> <li>PVA scale, administered at each visit, indicating amount of back pain experienced recently (within last 48h)</li> </ul>
SP-ZAL-III-02	17 centres (17 in Spain)	Multi-centre, R, DB, parallel-group, AC, Phase IV study	<ul style="list-style-type: none"> <li>T/A 37.5/325 mg: titrate over 6days to x2 tid; then: x2 tid-qid, for 84days, or</li> <li>A/COD 500/30 mg: same schedule</li> </ul>	To compare efficacy (in terms of functional recovery and QOL) and safety of T/A 37.5/325 mg to A/COD 500/30 mg as a Step 2 analgesic treatment of chronic pain associated with hip or knee	T/A: 117 (71 [60.7%]) A/COD: 119 (74 [62.2%])	94days	39 (16.5%) / 197 (83.5%) (63.5y [38-75y])	<ul style="list-style-type: none"> <li>18-75y</li> <li>male or female</li> <li>OP with symptomatic knee or hip joint osteoarthritis at functional class I-III (pain or disability ≥15days in prior month, and radiographic evidence [in last 1y] of osteophytes (and tightening of hip joint</li> </ul>	<ul style="list-style-type: none"> <li>change from randomization visit to EOS, of 'pain intensity at motion while walking over flat surface', measured on 100mm horizontal VAS</li> </ul>

				osteoarthritis				<ul style="list-style-type: none"> <li>space)</li> <li>· pain from osteoarthritis at target joint (main source of pain) ≥6months</li> <li>· taking appropriate daily mono-therapy with NSAID or iCOX2 ≥1month</li> <li>· ≥40mm in 100mm horizontal VAS on 'pain intensity at motion of target joint' despite NSAID or iCOX2 in last ≥15days, at Screening, and at randomization after washout period (first item of WOMAC questionnaire)</li> </ul>	
C-128	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, Phase III study	<ul style="list-style-type: none"> <li>· T/A 37.5/325 mg, or</li> <li>· T/A 75/650 mg, or</li> <li>· HYD/A 10/650 mg, or</li> </ul>	To demonstrate analgesic efficacy of T/A 37.5/325 mg for treatment of pain following oral surgical procedure	<p>T/A 37.5/325: 50 (47 [94.0%])</p> <p>T/A 75/650: 50 (45 [90.0%])</p> <p>HYD/A 10/650: 50 (46 [92.0%])</p> <p>PBO: 50 (47 [94.0%])</p>	Single dose	87 (43.5%) / 113 (56.5%) (21.4y [16-38y])	<ul style="list-style-type: none"> <li>· 16-75y</li> <li>· male or female</li> <li>· had surgical procedure involving extraction of 2 ipsilateral, or &gt;2, impacted third molars, with bone removal required for</li> </ul>	<ul style="list-style-type: none"> <li>· TOTPAR; 0-4h, 4-8h, 0-8h</li> <li>· SPID; 0-4h, 4-8h, 0-8h</li> <li>· SPRID; 0-4h, 4-8h, 0-8h</li> </ul>

			<ul style="list-style-type: none"> <li>• PBO</li> </ul>					<ul style="list-style-type: none"> <li>• <math>\geq 2</math> of the impacted third molars</li> <li>• completed Screening procedures, had at least moderate pain (PVA <math>\geq 50</math>mm) <math>\leq 5</math>h after oral surgical procedure, and was appropriate for pain management with an oral analgesic</li> </ul>	
C-241	1 centre (1 in USA)	R, DB, parallel-group, AC and PC, Phase IV study	<ul style="list-style-type: none"> <li>• T/A 75/650 mg, or</li> <li>• T 100 mg, or</li> <li>• PBO</li> </ul>	To establish that T/A 37.5/325 mg is superior to T 50 mg in analgesic efficacy for treatment of pain following oral surgery	T/A: 153 (144 [94.1%]) T:152 (148 [97.4%]) PBO:151 (149 [98.7%])	Single dose	166 (36.4%) / 290 (63.6%) (21.8y [18-49y])	<ul style="list-style-type: none"> <li>• 18-75y</li> <li>• male or female</li> <li>• had surgical procedure involving extraction of 2 ipsilateral, or <math>&gt;2</math>, impacted third molars, with bone removal required for <math>\geq 2</math> of the impacted third molars</li> <li>• completed Screening, had PVA <math>&gt;50</math>mm and at least moderate pain on Pain Intensity Scale <math>\leq 5</math>h after oral surgical procedure, and was appropriate for pain management with an oral analgesic</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR</li> <li>• SPID</li> <li>• SPRID</li> </ul>



C-105	30 centres (30 in USA)	Multi-centre, OP, R, DB, parallel- group, PC, Phase IIIb study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg: first dose: x1; then: x1-2 q4h-q6h, max 8/day, for 10days, or</li> <li>• T/A 37.5/325 mg: first dose: x2; then: x1-2 q4h-q6h, max 8/day, for 10days, or</li> <li>• PBO: first dose: x2  then: x1-2 q4h- q6h, max 8/day, for 10days</li> <li>• subjects were to continue stable daily dose of NSAID or iCOX2 throughout study</li> </ul>	To investigate analgesic efficacy and safety of T/A in treatment of painful flare of osteoarthritis	T/A 37.5/325: 102 (90 [88.2%]) T/A 75/650: 95 (79 [83.2%]) T/A combined: 197 (169 [85.8%]) PBO: 111 (105 [94.6%])	10days	87 (28.2%) / 221 (71.8%) (60.1y [37-80y])	<ul style="list-style-type: none"> <li>• 35-75y</li> <li>• male or female</li> <li>• symptomatic osteoarthritis of knee or hip (target joint) ≥1y as evidenced by pain and osteophyte formation, confirmed on x-ray taken within last year</li> <li>• taking stable daily dose of NSAID or iCOX2 ≥30days prior to study, and to remain on same dosage for duration of study</li> <li>• completed Screening procedures and experiencing a flare of osteoarthritis (significant increase in pain requiring supplemental analgesic medication and/or increase in NSAID or iCOX2 dosage) at target joint for 2-5days prior to study</li> <li>• PVA score ≥50mm and at least moderate</li> </ul>	<ul style="list-style-type: none"> <li>• average daily Pain Intensity Scores, Days 1-5</li> <li>• average daily Pain Relief Scores, Days 1-5</li> </ul>
-------	---------------------------	--	---	--	--	--------	--	---	---

								pain on four-point Pain Intensity Scale at study entry	
C-115	27 centres (27 in USA)	Multi-centre, R, DB, parallel-group, AC and PC, Phase IIIb study	<ul style="list-style-type: none"> <li>T/A 37.5/325 mg: first dose: x2; then: x1-2 qid, max 8/day, for 6±1days, or</li> <li>A/COD 300/30 mg: same schedule, or</li> <li>PBO: same schedule</li> </ul>	To demonstrate analgesic efficacy of T/A 37.5/325 mg for treatment of post-surgical pain	T/A: 98 (60 [61.2%]) A/COD: 109 (58 [53.2%]) PBO: 99 (46 [46.5%])	11days	215 (70.5%) / 90 (29.5%) (47.3y [18-79y])	<ul style="list-style-type: none"> <li>18-75y</li> <li>male or female</li> <li>completed Screening procedures</li> <li>had an orthopedic (any therapeutic arthroscopic procedure of knee or shoulder) or abdominal (repair of inguinal and/or ventral hernia) surgical procedure</li> <li>PVA &gt;40mm and Pain Intensity Scale rating of at least moderate, after surgery</li> <li>able to receive study medication on same day as surgical procedure performed</li> <li>able to receive study medication as first oral analgesic medication after surgical procedure</li> </ul>	<ul style="list-style-type: none"> <li>TOTPAR, SPID, and SPRID scores, first four hs on Day 1 after first dose of study medication</li> <li>primary comparison between T/A and PBO</li> </ul>

C-216	47 centres (47 in USA)	Multi-centre, IP/OP, R, DB, parallel-group, AC and PC, Phase IIIb study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg: first dose: x2; then: x1-2 up to qid prn, max 8/day, for 6days, or</li> <li>• HYD/A 7.5/650 mg: first dose: x1; then: x1 up to qid prn, max 4/day, for 6days, or</li> <li>• PBO: first dose: x2; then: x1-2 up to qid prn, max 8/day, for 6days</li> </ul>	To compare analgesic efficacy and safety of T/A vs HYD/A vs PBO for treatment of acute musculoskeletal pain from ankle sprain with partial ligament tear	T/A: 192 (166 [86.5%]) HYD/A: 204 (180 [88.2%]) PBO: 207 (177 [85.5%])	6days	315 (52.9%) / 281 (47.1%) (31.8y [18-81y])	<ul style="list-style-type: none"> <li>• 18-75y</li> <li>• male or female</li> <li>• experienced acute ankle sprain with partial ligament tear (pain on ambulation, swelling, ±ecchymosis) ≤48h prior to first study-related procedure</li> <li>• PVA ≥50mm and Pain Intensity Scale rating of at least moderate, at Baseline and immediately prior to first dose of study medication</li> </ul>	<ul style="list-style-type: none"> <li>• TOTPAR over 4h on Day 1 after first dose of study medication</li> </ul>
GRTF-ZAL1	33 centres (30 in France; 3 in Italy)	Multi-centre, OP, R, DB, parallel-group, Phase IIIb study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg: titrate over 5days to x2 qid; then: x2 qid for 4days, or</li> <li>• T 50 mg: same schedule</li> </ul>	To compare patient satisfaction of T/A vs T in treatment of sub-acute low back pain	-T/A: 59 (53 [89.8%]) -T: 60 (45 [75.0%])	10days	50 (42.7%) / 67 (57.3%) (55.2y [20-81y])	<ul style="list-style-type: none"> <li>• ≥18y</li> <li>• male or female</li> <li>• ambulatory</li> <li>• subacute low back pain, without radiculalgia</li> <li>• PVA score &gt;40mm at first visit</li> </ul>	<ul style="list-style-type: none"> <li>• 4-step patient satisfaction scale at Visit 2 and Final Visit</li> </ul>

ZAL-06	24 centres in 9 countries (7 in France; 2 in Belgium; 3 in Germany; 4 in Italy / Switzerland, 3 in The Netherlands/Sweden, 2 in Portugal, 3 in Spain)	Multi-centre, R, DB, double-dummy, parallel-group, Phase IIIb/IV study	<ul style="list-style-type: none"> <li>• T/A 37.5/325 mg: preop dose: x1; post-op dose in recovery: x1; then at home: x1 q6h (+ extra x1 30min after each dose prn), max 8/day, or</li> <li>• T 50 mg: same schedule</li> </ul>	Comparison of effectiveness and tolerability between T/A 37.5/325 mg and T 50 mg in post-operative pain	-T/A: 132 (128 [97.0%]) -T: 129 (128 [99.2%])	2days	99 (38.7%) / 157 (61.3%) (46.2-47.6y [18-77y])	<ul style="list-style-type: none"> <li>• 18-75y</li> <li>• male or female</li> <li>• pathologic condition involving bony or ligamentous structures of hand requiring surgical intervention</li> </ul>	<ul style="list-style-type: none"> <li>• treatment satisfaction at first post-operative day, assessed on 4-point verbal rating scale</li> </ul>
--------	---	--	---	---	--	-------	--	---	---

R = randomised; DB = double blind; PC = placebo controlled; AC = active controlled; OL = open-label; IP = inpatient; OP = outpatient; T=tramadol; APAP=acetaminophen; T/A=tramadol/acetaminophen; IBU=ibuprofen; PBO=placebo; A/COD=acetaminophen/codeine; HYD/A=hydrocodone bitartrate/acetaminophen; NSAID=non-steroidal anti-inflammatory drug; iCOX2=selective COX-2 inhibitor; vs=versus; wks=weeks; yrs=years.

## Dose response studies

T-A-007, CA, and CB examined various dose combinations of T/A in dental pain and Caesarean section pain models.

### ***A comparative study using a single dose of APAP, T/A, T alone, and placebo (PBO) in the treatment of post operative dental pain (T-A-007)***

This was a single centre, randomised, double blind (DB), parallel group, active and placebo (PBO) controlled, dose-ranging Phase IIb study in 300 male and female patients with moderate or severe pain from oral surgery, who randomly received one of six single-dose treatments (T/A 25/650 mg, T/A 50/650 mg, T 25 mg, T 50 mg, APAP 650 mg, PBO). Subjects could receive a supplemental analgesic during the study.

The objectives were to evaluate and compare analgesic efficacy and safety of the six single dose treatments over 8 h when in subjects with at least moderate post operative dental pain from mandibular third molar extraction.

Comment: Three summary efficacy variables are used in this and other studies, including the pivotal studies, to indicate overall analgesic effect and are derived from measures of:

- § pain relief (PAR; 0=none, 1=a little, 2=some, 3=a lot, 4=complete),
- § pain intensity difference (PID; difference between current pain intensity [0=none, 1=mild, 2=moderate, 3=severe] and baseline pain intensity [2=moderate or 3=severe]), and
- § the sum of the two (PRID [PAR+PID])

The summary efficacy variables are determined for a time interval and are:

- § total PAR (TOTPAR; the sum of hly PAR scores),
- § sum of PID (SPID; the sum of hly PID scores), and
- § sum of PRID (SPRID; sum of hly PAR and PID [PRID] scores).

These variables are commonly used as efficacy endpoints in pain studies and in the evaluator's judgement fulfil the recommendations for endpoints suggested in the TGA guidelines for medications to treat nociceptive pain<sup>39</sup>.

The three summary efficacy variables determined for the intervals 1-4 h, 5-8 h and 1-8 h, were TOTPAR, SPID, and SPRID.

Other efficacy variables were onset of analgesia (measured by stopwatch), duration of analgesia (time when half the subjects in a treatment group re-medicated), time to re medication, number (%) of subjects using supplemental analgesics at each time-point and subject's overall assessment of study medication.

Safety was assessed through adverse events (AEs) during the trial.

Three hundred patients enrolled (50 per treatment group); 1 subject discontinued from the APAP group and 2 subjects discontinued from the T 50 mg group due to vomiting within 30 minutes; 297 subjects completed the study. Baseline demographics and characteristics were generally comparable across the treatment groups: 42% male, 58% female; 72% White, 1% Black, 3% Asian, 24% Other; mean age was 22.3 years (range 16-62 years;) and baseline pain was moderate for 58% and severe for 42%.

---

<sup>39</sup> Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain, EMEA/CPMP/EWP/612/00, p7

Results for TOTPAR, SPID, and SPRID data and statistical comparisons for the interval 0-8 h; APAP 650 mg was statistically significantly superior to PBO for all variables ( $p < 0.001$ ) demonstrating sensitivity of the model.

The pain relief provided by T/A 50/650 mg was greater than each component for TOTPAR, SPID and SPRID, with the difference in scores statistically significant for all comparisons against T 50 ( $p \leq 0.047$ ) but only statistically significant against APAP for SPID ( $p = 0.05$ ). The pain relief provided by T/A 25/650 mg was statistically significantly greater than T 25 but similar to APAP for TOTPAR, SPID and SPRID. All active treatments were significantly better than PBO for all three variables. TOTPAR and SPRID scores for the T 50 mg treatment group were lower in subjects with severe baseline pain compared to subjects with moderate baseline pain; but all other comparisons by baseline intensity were unremarkable.

The median time to re-medication was greater for T/A 50/650 mg (257 min) than T 50 mg (120 min) and APAP 650 mg (195 min) and statistically greater than for PBO (119 min;  $p < 0.001$ ); and median time to re-medication was statistically greater for T/A 25/650 mg (180 min) than for T 25 mg (120 min;  $p = 0.009$ ) and PBO (119 min;  $p < 0.001$ ) but similar to APAP 650 mg (195 min). The onset of pain relief was statistically significantly quicker for both T/A combinations than component T doses ( $p \leq 0.041$ ) but not for APAP. The duration of pain relief was statistically significantly longer for T/A 50/650 mg (257 min) than for T 50 mg (120 min;  $p$ ), and longer than for APAP 650 mg (195 min); and the duration of pain relief was longer for T/A 25/650 mg (180 min) than for T (120 min) but less than for APAP (195 min). Forty-two percent of T/A 50/650 mg subjects rated their medication as 'very good' or 'excellent' compared to 36% of APAP 650 mg, 30% of T/A 25/650 mg, 22% of T 50 mg, 14% of T 25 mg, and 2% of PBO subjects. Subject's overall assessments of study medication were statistically significantly greater for both T/A groups than for their T component dose groups ( $p < 0.001$ ); and T/A 50/650 mg was greater while T/A 25/650 mg was similar to the APAP 650 mg group.

#### ***T with APAP: factorial efficacy in dental-extraction pain (CA)***

This was a single centre, randomised, DB, outpatient (OP), Phase II, pilot study to determine the efficacy and safety of T and APAP alone or in combination in 215 male and female patients with moderate or severe pain from oral surgery who randomly received one of four single dose treatments (T/A 100/500 mg, T 100 mg, APAP 500 mg, PBO). Efficacy parameters (pain intensity, PAR, global evaluation of therapy, time to re-medication) were evaluated pre dose, and 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h post dose and variables, TOTPAR, SPID and SPRID scores were calculated. Safety was assessed through adverse events (AEs) during the trial.

Two hundred fifteen patients were enrolled (53-55 per treatment group); 13 subjects discontinued treatment prematurely (5 T/A, 5 T, 0 APAP, 3 PBO) and 166 took supplemental analgesia and completed the 8 h follow up. Thirty-six subjects completed the 8 h study without using supplemental analgesia. Baseline demographics and characteristics were: 47% male, 53% female; 82% White, 18% Other; mean age was 24.0-25.2 years (range 16-49 years); and baseline pain was moderate for 79-85%.

With respect to TOTPAR, SPID and SPRID for the intervals 0-4 h, 4-8 h and 0-8 h, T/A 100/500 mg was statistically significantly superior compared to PBO ( $p \leq 0.012$ ) and APAP 500 mg ( $p \leq 0.022$ ) for all variables at all time points but was only statistically significantly superior to T 100 mg for TOTPAR, SPID and SPRID for the interval 0-4 h ( $p \leq 0.046$ ); T 100 mg was only statistically significantly superior to PBO for SPID in the 4-8 h interval; and APAP 500 mg was not statistically significantly superior to PBO for any of the variables in any time intervals.

Onset of pain relief was quicker for T/A 100/500 mg (24 min) than for PBO (52 min), T 100 mg (33 min) or APAP 500 mg (34 min); and duration of pain relief was longer for T/A 100/500 mg (4.6 h) than for PBO (2.7 h), T 100 mg (3.1 h) or APAP 500 mg (3.7 h). In keeping with the duration of pain relief data, time to re-medication was longer for T/A 100/500 mg than for T 100 mg ( $p=0.059$ ) and statistically significantly longer for T/A 100/500 mg than for PBO ( $p=0.007$ ) and APAP 500 mg ( $p=0.027$ ). Thirty-one percent of T/A 100/500 mg subjects rated their medication as 'very good' or 'excellent' compared to 16% of T 100 mg, 17% of APAP 500 mg and 12% of PBO subjects.

### ***T with APAP in pain of Caesarean section (CB)***

This was a single centre, DB, parallel group, Phase II, pilot study to evaluate the analgesic efficacy of T and A alone and in combination in 160 female patients with moderate or severe pain after Caesarean section who received one of four single dose treatments (T/A 25/500 mg, T 25 mg, APAP 500 mg, PBO). Subjects could receive a rescue analgesic during the study. Efficacy parameters (pain intensity, PAR, time to re-medication, subject's overall assessment of therapy) were evaluated pre dose and 0.5, 1, 2, 3, 4, 5, and 6 h post dose or till rescue analgesia was taken; and variables, TOTPAR, SPID, SPRID and peak PID (PEAKPID) scores were calculated. Safety was assessed through AEs during the trial.

One hundred sixty patients enrolled (40 per treatment group) and all completed the study; 47 by taking rescue analgesia and 113 subjects completed the 6 h follow up without using rescue analgesia. Baseline demographics and characteristics were: 100% female; 33% White, 35% Black, 32% Other; the mean age was 26 years (range 18-39 years); all patients had severe baseline pain.

With respect to TOTPAR, SPID, and SPRID for the intervals 0-3 h, 3-6 h and 0-6 h, the pain relief provided by T/A 25/500 mg was statistically significantly greater than PBO ( $p\leq 0.02$ ) but not statistically significantly superior to either component for TOTPAR, SPID and SPRID for all time intervals. There were also no statistically significant overall treatment effects seen for PEAKPID and time to re-medication.

### **Main (pivotal) studies**

Due to close similarities of design and findings, the three pivotal studies are reported together.

#### ***Evaluation of the Efficacy and Safety of RWJ-10628 in Oral Surgical Pain (T-A-010); Evaluation of the Efficacy and Safety of RWJ-10628 in Oral Surgical Pain (T-A-012); Evaluation of the Efficacy and Safety of RWJ-10628 in Oral Surgical Pain (T-A-013)***

Studies T-A-010, T-A-012 and T-A-013 were three single centre, randomised, DB, parallel group, active and PBO controlled, factorial-design, Phase III studies in 1200 male and female patients (400 in each study) with pain from an oral surgical procedure, who randomly (with stratification on baseline pain severity: moderate, severe) received one of five single dose treatments (T/A 75/650 mg, T 75 mg, APAP 650 mg, ibuprofen [IBU] 400 mg, PBO). Subjects could receive a supplemental analgesic during the studies.

### **Methods**

#### ***Objectives***

Objectives of these superiority studies were to evaluate efficacy and safety of combination T 75 mg with APAP 650 mg in subjects experiencing pain from an oral surgical procedure and to demonstrate the contribution of each component to the analgesic effect of the combination.

### *Study Participants*

The studies were each conducted in one centre in the USA. Inclusion criteria were male or female (non pregnant, using adequate contraception) patients,  $\geq 16$  years old, with moderate or severe pain from an oral surgical procedure (extraction of 2 ipsilateral, or  $>2$ , third molars requiring bone removal). Patients were excluded if they had renal or hepatic dysfunction or peptic ulcer disease; a recent history of seizures or disease or medications that may increase the risk of seizures; had received any analgesic within 12 h of the study (other than short acting pre or intra operative anaesthetic medication) or had received a long acting non-steroidal anti-inflammatory drug (NSAID) within 3 days of the study; or had any concerns that might cause safety issues for the subject.

### *Treatments*

After Screening, subjects were randomised to receive a single dose of T/A 75/650 mg, T 75 mg, APAP 650 mg, IBU 400 mg or PBO.

### *Outcomes/endpoints*

The three primary summary efficacy variables derived from categorical ratings of pain, common to all three studies, were TOTPAR, SPID and SPRID and were measured over the intervals 0-4 h, 4-8 h and 0-8 h.

Besides categorical ratings of pain, patients in T-A-013 also rated pain numerically on a scale from 0-10 enabling derivation of a further two primary summary efficacy variables:

- sum of numerical pain intensity difference (NSPID), sum of hly measures of difference in numerical pain intensity (NPID) scores (0=no pain . . . 10=worst pain) from baseline, over the intervals 0-4 h, 4-8 h and 0-8 h.
- sum of pain relief and numerical pain intensity difference (NSPRID), sum of hly measures of PAR+NPID over the intervals 0-4 h, 4-8 h and 0-12 h.

Secondary efficacy variables were:

- use of supplemental analgesic medication (T-A-010 only)
- time to onset of perceptible pain relief
- time to onset of meaningful pain relief
- onset of analgesia (time when group mean PRID score would first reach 1)
- duration of analgesia (time when half of group had re-medicated)
- time to re-medication
- subject's overall assessment of trial medication, after 8 h or after taking rescue medication (1=poor, 2=fair, 3=good, 4=very good, 5=excellent)

Safety was assessed through AEs, during and after the trial.

### *Sample size*

For each study: based on previous studies, using two-sided significance 0.05 and assuming a standard deviation (SD) of 9, 80 subjects per treatment group would detect a difference in TOTPAR of 4 between T/A and APAP group with 80% power. For SPID, a detectable difference between T/A and APAP would be seen with  $>80\%$  power; and for both TOTPAR and SPID a detectable difference between T/A and T would be seen with  $>80\%$  power.

### *Randomisation*

Computer generated randomisation lists were used with 1:1:1:1:1 ratios for the five treatments in blocks of 10, with stratification on baseline pain severity (moderate, severe).



### *Blinding (masking)*

Patients received DB medications in separate containers per subject as single doses of two tablets and two capsules. Blinding was achieved using double-dummy designs with matching PBO tablets and capsules. Individual treatment assignments were concealed on tear-off labels from the trial medication which were then attached to the subjects case report forms and could be unblinded in an emergency.

### *Statistical methods*

An analysis was performed in T-A-013 to compare the numerical pain intensity scale to the categorical pain intensity scale. For all three pivotal studies, hly PAR, PID and PRID scores (and NPID and NPRID in T-A-013) were analysed using one-way analysis of variance (ANOVAs). Two-sample t-tests were performed on the derived summary primary efficacy variables, TOTPAR, SPID and SPRID (and NSPID and NSPRID in T-A-013), to compare T/A to each component and PBO and to compare IBU and PBO for the intervals 0-8 h, 0-4 h and 4-8 h. Consistency of treatment effects across levels of baseline pain intensity (as measured by TOTPAR, SPID, and SPRID) were analysed using a two-way ANOVA with interaction.

Secondary endpoints were analysed using bivariate analysis using Wei, Lin, Weissfeld marginal distribution method±univariate log-rank tests, comparison of 95% confidence limits, Kaplan-Meier method or Wilcoxon rank-sum test. No adjustments were made for multiple comparisons.

- Note that for two of the secondary efficacy endpoints: in the Protocol the Kaplan-Meier method and Wilcoxon was to be used instead of the Wei, Lin, Weissfeld marginal distribution method, to estimate times to onset of perceptible and meaningful pain relief. The WLW method is an appropriate, robust, well developed method for dealing with ordered events such as this situation<sup>40</sup>.

## **Results**

### *Participant flow*

Study participant flow for the three pivotal studies is summarised in Table 10. In each study, 400 patients were enrolled and randomised to DB treatment (80 to each treatment group). Premature discontinuations were greatest with PBO (45-56%) and T (33-8%) in all three trials and less consistent for the other active treatments (T/A 6-18%, APAP 8-16%, IBU 8-25%). They were largely due to the patient taking rescue analgesia (87-100% for any one treatment group in any study). For all three trials, the greatest numbers of patients completing treatment without requiring rescue analgesia came from the IBU (19-35/study) and T/A (21-29/study) treatment groups compared to the component medications T (9-22/study), APAP (8-12/study) and PBO (3-7/study).

Protocol exceptions were made to the inclusion criteria for 54 subjects in Study T-A-010 (including 30 who had bone removal for only one molar and others with the wrong type of molar removed), 25 subjects in T-A-012 (including 1 with the wrong type of molars removed) and 20 subjects in T-A-013 (including 1 who had bone removal for only one third molar).

In each of the studies, subjects could take supplementary pain relief at any time after receiving the trial medication dose but were encouraged if possible to wait  $\geq 2$  h if there was no analgesic response or until pain returned to baseline level if there was some analgesic response.

---

<sup>40</sup> <http://www.stata.com/support/faqs/stat/stmfail.html>; Wei, LJ & Glidden, DV. (1997) An overview of statistical methods for multiple failure time data in clinical trials. *Statistics in Medicine*, Vol 16, pp833-839

**Table 10. Pivotal studies: Participant flow: T-A-010, T-A-012, T-A-013. Table continued across two pages.**

		T/A 75/650 mg	T 75 mg	APAP 650 mg	IBU 400 mg	PBO	Total
T-A-010							
Enrolment	Randomised						400 (100%)
Allocation	Allocated to treatment	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
	No post-baseline data		2 (2.5%)			1 (1.3%)	3 (0.8%)
Follow-up	Completed	66 (82.5%)	50 (62.5%)	67 (83.8%)	60 (75.0%)	44 (55.0%)	287 (71.8%)
	•no rescue analgesic	•21 (31.8)	•9 (18.0)	•8 (11.9)	•19 (31.7)	•3 (6.8)	•60 (20.9)
	•took rescue analgesic	•45 (68.2)	•41 (82.0)	•59 (88.1)	•41 (68.3)	•41 (93.2)	•227 (79.1)
	Discontinued prematurely	14 (17.5%)	30 (37.5%)	13 (16.3%)	20 (25.0%)	36 (45.0%)	113 (28.3%)
	•AE	•0	•3 (10.0)	•0	•2 (10.0)	•2 (5.6)	•7 (6.2)
	•subject withdrew	•1 (7.1)	•1 (3.3)	•0	•0	•0	•2 (1.8)
	•took rescue analgesic	•13 (92.9)	•26 (86.7)	•13 (100)	•18 (90.0)	•34 (94.4)	•104 (92.0)
Analysis	Efficacy group	80 (100%)	78 (97.5%)	80 (100%)	80 (100%)	79 (98.8%)	397 (99.3%)
	Safety group	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
T-A-012							
Enrolment	Randomised						400 (100%)
Allocation	Allocated to treatment	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
Follow-up	Completed	70 (87.5%)	53 (66.3%)	74 (92.5%)	61 (76.3%)	39 (48.8%)	297 (74.3%)
	•no rescue analgesic	•29 (41.4)	•14 (26.4)	•14 (18.9)	•35 (57.4)	•7 (17.9)	•99 (33.3)
	•took rescue analgesic	•41 (58.6)	•39 (73.6)	•60 (81.1)	•26 (42.6)	•32 (82.1)	•198 (66.7)
	Discontinued prematurely	10 (12.5%)	27 (33.8%)	6 (7.5%)	19 (23.8%)	41 (51.3%)	103 (25.8%)

		T/A 75/650 mg	T 75 mg	APAP 650 mg	IBU 400 mg	PBO	Total
	•re-medicated before 2h evaluation	•9 (90.0)	•27 (100)	•6 (100)	•18 (94.7)	•41 (100)	•101 (98.1)
	•took rescue analgesic before pain intensity returned to baseline	•1 (10.0)	•0	•0	•1 (5.3)	•0	•2 (1.9)
Analysis	Efficacy group	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
	Safety group	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
T-A-013							
Enrolment	Randomised						400 (100%)
Allocation	Allocated to treatment	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
Follow-up	Completed	75 (93.8%)	54 (67.5%)	70 (87.5%)	74 (92.5%)	35 (43.8%)	308 (77.0%)
	•no rescue analgesic	•23 (30.7)	•22 (40.7)	•12 (17.1)	•35 (47.3)	•7 (20.0)	•99 (32.1)
	•took rescue analgesic	•52 (69.3)	•32 (59.3)	•58 (82.9)	•39 (52.7)	•28 (80.0)	•209 (67.9)
	Discontinued prematurely	5 (6.3%)	26 (32.5%)	10 (12.5%)	6 (7.5%)	45 (56.3%)	92 (23.0%)
	•re-medicated before 2h evaluation	•5 (100)	•25 (96.2)	•9 (90.0)	•6 (100)	•44 (97.8)	•89 (96.7)
	•took rescue analgesic before pain intensity returned to baseline	•0	•1 (3.8)	•1 (10.0)	•0	•1 (2.2)	•3 (3.3)
Analysis	Efficacy group	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)
	Safety group	80 (100%)	80 (100%)	80 (100%)	80 (100%)	80 (100%)	400 (100%)

### Recruitment

T-A-010 was conducted from 8 December 1997 to 6 August 1998; T-A-012 was conducted from 15 December 1997 to 9 July 1998; and T-A-013 was conducted from 20 March 1998 to 10 July 1998.

### Conduct of the study

In spite of all amendments being made after the studies commenced (first amendment after 18 subjects enrolled, second 'clarification' after 273 subjects enrolled, in T-A-010; amendment after 16 subjects enrolled, in T-A-012; first amendment after 320 subjects enrolled, second amendment simply to change 'RWJ-10628' to 'Tramadol/APAP', in T-A-

013), in the evaluators opinion the changes have been made for the purposes of clarity and to ensure subjects recruited would have as similar an experience of pain as possible and would not significantly affect the study.

#### *Baseline data*

With respect to the baseline demographics and characteristics of all three pivotal studies; in T-A-010 the proportion of females in the T/A group (53%) was smaller than in the other groups (60-69%) and in T-A-012 the proportion of females in the T group (66%) was greater than in the other groups (49-55%); but otherwise groups were comparable within each study. Across the studies most subjects were female (55-63%); Caucasian (75-93%); and mean age was 21.1-21.7 years (range 16-46 years). Baseline pain was consistent across the studies (moderate for 66-70%, severe for 30-34%; mean rating 6.1-6.2); and the majority of subjects had 4 molars removed (64-83%). Almost all the subjects in Studies T-A-010 and 012 (99-100%), and over half the subjects in Study T-A-013 (57%) had substantial bone removal.

All but one subject received a single dose of two tablets and two capsules of study medication (a single tablet was found dropped on the floor after dosing for one subject in T-A-010).

#### *Numbers analysed*

The safety analysis groups included all 400 randomised subjects in each study; while the efficacy analysis groups included all subjects with post baseline data for the primary summary efficacy variables (397/400 T-A-010, 400/400 for both T-A-012 and T-A-013). If a subject took rescue medication or discontinued prematurely, remaining observation points were filled using the last observation carried forward (LOCF) method.

#### *Outcomes and estimation*

##### *Primary efficacy endpoints*

Table 11 presents the primary summary efficacy variables (TOTPAR, SPID, and SPRID) and statistical comparisons for the intervals 0-4 h, 4-8 h and 0-8 h for each of the pivotal studies. In every case, the efficacy shown with IBU was significantly greater ( $p < 0.001$ ) than that shown with PBO, demonstrating sensitivity of the models.

In T-A-010, the TOTPAR and SPRID scores demonstrate that T/A provided statistically significantly greater pain relief than T, APAP or PBO ( $p \leq 0.037$ ) for the time intervals 0-4 h, 4-8 h and 0-8 h. The SPID scores demonstrate that T/A provided greater pain relief than T, APAP or PBO for the time intervals 0-4 h, 4-8 h and 0-8 h; with the difference in scores non-significant for T/A versus APAP for the 0-4 h interval ( $p = 0.066$ ) but statistically significant for all other comparisons ( $p \leq 0.017$ ). T and APAP provided statistically significantly greater pain relief than PBO for all time intervals for TOTPAR, SPID and SPRID ( $p \leq 0.002$ ).

For T-A-012, the TOTPAR and SPRID scores demonstrate that T/A provided greater pain relief than T, APAP or PBO ( $p \leq 0.033$ ) for the time intervals 0-4 h, 4-8 h and 0-8 h. The SPID scores demonstrate that T/A provided greater pain relief than T, APAP or PBO for the time intervals 0-4 h, 4-8 h and 0-8 h; with the difference in scores non-significant for T/A versus APAP for the 0-4 h interval ( $p = 0.096$ ) but statistically significant for all other comparisons ( $p \leq 0.026$ ). T and APAP provided statistically significantly greater pain relief than PBO for all time intervals for TOTPAR, SPID and SPRID ( $p \leq 0.049$ ).

For T-A-013, the scores demonstrate that the pain relief provided by T/A was greater than each component for all time intervals for TOTPAR, SPID and SPRID; with the difference in scores non-significant for TOTPAR and SPRID with T in the interval 4-8 h but statistically significant for all other comparisons ( $p \leq 0.046$ ). T and APAP provided greater pain relief

than PBO for all time intervals for TOTPAR, SPID and SPRID; with the difference in scores non significant for TOTPAR with T in the interval 0-4 h, and TOTPAR and SPRID with APAP in the interval 4-8 h but statistically significant for all other comparisons ( $p \leq 0.045$ ).

In all three studies, there were no statistically significant differences for TOTPAR, SPID and SPRID scores for subjects reporting moderate baseline pain intensity compared to those reporting severe baseline pain intensity.

**Table 11. Primary summary efficacy variables: TOTPAR, SPID, and SPRID scores, pivotal studies: T-A-010, T-A-012, T-A-013, efficacy analysis groups. Table continued across two pages.**

Variable	Treatment	N	0-4 h			4-8 h			0-8 h		
			Mean (SD)	T/A versus component	Active treatment versus PBO	Mean (SD)	T/A versus component	Active treatment versus PBO	Mean (SD)	T/A versus component	Active treatment versus PBO
<b>T-A-010</b>											
<b>TOTPAR</b>	T/A	80	7.7 (4.12)		<0.001	6.0 (4.75)		<0.001	13.7 (8.19)		<0.001
	T75	78	4.3 (4.26)	<0.001	0.001	3.9 (4.45)	0.001	<0.001	8.1 (8.45)	<0.001	<0.001
	APAP650	80	6.5 (4.11)	0.032	<0.001	3.5 (3.73)	<0.001	0.002	10.1 (7.13)	0.002	<0.001
	IBU400	80	7.6 (4.69)		<0.001	6.0 (5.09)		<0.001	13.6 (9.09)		<0.001
	PBO	79	2.2 (3.02)			1.5 (3.28)			3.7 (6.02)		
<b>SPID</b>	T/A	80	3.1 (2.94)		<0.001	1.9 (3.35)		<0.001	5.0 (5.95)		<0.001
	T75	78	1.1 (3.17)	<0.001	0.001	0.8 (3.42)	0.008	0.001	1.8 (6.48)	<0.001	0.001
	APAP650	80	2.4 (2.81)	0.066	<0.001	0.7 (2.50)	0.005	0.001	3.1 (5.00)	0.017	<0.001
	IBU400	80	3.3 (3.39)		<0.001	2.3 (3.35)		<0.001	5.6 (6.42)		<0.001
	PBO	79	-0.3 (2.20)			-0.8 (2.47)			-1.1 (4.53)		
<b>SPRID</b>	T/A	80	10.8 (6.75)		<0.001	7.9 (7.73)		<0.001	18.7 (13.47)		<0.001
	T75	78	5.3 (7.10)	<0.001	0.001	4.6 (7.46)	0.002	<0.001	10.0 (14.22)	<0.001	<0.001
	APAP650	80	8.9 (6.67)	0.037	<0.001	4.2 (5.84)	0.001	0.001	13.1 (11.53)	0.003	<0.001
	IBU400	80	10.9 (7.80)		<0.001	8.4 (8.08)		<0.001	19.2 (14.89)		<0.001
	PBO	79	1.8 (4.86)			0.8 (5.29)			2.6 (9.73)		
<b>T-A-012</b>											
<b>TOTPAR</b>	T/A	80	6.8 (4.92)		<0.001	4.4 (5.42)		<0.001	11.1 (9.72)		<0.001
	T75	80	2.7 (3.85)	<0.001	0.031	2.3 (4.82)	0.002	0.033	5.0 (8.31)	<0.001	0.024

Variable	Treatment	N	0-4 h			4-8 h			0-8 h		
			Mean (SD)	T/A versus component	Active treatment versus PBO	Mean (SD)	T/A versus component	Active treatment versus PBO	Mean (SD)	T/A versus component	Active treatment versus PBO
	APAP650	80	5.4 (4.11)	0.019	<0.001	2.1 (4.12)	0.001	0.049	7.5 (7.35)	0.003	<0.001
	IBU400	80	6.9 (4.89)		<0.001	5.8 (5.49)		<0.001	12.7 (9.80)		<0.001
	PBO	80	1.5 (2.70)			0.9 (3.02)			2.4 (5.43)		
<b>SPID</b>	T/A	80	2.9 (3.19)		<0.001	1.8 (3.49)		<0.001	4.7 (6.46)		<0.001
	T75	80	0.4 (2.66)	<0.001	0.028	0.1 (3.36)	<0.001	0.016	0.4 (5.82)	<0.001	0.018
	APAP650	80	2.3 (2.66)	0.096	<0.001	0.6 (2.48)	0.008	0.001	2.9 (4.75)	0.026	<0.001
	IBU400	80	2.9 (3.61)		<0.001	2.3 (3.55)		<0.001	5.2 (6.91)		<0.001
	PBO	80	-0.5 (2.42)			-1.0 (2.58)			-1.5 (4.91)		
<b>SPRID</b>	T/A	80	9.6 (7.86)		<0.001	6.2 (8.66)		<0.001	15.8 (15.72)		<0.001
	T75	80	3.1 (6.23)	<0.001	0.025	2.3 (7.87)	0.001	0.020	5.4 (13.52)	<0.001	0.017
	APAP650	80	7.7 (6.51)	0.033	<0.001	2.7 (6.35)	0.002	0.009	10.4 (11.63)	0.006	<0.001
	IBU400	80	9.8 (8.23)		<0.001	8.1 (8.72)		<0.001	17.9 (16.12)		<0.001
	PBO	80	0.9 (4.75)			-0.1 (5.09)			0.8 (9.50)		
<b>T-A-013</b>											
<b>TOTPAR</b>	T/A	80	7.0 (5.01)		<0.001	4.4 (6.13)		<0.001	11.4 (10.44)		<0.001
	T75	80	3.3 (4.40)	<0.001	0.066	3.7 (5.91)	0.219	0.010	7.0 (10.03)	0.002	0.020
	APAP650	80	5.6 (5.12)	0.033	<0.001	2.5 (5.03)	0.020	0.145	8.2 (9.53)	0.020	0.002
	IBU400	80	8.2 (5.15)		<0.001	6.4 (6.40)		<0.001	14.6 (10.85)		<0.001
	PBO	80	2.2 (3.96)			1.6 (4.22)			3.8 (7.85)		
<b>SPID</b>	T/A	80	2.9 (3.61)		<0.001	1.5 (4.29)		<0.001	4.4 (7.50)		<0.001
	T75	80	0.2 (3.52)	<0.001	0.034	0.4 (4.35)	0.046	0.007	0.6 (7.64)	<0.001	0.012
	APAP650	80	2.0 (3.71)	0.046	<0.001	0.3 (3.66)	0.030	0.011	2.2 (7.07)	0.032	<0.001
	IBU400	80	3.8 (3.67)		<0.001	2.9 (4.51)		<0.001	6.7 (7.82)		<0.001
	PBO	80	-0.8 (3.15)			-1.2 (3.66)			-2.1 (6.70)		

Variable	Treatment	N	0-4 h			4-8 h			0-8 h		
			Mean (SD)	T/A versus component	Active treatment versus PBO	Mean (SD)	T/A versus component	Active treatment versus PBO	Mean (SD)	T/A versus component	Active treatment versus PBO
SPRID	T/A	80	9.9 (8.38)		<0.001	5.9 (10.16)		<0.001	15.8 (17.47)		<0.001
	T75	80	3.5 (7.65)	<0.001	0.045	4.1 (9.99)	0.115	0.007	7.5 (17.14)	<0.001	0.013
	APAP650	80	7.6 (8.58)	0.034	<0.001	2.8 (8.25)	0.020	0.052	10.4 (15.98)	0.021	<0.001
	IBU400	80	12.0 (8.58)		<0.001	9.3 (10.65)		<0.001	21.3 (18.20)		<0.001
	PBO	80	1.3 (6.82)			0.4 (7.54)			1.7 (13.94)		

### Secondary efficacy endpoints

Median time to onset of perceptible pain relief was under 30 min and similar for T/A (21.1-27.9 min) and APAP (23.5-29.8 min), and statistically significantly quicker for T/A than for T (30.7-74.3 min;  $p \leq 0.002$ ) and PBO (43.5 min;  $p < 0.001$ ); whilst median time to onset of meaningful pain relief was similar within each study for T/A (54.5-103.0 min) and APAP (51.8-99.8 min). Perceptible pain relief was not experienced for over half the subjects in the PBO group in T-A-012 and T-A-013; and meaningful pain relief was not attained for over half the subjects in the T and PBO groups in any of the pivotal studies.

Onset and duration of pain relief as estimated from group mean PRID score (as opposed to actual stopwatch measured times) were analysed to allow for comparison to previous studies. Onset of pain relief was similar for T/A (14-22 min) and APAP (14-31 min), both treatments being quicker than T (31-100 min) and PBO (46-86 min); and duration of pain relief was longest for T/A (245-326 min) compared to APAP (165-242 min), T (122-4 min) and PBO (104-122 min).

Table 12 shows the cumulative number of subjects requiring re-medication each h post dose for the three pivotal studies. In T-A-010 and T-A-012, T/A had a greater number of subjects not requiring re-medication at any time during the study (26-36%) compared to T (14-18%), APAP (10-18%) and PBO (5-9%). In T-A-013, T/A and T had a similar number of subjects not requiring re-medication at any time during the study (28-29%) and this was greater than for APAP (15%) and PBO (9%). It was apparent in the studies that APAP has a quick onset, short acting nature with only 6-7 subjects in each study requiring re-medication by 2 h but 31-43 subjects requiring re-medication by 3 h. Similarly, the slower onset, longer acting nature of T was apparent with 18-32 subjects requiring re-medication by 2 h, 52-53 subjects by 3 h but only a further 6-14 subjects over the following 5 h interval. In contrast to the two component drugs, only 6-9 T/A subjects required re-medication by 2 h, 21-27 subjects by 3 h and 29-38 subjects by 4 h, thereby providing support for the rationale for combining the two medications.

**Table 12. Number of subjects requiring rescue medication at each hour, pivotal studies: T-A-010, T-A-012, T-A-013**

Treatment	N	Cumulative number of subjects re-medicated at each hour (total number of subjects re-medicated during specified hour)								Total (%) not Re- medicating
		1	2	3	4	5	6	7	8	
<b>T-A-010</b>										
T/A	80	0 (0)	6 (6)	21 (15)	29 (8)	35 (6)	43 (8)	54 (11)	58 (4)	22 (28%)
T75	78	0 (0)	18 (18)	53 (35)	59 (6)	61 (2)	62 (1)	66 (4)	67 (1)	11 (14%)
APAP650	80	0 (0)	7 (7)	34 (27)	47 (13)	55 (8)	63 (8)	68 (5)	72 (4)	8 (10%)
IBU400	80	0 (0)	9 (9)	26 (17)	31 (5)	39 (8)	47 (8)	55 (8)	59 (4)	21 (26%)
PBO	79	0 (0)	34 (34)	64 (30)	71 (7)	73 (2)	73 (0)	74 (1)	75 (1)	4 (5%)
<b>T-A-012</b>										
T/A	80	0 (0)	9 (9)	27 (18)	34 (7)	40 (6)	46 (6)	49 (3)	51 (2)	29 (36%)
T75	80	4 (4)	27 (23)	53 (26)	58 (5)	61 (3)	64 (3)	65 (1)	66 (1)	14 (18%)
APAP650	80	1 (1)	6 (5)	31 (25)	39 (8)	53 (14)	59 (6)	64 (5)	66 (2)	14 (18%)
IBU400	80	4 (4)	18 (14)	24 (6)	25 (1)	28 (3)	35 (7)	40 (5)	45 (5)	35 (44%)
PBO	80	5 (5)	41 (36)	66 (25)	70 (4)	73 (3)	73 (0)	73 (0)	73 (0)	7 (9%)
<b>T-A-013</b>										
T/A	80	1 (1)	8 (7)	27 (19)	38 (11)	44 (6)	50 (6)	53 (3)	57 (4)	23 (29%)
T75	80	6 (6)	32 (26)	52 (20)	56 (4)	56 (0)	57 (1)	57 (0)	58 (1)	22 (28%)
APAP650	80	0 (0)	21 (21)	43 (22)	50 (7)	59 (9)	64 (5)	67 (3)	68 (1)	12 (15%)
IBU400	80	0 (0)	6 (6)	20 (14)	25 (5)	29 (4)	35 (6)	40 (5)	45 (5)	35 (44%)
PBO	80	6 (6)	47 (41)	61 (14)	65 (4)	68 (3)	70 (2)	72 (2)	73 (1)	7 (9%)

In all three pivotal studies, the median time to re-medication was significantly greater for T/A over T and APAP ( $p \leq 0.012$ ) and significantly greater for all active treatments over PBO ( $p \leq 0.007$ ).

Half (47-48%) of all T/A subjects in Studies T-A-010 and T-A-012 rated their medication as 'very good' or 'excellent' compared to 21-36% of APAP, 18-23% of T and 4-8% of PBO subjects. In T-A-013, a similar number of T/A and APAP subjects rated their medications as 'very good' or 'excellent' (29-30%), double that of T or PBO (13-14%). The assessment of study medication was significantly greater for the T/A group compared to the T and PBO groups ( $p < 0.001$ ) and for the T and APAP groups compared to the PBO group



( $p \leq 0.026$ ) in all three pivotal studies. It was also significantly greater for the T/A group compared to the APAP group ( $p = 0.003$ ) in T-A-012.

### ***Analysis performed across trials (pooled analyses and meta-analysis)***

Two meta-analyses (and an update) of T/A were included with the current submission: one in acute and one in chronic, pain.

#### *Individual patient data meta-analysis of single-dose oral T/A in acute post-operative pain.*

This was an analysis of data from 7 randomised, DB, PBO controlled trials to quantitatively assess efficacy and adverse effects of single dose oral T/A in moderate to severe post operative pain; the studies were T-A-002, T-A-003, T-A-010, T-A-012 and T-A-013 in post-oral surgical pain and T-A-004 and T-A-005 in post surgical pain. All studies used identical methods. Endpoints able to be assessed in the meta-analysis were: Pain Intensity and Pain Relief data converted to give number of patients gaining at least 50% relief, patient global ratings of treatment effect and AEs.

In terms of efficacy, T/A 75/650 mg was statistically significantly superior to T 75 mg, APAP 650 mg and PBO for the treatment of moderate to severe acute dental or post surgical pain (compared to PBO, number-needed-to-treat [NNT] with single dose T/A (75/650 mg or 112.5/1975 mg) over 6 h and over 8 h were 3.0-3.5 and 3.2-4.0, respectively). Overall, single-dose T/A was statistically superior to its equivalent dosage components and showed similar efficacy to IBU 400 mg in the treatment of acute post surgical pain.

#### *Single-dose oral T and T/A in acute postoperative pain: an updated meta-analysis.*

A re analysis of the above data found no effect according to baseline pain intensity. There was a dose response seen for efficacy with increasing dose of T; and T/A was superior in efficacy to both T and APAP.

#### *Oral T and T/A in chronic pain: a meta-analysis.*

This was an analysis of data from 4 randomised, DB, PBO controlled trials to quantitatively assess efficacy and adverse effects of multiple dose oral T/A in chronic pain; the studies (C-104, C-112, C-113, C-114) were conducted over 28-91 days, and in the case of C-114 the study medication was given in addition to a selective cyclooxygenase 2 (COX-2) inhibitor (iCOX2). Data was compared to data from 4 similar randomised, DB studies of T compared to PBO or IBU (C-051, TPS OA, TPS BP and TPS FM) conducted over 28-91 days. Endpoints common to all studies that were able to be assessed in a meta-analysis were: patient global ratings of pain ('good' or 'very good'), discontinuations due to lack of efficacy and discontinuations due to AEs.

In studies of T/A, the median daily dose of T and APAP were 150 mg and 1300 mg respectively compared to studies of T where the median daily dose of T was 200-400 mg and that of IBU was 2400 mg. In terms of efficacy, more subjects gave T/A and T a rating of 'good' or 'very good' compared to PBO for the treatment of moderate or severe chronic pain over 91 days and the comparison was statistically significant (number needed to treat (NNT) approximately 6). T was statistically significantly inferior to IBU and the addition of T/A to iCOX2 improved analgesic efficacy. Overall, similar efficacy was seen for T/A and T in studies of up to 91 days.

### **Supportive studies**

Two pain models were investigated in the early development program of T/A: T-A-002, T-A-003 and T-A-011 (non supportive) were 3 single dose studies in acute pain from oral surgery and T-A-004 and T-A-005 were 2 single dose studies in acute pain from gynaecologic and orthopaedic surgery respectively. In the readily available, widely

reproducible dental pain model, APAP was expected to be more effective due to the faster onset; while in the post general surgical model, T was expected to be more effective due to its slower onset and  $\mu$ -opioid activity. The results from these early studies helped determine the design used in the pivotal studies which used a dental pain model, more severe baseline pain (through only including patients with multiple molar extractions) and an increased sample size.

T-A-008 (in osteoarthritis) and T-A-009 (in low back pain) were two multiple dose studies which investigated the use of T/A in the management of chronic pain. T-A-006 was a multiple dose study comparing T/A to a standard combination treatment (APAP/codeine [A/COD]) in chronic pain; and long-term safety of T/A was examined in T-A-006-OL (the OL extension of T-A-006) and T-A-015.

Further efficacy data has been collected from studies completed after the initial 2001 application.

C-104 and C-114 (in osteoarthritis), C-112 and PRI/TRP-CAN-1 (in low back pain) and C-113 (in fibromyalgia), were 5 multiple dose, PBO controlled studies in patients with at least moderate chronic pain (and who were also receiving an iCOX2 in C-114). SP-ZAL-III-02 was a multiple dose study comparing T/A to A/COD in the treatment of chronic pain.

C-128 compared T/A (1 or 2 tablets) to hydrocodone bitartrate (HYD)/APAP (HYD/A) and C-241 compared T/A to T in the single dose treatment of post surgical pain. C-105, C-115, C-216, GRTF-ZAL1, and ZAL-06 were 5 short term (2-10 days) multiple dose studies in acute pain. C-105 compared T/A versus PBO in osteoarthritis patients also taking an NSAID or iCOX2; GRTF-ZAL1 compared T/A and T in patients with low back pain; C-216 compared T/A and HYD/A in acute musculoskeletal pain. Study C-115 compared T/A and A/COD and Study ZAL-06 compared T/A and T, post surgery.

In the TGA adopted EU guideline for evaluation of products for the treatment of nociceptive pain<sup>41</sup>, examples are given of study models that reflect 'mild to moderate' or 'moderate to severe', acute or chronic pain.

The studies presented variously used a pain visual analogue (PVA) scale score of  $\geq 40$  mm or  $\geq 50$  mm to represent 'moderate pain'; a PVA score corresponding to 'severe pain' was not defined. Collins, Moore and McQuay (1997)<sup>42</sup> equated a 4-point categorical pain intensity scale to a pain intensity visual analogue scale (VAS) to determine that: 85% of patients reporting moderate pain scored  $>30$  mm with a mean score of 49 mm and 85% of patients reporting severe pain scored  $>54$  mm with a mean score of 75 mm.

Of these additional studies completed after the initial 2001 application, the only studies that fit the 'moderate to severe' category of pain according to study model are C-128 and C-241, the two single dose studies in acute pain. Both of these studies required a baseline PVA score of  $\geq 50$  mm. As none of the studies involved cancer or skeletal metastases there were no studies in chronic pain that fit the 'moderate to severe' category of pain according to study model. There were another 3 studies, however, that required a baseline PVA score of  $\geq 50$  mm that could be included as studies of 'moderate to severe' pain despite using a model indicative of 'mild to moderate' pain: C-216 (acute pain model: sprain), C-114 (chronic pain model: osteoarthritis) and C-105 (acute on chronic pain model: osteoarthritis flare). As the requested indication for T/A is for 'the symptomatic treatment of moderate to severe pain', these 5 supporting studies are considered to be of greater relevance and are therefore presented in greater depth.

<sup>41</sup> Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain, EMEA/CPMP/EWP/612/00, pp4-5

<sup>42</sup> Collins SL, Moore RA, McQuay HJ. (1997) The visual analogue pain intensity scale: what is moderate pain in millimetres?; Pain. Aug; 72(1-2):95-97.

**Primary source studies in acute pain:*****Evaluation of the efficacy and safety of T with APAP (RWJ-26898-002-AQ-22) in oral surgical pain (T-A-002);******Evaluation of the efficacy and safety of T with APAP (RWJ-26898-002-AQ-22) in oral surgical pain (T-A-003);******Evaluation of the efficacy and safety of T with APAP (RWJ-26898-002-AQ-22) in gynaecological surgical pain (T-A-004);******Evaluation of the efficacy and safety of T with APAP (RWJ-26898-002-AQ-22) in orthopaedic surgical pain (T-A-005);******Evaluation of the efficacy and safety of RWJ-10628 in oral surgical pain (RWJ-10628) (T-A-011)***

These were 5 single centre, single dose, randomised, DB, parallel group, active and PBO controlled, factorial-design, Phase III studies to evaluate efficacy and safety of T/A and to demonstrate the contribution of each component to the effect of the combination. T-A-002, T-A-003, and T-A-011 included male and female patients (250 each in T-A-002 and T-A-003, 156 in T-A-011) with pain from an oral surgical procedure, who randomly (with stratification on baseline pain severity: moderate, severe in T-A-011) received one of five single dose treatments (T/A 75/650 mg, T 75 mg, APAP 650 mg, IBU 400 mg, PBO). T-A-004 included 200 female patients with pain from a gynaecological surgical procedure and T-A-005 included 200 male and female patients with pain from an orthopaedic surgical procedure who randomly received one of four single dose treatments (T/A 112.5/975 mg, T 112.5 mg, APAP 975 mg, PBO). In each of the studies subjects could receive a supplemental rescue analgesic.

Note: T-A-011 was stopped prematurely due to data integrity problems after evaluation of 156 of the 400 planned subjects, it was subsequently analysed for safety but not efficacy.

The three primary summary efficacy variables determined for the intervals 1-4 h, 5-8 h, and 1-8 h were: TOTPAR, SPID and SPRID. Secondary efficacy variables were: time to re-medication; onset and duration of pain relief; subject's overall assessment of study drug, after 8 h or after taking rescue medication. Safety was assessed through AEs during each of the trials.

Note: For T-A-005, the investigator only monitored patients who took a supplemental analgesic for 1 h after taking the supplemental and so AEs were possibly underreported in those patients.

***T-A-002***

Two hundred and fifty patients enrolled (50 per treatment group); 1 subject was lost to follow up from the PBO group and 249 subjects completed the study. Of these, 171 used rescue analgesia (31 T/A, 43 T, 34 APAP, 22 IBU, 41 PBO) and 78 did not use any rescue analgesia (19 T/A, 7 T, 16 APAP, 28 IBU, 8 PBO). The groups showed some variation in terms of baseline demographics and characteristics: 32-56% male, 44-68% female; 62-78% Caucasian, 2-10% Black, 0-6% Asian and 10-32% Other; mean age was 23.9 years (range 16-48 years). Baseline pain was moderate for 74-86% of subjects and severe for 14-26% of subjects across the groups. The majority of subjects had partial bony extractions (50-70%) or full bony extractions (36-56%), with 26-32% having other types of extractions.

With respect to TOTPAR, SPID and SPRID data and statistical comparisons for the intervals, 0-4 h, 4-8 h and 0-8 h; IBU 400 mg was statistically significantly superior to PBO for all variables ( $p < 0.001$ ) and this demonstrated sensitivity of the model. The pain relief

provided by T/A 75/650 mg was greater than for each component for all time intervals for TOTPAR, SPID and SPRID; with the difference in scores statistically significant for all comparisons against T 75 mg ( $p \leq 0.001$ ) but not statistically significant against APAP 650 mg. APAP 650 mg provided statistically significantly greater pain relief than PBO for all time intervals for TOTPAR, SPID and SPRID ( $p \leq 0.031$ ); but T 75 mg was not superior to PBO. T/A 75/650 mg was significantly superior to both T 75 mg and APAP 650 mg in subjects with severe baseline pain but T/A 75/650 mg was only superior to T 75 mg in subjects with moderate baseline pain for TOTPAR, SPID and SPRID.

The cumulative number of subjects requiring re-medication each h after treatment showed that T/A 75/650 mg had a greater number of subjects not requiring re-medication at any time during the study; 38% compared to APAP (32%), PBO (16%) and T (14%). The slower onset, longer acting nature of T was apparent with 42 subjects requiring re-medication by 3 h but only 1 subject requiring re-medication in the following 5 h; while the quick onset nature of APAP was apparent with 16 subjects requiring re-medication by 2 h and 22 subjects by 3 h (approximately half that of T). In contrast to the two component drugs, only 6 T/A subjects required re-medication by 2 h and 11 subjects by 3 h. Median time to re-medication was significantly greater for T/A (321 min) than T (88 min;  $p < 0.001$ ), and significantly greater for T/A (321 min) and APAP (104 min) over PBO (63 min;  $p \leq 0.001$ ). Onset of pain relief was similar for T/A (21 min) and APAP (18 min) and significantly quicker for T/A than for T (88 min) and PBO (68 min). Duration of pain relief was longest for T/A (321 min) and APAP (243 min), compared to T (88 min) and PBO (63 min). Forty-two percent of T/A subjects rated their medication as 'very good' or 'excellent' compared to 28% of APAP, 12% of T and 12% of PBO subjects. Subject's overall assessment of study medication was significantly greater for the T/A group than for the T, APAP and PBO groups ( $p \leq 0.043$ ) and significantly greater for the APAP group than for the PBO group ( $p < 0.001$ ).

#### *T-A-003*

Two hundred and fifty patients were enrolled (50 per treatment group); 3 subjects discontinued due to AEs ( $n=1$  T/A,  $n=1$  T,  $n=1$  IBU) and 1 subject chose to discontinue ( $n=1$  PBO); 246 subjects completed the study, 126 with rescue analgesia (22 T/A, 28 T, 25 APAP, 19 IBU, 32 PBO) and 120 without any rescue analgesia (27 T/A, 21 T, 25 APAP, 30 IBU, 17 PBO). The groups were generally comparable for baseline demographics and characteristics: 40-60% male, 40-60% female; 94-100% Caucasian, 0-2% Black, 0-2% Asian, 0-6% Other; mean age was 18.8 years (range 16-33 years). Baseline pain was moderate for 58-78% and severe for 22-42% across the groups. The majority of subjects had full bony extractions (88%) and the remainder had partial bony extractions (12%).

With respect to TOTPAR, SPID and SPRID data and statistical comparisons for the intervals, 0-4 h, 4-8 h and 0-8 h; IBU 400 mg was statistically significantly superior to PBO for all variables ( $p < 0.001$ ) and this demonstrated the sensitivity of the model. The pain relief provided by T/A 75/650 mg was statistically significantly greater than that of T and PBO for all time intervals for TOTPAR, SPID and SPRID ( $p \leq 0.017$ ) but not statistically superior to APAP. APAP 650 mg provided statistically significantly greater pain relief than PBO for all time intervals for TOTPAR, SPID and SPRID ( $p \leq 0.006$ ) but T 75 mg was not superior to PBO.

Results analysed by baseline pain intensity found no statistically significant differences between treatments for TOTPAR, SPID and SPRID.

The cumulative number of subjects requiring re-medication each h post dose showed T/A 75/650 mg had a greater number of subjects not requiring re-medication at any time during the study (56%) compared to APAP (50%), T (44%) and PBO (36%). The greatest difference to T/A was seen for T and PBO at 2 h (6, 21, and 29 subjects re-medicated respectively). Median time to re-medication could not be calculated if less than half of the

subjects in those groups re-medicated; the median time to re-medication was greater for T over PBO but not significantly so ( $p=0.299$ ) and significantly greater for T/A and APAP over PBO ( $p\leq 0.009$ ). Onset of pain relief was similar for T/A (22 min) and APAP (17 min), and quicker for both compared to T (54 min) and PBO (75 min). Duration of pain relief could only be calculated for T (350 min) and PBO (90 min). Sixty percent of T/A subjects rated their medication as 'very good' or 'excellent' compared to 56% of APAP, 34% of T and 20% of PBO subjects. Subject's overall assessment of study medication was significantly greater for the T/A group than for the T and PBO groups ( $p\leq 0.002$ ) and significantly greater for the APAP group than for the PBO group ( $p<0.002$ ).

#### *T-A-004*

Two hundred patients were enrolled (49-51/treatment group); 1 subject took another analgesic 10 min prior to the study drug and was not included in the efficacy analysis; 7 subjects discontinued treatment prematurely ( $n=1$  T,  $n=4$  APAP,  $n=2$  PBO), 2 due to AEs ( $n=1$  APAP,  $n=1$  PBO); 193 subjects completed the study, 66 with rescue analgesia (10 T/A, 12 T, 15 APAP, 29 PBO) and 127 without any rescue analgesia (41 T/A, 36 T, 31 APAP, 19 PBO). The groups were generally comparable for baseline demographics and characteristics: all subjects were female and Hispanic; with mean age 26.5 years (range 18-49 years). Baseline pain was moderate for 10-24% and severe for 76-90% across the groups. Most of the surgical procedures were Caesareans (94%).

With respect to TOTPAR, SPID and SPRID data and statistical comparisons for the intervals 0-4 h, 4-8 h and 0-8 h; the pain relief provided by T/A 112.5/975 mg was statistically significantly superior to PBO for all comparisons ( $p<0.001$ ); and greater than each component for all comparisons but only significant for APAP for TOTPAR and SPRID at 4-8 h and 0-8 h ( $p\leq 0.025$ ) and for SPID at 4-8 h ( $p=0.012$ ). Both T and APAP provided statistically significantly greater pain relief than PBO for all time intervals for TOTPAR, SPID and SPRID ( $p\leq 0.002$ ). There were no differences in treatment effects for subjects with moderate versus severe baseline pain intensity.

The cumulative number of subjects requiring re-medication each h post dose showed that more T (25%), APAP (36%) and PBO (60%) subjects required re-medication at some point during the study than T/A subjects (20%). The greatest differences were seen between T/A and T at 5-6 h and between T/A and APAP at 5-8 h. Median time to re-medication was only calculable for PBO (245 min) and was significantly greater for T/A, T and APAP compared to PBO ( $p<0.004$ ). Mean onset of pain relief was similar for T/A (13 min), T (15 min) and APAP (12 min) and all of them were quicker than for PBO (19 min). Median duration of pain relief was only measurable for PBO (245 min). Sixty-seven percent of T/A subjects rated their medication as 'very good' or 'excellent' compared to 46% of T, 28% of APAP and 22% of PBO subjects. Assessment of study medication was significantly greater for the T/A group than for the T and APAP groups ( $p\leq 0.040$ ) and significantly greater for the T/A, T and APAP groups than for the PBO group ( $p<0.033$ ).

#### *T-A-005*

Two hundred were patients enrolled (50 per treatment group); 7 subjects discontinued treatment prematurely ( $n=2$  T,  $n=2$  APAP,  $n=3$  PBO), 3 due to AEs ( $n=1$  T,  $n=1$  APAP,  $n=1$  PBO); 193 subjects completed the study, 162 with rescue analgesia (36 T/A, 41 T, 43 APAP, 42 PBO) and 31 without any rescue analgesia (14 T/A, 7 T, 5 APAP, 5 PBO). The groups were generally comparable for baseline demographics and characteristics: the majority of subjects were male (58%) and Caucasian (85%); with a mean age of 45.4 years (range 20-83 years); and baseline pain was moderate for 74-82% and severe for 18-26%. Most surgical procedures involved the foot or ankle (80%).

With respect to TOTPAR, SPID and SPRID data and statistical comparisons for the intervals 0-4 h, 4-8 h and 0-8 h: the pain relief provided by T/A 112.5/975 mg was statistically

significantly greater than PBO for all comparisons ( $p \leq 0.003$ ); superior to T and APAP for all comparisons but only significant for T for TOTPAR at 4-8 h and for APAP for TOTPAR at 4-8 h and 0-8 h and for SPID and SPRID at 4-8 h ( $p \leq 0.044$ ). Both T and APAP were superior to PBO for all comparisons but these were only significant for T for SPID at 0-4 h, 4-8 h and 0-8 h and SPRID at 0-4 h and 0-8 h; and for APAP for TOTPAR at 0-4 h, SPID at 0-4 h and 0-8 h and SPRID at 0-4 h ( $p \leq 0.038$ ). There were no differences in treatment effects for subjects with moderate versus severe baseline pain intensity.

The cumulative number of subjects requiring re-medication each h post dose showed that more T (18%), APAP (14%) and PBO (16%) subjects required re-medication at some point during the study than T/A subjects (28%). The greatest differences were seen between T/A and T at 3-5 h and 8 h and between T/A and APAP at 5-8 h. Median time to re-medication was greater for T/A (260 min) than T (200 min), APAP (233 min) and PBO (139 min); but significantly greater only for T/A compared to PBO ( $p = 0.022$ ). Mean onset of pain relief was similar for T/A (19 min), T (18 min) and APAP (18 min) and all were quicker than for PBO (26 min). Median duration of pain relief was longer for T/A (260 min) than for T (200 min), APAP (233 min) and PBO (139 min). Fifty percent of T/A subjects rated their medication as 'very good' or 'excellent' compared to 34% of T, 46% of APAP and 22% of PBO subjects. Assessment of study medication was significantly greater for the T/A, T and APAP groups than for the PBO group ( $p \leq 0.024$ ).

***Primary source studies in chronic pain:***

***T with APAP in the pain of osteoarthritis of the hip or knee (T-A-008);***

***T with APAP in low back pain of non-malignant origin (RWJ-26898-006-AQ-22) (T-A-009);***

***Evaluation of the relative potency and safety of T with APAP (RWJ-26898-002-AQ-22) compared to APAP with COD in chronic pain of benign origin: DB phase (T-A-006);***

***Evaluation of the relative potency and safety of T with APAP (RWJ-26898-002-AQ-22) compared to APAP with COD in chronic pain of benign origin: OL phase (T-A-006);***

***Evaluation of the safety and efficacy of T/A in subjects with chronic pain of benign origin (T-A-015)***

These were 4 multi centre multiple dose, Phase III studies.

T-A-008, T-A-009 and T-A-006 were 3 randomised, DB, parallel group, active controlled studies to evaluate relative potency and safety of T/A compared to IBU (T-A-008, T-A-009) or A/COD (T-A-006). T-A-008 and T-A-009 also provided information on the average dosing requirements of such treatment in male and female subjects with moderate to severe pain.

In T-A-008 and T-A-009, 244 patients with pain from osteoarthritis of the hip or knee and 302 patients with low back pain of benign origin who were on a stable daily dose of oral pain medication, entered a 1 week run-in phase during which all analgesics were discontinued and OL T/A 37.5/325 mg was titrated prn for pain (x1-2 four times a day (qid)), before patients who tolerated OL T/A then randomly received T/A 37.5/325 mg or IBU 200 mg, (x1-2 q4h-q6h, maximum [max] of 10/day [8/day if >75 years]) for 56 days. Supplementary analgesia was available if required (containing PBO [for T/A treatment group] or IBU 200 mg [for IBU treatment group], x1 prn, max of 6/day).

In T-A-006, 462 patients with chronic pain of benign origin randomly received T/A 37.5/325 mg or A/COD 300/30 mg, (x1-2 q4h-q6h, max of 10/day [8/day if >75 years]) for 4 weeks. Supplementary analgesia was available if required (IBU 400 mg q4h-q6h prn).

T-A-006-OL and T-A-015 were 2 OL studies evaluating safety and efficacy of long term use of T/A in male and female patients with chronic pain of benign origin. T-A-006-OL included 311 subjects who had completed DB treatment with T/A 37.5/325 mg or A/COD 300/30 mg for 1 month. T-A-015 included 369 subjects who received OL T/A 37.5/325 mg (x1-3 q4h-q6h prn for pain, max of 10/day [8/day if >75 years]), for 23 months and 6 months, respectively. Supplementary analgesia was allowed (IBU in T-A-006-OL, Motrin IB in T-A-015). In T-A-006-OL, analysis of T/A exposed subjects also included subjects in the T/A group who discontinued during the DB phase of the trial (61 subjects) and subjects who completed the DB phase of the trial but did not continue into the OL phase of the trial (31 subjects; total 403 subjects).

For T-A-008, T-A-009 and T-A-006, the three primary summary efficacy variables determined for the interval 0-6 h were TOTPAR, SPID and SPRID. Further efficacy variables common to all the studies were: subject's assessment of medication after each 6 h evaluation period; subject's and investigator's overall assessment of the study drug; daily dosage of the study drug; and use of supplemental medication. Other efficacy variables were relative potency of number of tablets of T/A to number of capsules of active treatment in T-A-008, T-A-009 and T-A-006; the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Questionnaire in T-A-008; the Roland Disability Questionnaire (RDQ index) in T-A-009; and max pain relief in T-A-006. Safety was assessed through AEs during each trial.

#### *T-A-008*

Three hundred thirteen patients were enrolled in the OL phase; 69 discontinued and 244 were randomised to DB treatment (119 T/A, 125 IBU). Fifty-seven patients discontinued prematurely (28 T/A, 19 IBU); 32 due to AEs (17 T/A, 15 IBU). Some 197 completed the study (91 T/A, 106 IBU). The treatment groups were comparable for baseline demographics and characteristics: the majority of patients were female (58-61%); White (86-87%) and the mean age was 62.2 years (range 41-85 years) for T/A and 64.1 years (range 35-89 years) for IBU. Baseline pain was mild for 2-3%, moderate for 65-67% and severe for 30-34% of the subjects. The knee joint was affected in 76-78% of subjects and the hip joint was affected in 22-24% of subjects.

Hourly mean pain assessment scores (PAR, PID, PRID) were similar for T/A and IBU. With respect to TOTPAR, SPID and SPRID data and statistical comparisons for the 6 h interval of each measurement day; the pain relief provided by T/A was similar to that provided by IBU and appeared to be consistent throughout the 56 days as measured by TOTPAR, SPID and SPRID.

Average scores on the WOMAC Osteoarthritis Questionnaire were similar for T/A and IBU throughout the study with a statistically significant difference between the two groups seen only on Day 15; 53-83% T/A and 53-77% patients reported osteoarthritis (pain, stiffness, physical function and overall) as 'better' during the study (Days 1, 15, 29, 57, Final Visit). The percentage of subject's assessing study medication as 'very good' or 'excellent' was similar for T/A (Day -7: 16%; Day 2: 10%; Day 14: 17%; Day 28: 23%; Day 56: 20%) and IBU (Day -7: 14%; Day 2: 8%; Day 14: 19%; Day 28: 23%; Day 56: 28%) throughout the study. Subject's and investigator's overall assessment of study medication were similar for both T/A (both 2.7) and IBU (both 2.9). During the DB period, the average daily dose of T taken was 175.8 mg (range 26-305 mg), the average daily dose of APAP taken was 1523.9 mg (range 228-2646 mg); and the average daily dose of IBU taken was 1138.5 mg (range 200-2739 mg). During the DB phase, the number of T/A tablets taken daily (4.4-4.9) and the number of IBU capsules taken daily (5.0-6.3) remained constant suggesting patients did not build tolerance to either treatment. The proportion of patients taking supplemental medication also remained constant during the study for T/A (40-49%) and IBU (50-55%).



*T-A-009*

Three hundred ninety-five patients enrolled in the OL phase; 93 discontinued and 302 were randomised to DB treatment (151 T/A, 151 IBU). Seventy-three patients discontinued prematurely (36 T/A, 37 IBU), 44 due to AEs (22 T/A, 22 IBU). Some 229 subjects completed the study (115 T/A, 114 IBU). The treatment groups were comparable for baseline demographics and characteristics: 48-53% male, 52-56% female; 87-90% White, 4-5% Black, 0-1% Asian; 6-7% Other; with a mean age 55.0 years (range 20-86 years) for T/A and 54.7 years (range 25-83 years) for IBU. Baseline pain was mild for 3%, moderate for 67-72% and severe for 25-30% of subjects.

Hourly mean pain assessment scores (PAR, PID, PRID) were similar although numerically greater for T/A compared to IBU. With respect to TOTPAR, SPID and SPRID data and statistical comparisons for the 6 h interval of each evaluation day; the pain relief provided by T/A was similar to that provided by IBU as measured by SPID and SPRID, and appeared to be greater with T/A than with IBU as measured by TOTPAR throughout the 56 days.

The proportion of patients showing an improvement from baseline on the RDQ index was comparable for the two treatment groups at each visit. The percentage of subject's assessing study medication as 'very good' or 'excellent' was similar for T/A (Day -7: 18%; Day 2: 19%; Day 14: 26%; Day 28: 22%; Day 56: 29%) and IBU (Day -7: 25%; Day 2: 17%; Day 14: 21%; Day 28: 20%; Day 56: 23%) throughout the study. Subject's and investigator's overall assessment of study medication were similar for both T/A (3.0 and 3.1, respectively) and IBU (both 2.8). During the DB period, the average daily dose of T taken was 176.2 mg (range 33-328 mg), the average daily dose of APAP taken was 1527.3 mg (range 284-2844 mg); and the average daily dose of IBU taken was 1084.4 mg (range 117-2986 mg). During the DB phase, the number of T/A tablets taken daily (4.3-5.1) and the number of IBU capsules taken daily (4.8-5.7) remained constant suggesting patients did not build tolerance to either treatment. The proportion of patients taking supplemental medication also remained constant during the study for T/A (45-55%) and IBU (51-59%).

*T-A-006*

Four hundred sixty-two patients enrolled and were randomised to DB treatment (309 T/A, 153 A/COD). Ninety-three patients discontinued prematurely (61 T/A, 32 A/COD), 58 due to AEs (37 T/A, 21 A/COD). Some 369 subjects completed the study (248 T/A, 121 A/COD). The treatment groups were comparable for baseline demographics and characteristics: the majority of patients were female (62%) and White (87%); and had mean age of 57.6 years (range 22-91 years). Patients had low back pain (24%), osteoarthritis (35%) or both (41%); and the joints involved with osteoarthritis were closely comparable for both groups. Baseline pain was mild for 21%, moderate for 56-60% and severe for 16-21% of subjects.

Hourly mean pain assessment scores (PAR, PID, PRID) were similar for T/A and A/COD. With respect to TOTPAR, SPID and SPRID data and comparisons for the 6 h interval of each evaluation day; the pain relief provided by T/A was similar to that provided by A/COD.

On Day 1, 41% of T/A and 46% of A/COD subjects rated their max pain relief at the end of 6 h as 'a lot' or 'complete'; degree of relief was very comparable for the two treatment groups throughout the duration of the study. On Day 1, 22% of subjects assessed T/A as 'very good' or 'excellent' compared to 20% of A/COD subjects; assessment of study medication was very comparable for the two treatment groups throughout the duration of the study. At the end of the study, the subject's and the investigator's assessments of T/A and A/COD were very comparable. For the T/A group, the average daily dose of T was 131 mg (range 3-365 mg) and the average daily dose of APAP was 1133 mg (range 38-3160 mg); while for the A/COD group the average daily dose of COD was 105 mg (range 9-253



mg) and the average daily dose of APAP was 1054 mg (range 86-2534 mg). When analysed for gender, males took slightly more medication than females in both treatment groups. The mean number of tablets and capsules taken each week of the study and overall was very comparable for the two treatment groups. The proportion of patients taking supplemental medication was consistent throughout the study, suggesting that tolerance did not develop to either medication. Similar potency was shown between both treatments throughout the duration of the study in terms of average number of tablets and capsules taken per day throughout the trial (3.5 for both groups) and in terms of max tablets and capsules taken per day throughout the trial (14 T/A, 12 A/COD).

#### *T-A-006-OL*

Of the 462 patients enrolled and randomised to DB treatment (309 T/A, 153 A/COD), 311 continued into the OL extension phase (217 T/A, 94 A/COD). The 92 patients from the T/A group who did not continue were included in analyses due to their exposure to T/A (309 T/A, 94 A/COD). Two hundred forty-nine patients discontinued prematurely (188 T/A, 61 A/COD), 97 due to AEs (75 T/A, 22 A/COD) and 94 due to the subject's choice (70 T/A, 24 A/COD). Some 154 subjects completed the study (121 T/A, 33 A/COD). Data from 311 subjects in the OL extension phase of the study and 92 from the T/A treatment group from the DB phase of the study were analysed for this report. The majority of patients were female (62%) and White (88%); and had a mean age 57.5 years (range 22-91 years). Patients had low back pain (26%), osteoarthritis (36%) or both (38%). Baseline pain was mild for 21%, moderate for 60% and severe for 17% of subjects.

The mean max pain relief recorded during the period 0-6 h Day 1 of each week ranged from 2.2 to 2.7 (scale 0 [no relief] – 4 [complete relief]) over the 85 weeks of the study, compared to a pre dose mean max pain relief ranging from 1.8-2.1. Subject's assessment of study medication at end of 0-6 h Day 1 of each week ranged from 2.9 to 3.7 (scale 1 [poor] – 5 [excellent]) over the 85 weeks of the study; the mean score tended to increase from 2.9 at Week 1 to 3.4 at Week 13 and then generally remained between 3.3 and 3.6 until Week 85 (the sponsor suggested a possible explanations for the increase in score: subjects remaining in the study had good pain relief with the medication; or average daily dose of medication plateaued; or subjects found an appropriate dose to relieve their pain). Thirty-nine percent of subjects rated the study medication as 'very good' or 'excellent'; both subjects and investigators gave the study medication an assessment score of 3.1 (a good medication would be expected to score a 3.0 or above).

The average daily dose of T was 157 mg (range 0-376 mg) while the average daily dose of APAP was 1363 mg (range 0-3262 mg). The mean number of tablets of T/A taken during the study was 4.2 tablets daily (157.3 mg T, 1363.4 mg APAP); from Weeks 1-9 the range was from 3.2-4.8 and from Weeks 13-97 the range was from 4.9-5.2. The relatively constant mean number of tablets throughout the study suggested subjects did not build up a tolerance to T/A. The mean max number of T/A tablets taken during the study was 6.7 tablets daily; from Weeks 1-5 the range was from 4.3-5.6 tablets and from Weeks 9-97 it was from 5.7-6.1 tablets. Half the subjects (49%) took more than 8 tablets a day at least once during the study.

Thus, 1-3 T/A tablets q4h-q6h was effective in controlling chronic, non-malignant pain up to 27 months without development of tolerance.

*T-A-015*

This was a multi centre, OL, Phase III, study evaluating the safety and efficacy of T/A 37.5/325 mg and to meet the EU guideline of 300 subjects with six months drug exposure. Some 369 male and female patients with chronic pain of benign origin received OL T/A 37.5/325 mg, x1-3 tablets q4h-q6h prn for pain (max of 10/day [8/day if >75 years]) for 6 months. If their analgesia was insufficient patients could supplement with Motrin IB (max 6/day).

Efficacy evaluations included: subject's assessment of study medication, subject's and investigator's overall assessment of study drug, daily dosage of study drug and use of supplemental analgesia. Safety was assessed through AEs occurring during the trial.

Of the 369 patients enrolled in the OL study, 178 discontinued prematurely (98 due to AEs, 36 due to lack of efficacy and 26 due to subject choice). Some 191 subjects completed the study. Of the 369 patients, 133 were male and 236 female; 336 were White, 19 Black and 14 Other; and mean age was 58.4 years (range 20-90 years). Eighty-seven patients had low back pain (24%), 116 had osteoarthritis (31%) and 166 had both (45%).

Thee approximately monthly subject's assessment of study medication ranged from 3.2 to 3.8 (scale 1 [poor] – 5 [excellent]) over the 6 months of the study. Both subjects and investigators gave the study medication an average assessment score of 3.2 (a good medication would be expected to score a 3.0 or above). The average daily dose of T was 173 mg (range 9-447 mg); the average daily dose of APAP was 1503 mg (range 75-3877 mg); and the average daily dose of supplemental Motrin was 194 mg (range 0-3800 mg). The overall mean number of tablets of T/A taken during the study was 4.6 tablets daily; and the mean number rose over time (Month 1: 4.0; Month 2: 4.8; Month 3: 5.1; Month 4-6: 5.4) although the median number remained fairly constant (Month 1: 4; Month 2: 4; Month 3: 5; Month 4-6: 5; Overall: 4). The mean number of tablets of Motrin taken during the study was 1.0 tablet daily.

Thus, 1-3 T/A tablets q4h-q6h was effective in controlling chronic, non-malignant pain up to 6 months without development of tolerance.

***Studies post-2001 in moderate to severe acute pain:***

***A comparison of the analgesic efficacy of Ultracet (T/A) versus HYD/A versus PBO for the treatment of pain following oral surgery (C-128);***

***A comparison of the efficacy and safety of Ultracet (T/A) versus Ultram (T) versus PBO in subjects with pain following oral surgery (C-241);***

***A comparison of the efficacy and safety of T/A versus PBO in subjects with acute musculoskeletal pain (C-216); A comparison of the analgesic efficacy and safety of T/A versus PBO for the treatment of a painful flare of osteoarthritis (C-105)***

*CAPSS-128*

This was a single centre, randomised, DB, parallel group, active and PBO controlled, Phase III study in 200 male and female patients with pain from an oral surgical procedure who randomly received one of four single dose treatments (T/A 37.5/325 mg, T/A 75/650 mg, HYD/A 10/650 mg, PBO). Subjects could receive a supplemental analgesic during the study.

*Methods**Objectives*

The objective of this study was to demonstrate the analgesic efficacy of Ultracet (T/A) for the treatment of pain following an oral surgical procedure.

### *Study Participants*

The study was conducted in 1 centre in the USA. Inclusion criteria were male or female (non pregnant, using adequate contraception) subjects, 16-75 years old, with at least moderate pain (PVA $\geq$ 50mm) within 5 h following an oral surgical procedure (extraction of 2 ipsilateral, or >2, impacted third molars;  $\geq$ 2 requiring bone removal) and appropriate pain management with an oral analgesic. Patients were excluded if they had a significant unstable medical disease, significantly abnormal renal or hepatic function or any condition that might affect absorption, distribution, metabolism or excretion (ADME) of the test medications or safety for the subject; or had received any analgesic within 24 h prior (other than short acting pre or intra operative anaesthetic agents) or after completion of the oral surgical procedure, or had received a long-acting NSAID within 3 days of the study.

### *Treatments*

After screening, subjects were randomised to receive a single oral dose of T/A 37.5/325 mg, T/A 75/650 mg, HYD/A 10/650 mg or PBO. Subjects were encouraged but not required to wait at least an h after dosing if there was no analgesic response or to wait till pain level returned to baseline if there was an analgesic response, for supplemental analgesic medication which could be requested at any time during the 8 h observation period.

### *Variables/outcomes*

The three primary efficacy variables were TOTPAR, SPID and SPRID, which were determined for the intervals 0-4 h, 4-8 h and 0-8 h.

Secondary efficacy variables were:

- PAR, PID
- duration of pain relief
- time to onset of perceptible pain relief
- time to onset of meaningful pain relief
- rate of re-medication with supplemental analgesic medication
- time to re-medication with supplemental analgesic medication
- overall medication assessment

Safety was assessed through AEs during the trial, vital signs, medical history and physical examination.

### *Sample size*

The sample size was based on FDA analgesic guidelines.

### *Randomisation*

Computer generated randomisation lists were used with 1:1:1:1 ratios for the four treatments, in blocks of 8.

### *Blinding (masking)*

Patients received the DB medication as a single dose of four tablets. Blinding was achieved using matching PBO tablets. Individual treatment assignments were concealed on tear-off labels from the trial medication which were attached to the subjects case report forms and could be unblinded in an emergency.

### *Statistical methods*

Primary analysis was an analysis of co variance (ANCOVA) with baseline pain intensity as covariate and treatment as a qualitative independent factor. A Tamhane, Hochberg and Dunnett step-down multiple testing procedure was performed on the derived summary primary efficacy variable, TOTPAR, to compare the two T/A groups to the PBO group. Model sensitivity was considered established if either the T/A 75/650 mg or HYD/A 10/650 mg groups separated significantly ( $p \leq 0.05$ ) from the PBO group in terms of TOTPAR for the 0-8 h interval. A dose response analysis of PBO, T/A 37.5/325 mg and T/A 75/650 mg was conducted using Jonckheere-Terpstra non parametric ordered regression methodology.

Secondary endpoints were analysed using Kaplan-Meier estimate, logistic regression analysis, bi-variate analysis using Wei, Lin, Weissfeld marginal distribution method or Wilcoxon rank-sum test.

### *Results*

#### *Participant flow*

Subjects were considered to have completed the study if they:

- completed the 8 h observation period without using supplemental analgesia
- had no analgesic response to study medication but completed  $\geq 1$  h of the 8 h observation period without using supplemental analgesia
- had an analgesic response to study medication, completed  $\geq 1$  h of the 8 h observation period and waited till pain intensity returned to baseline level before taking supplemental analgesic medication

Two hundred patients enrolled (50 per treatment group); 15 subjects (8%; 3 [6%] T/A 75/650 mg, 5 [10%] T/A 37.5/325 mg, 4 [8%] HYD/A, 3 [6%] PBO) had an analgesic response but took supplemental medication before their pain intensity returned to baseline and were considered discontinued from the study. Some 185 subjects completed the study (93%). Of those completing the study, 160 (80%) had no analgesic response and took supplemental medication (36 [72%] T/A 75/650 mg, 42 [84%] T/A 37.5/325 mg, 38 [76%] HYD/A, 44 [88%] PBO), and 25 (13%) completed the 8 h study without using supplemental analgesia (11 [22%] T/A 75/650 mg, 3 [6%] T/A 37.5/325 mg, 8 [16%] HYD/A, 3 [6%] PBO).

#### *Recruitment*

CAPSS-128 was conducted from 25 August 2000 to 30 October 2000.

#### *Conduct of the study*

The study and statistical analysis were conducted as planned.

#### *Baseline data*

The treatment groups were generally comparable for baseline demographics and characteristics: 38-50% male, 50-62% female; 76-92% White, 4-14% Black, 2-10% Asian; with a mean age of 21.0-22.0 years (range 16-38 years). The mean PVA baseline score was similar across the groups (63.9-64.6 mm); but baseline pain intensity showed greater variation with 78-92% patients reporting moderate and 8-22% patients reporting severe baseline pain intensity (Table 13).

**Table 13. Baseline PVA score and baseline pain, CAPSS-128**

		T/A 75/650	T/A 37.5/325	HYD/A 10/650	PBO	Total
<b>N</b>		50	50	50	50	200
<b>Baseline PVA (mm)</b>	<b>Mean±SD</b>	63.9±9.06	64.7±11.13	64.6±10.24	64.3±11.62	64.4±10.48
	<b>Range</b>	50-85	51-96	51-93	51-100	50-100
<b>Baseline Pain Intensity (n [%])</b>	<b>Moderate</b>	44 (88.0)	39 (78.0)	46 (92.0)	46 (92.0)	175 (87.5)
	<b>Severe</b>	6 (12.0)	11 (22.0)	4 (8.0)	4 (8.0)	25 (12.5)

*Numbers analysed*

All 200 subjects were analysed for efficacy and safety.

*Results for Primary Efficacy Outcome*

With respect to TOTPAR, SPID and SPRID data and comparisons for the 0-4 h, 4-8 h and 0-8 h intervals; T/A 75/650 mg and HYD/A 10/650 mg were both statistically superior to PBO for all variables for all time intervals; whilst T/A 37.5/325 mg was statistically superior to PBO for TOTPAR and SPRID only for the 0-4 h interval. The pain relief provided by T/A 75/650 mg was similar to that provided by HYD/A 10/650 mg, with no significant differences for any comparisons. A statistically significant dose response was seen for PBO, T/A 37.5/325 mg and T/A 75/650 mg for the three primary efficacy variables at all 3 time intervals.

*Results for Other Efficacy Outcomes*

Median time to onset of perceptible pain relief was similar for T/A 75/650 mg (34.0 min) and T/A 37.5/325 mg (33.3 min), both slower than for HYD/A (25.4min); whilst the median time to onset of meaningful pain relief was quicker for HYD/A (63.8 min) than for T/A 75/650 mg (113.9 min).

Perceptible pain relief was not experienced for over half the subjects in the PBO group; and meaningful pain relief was not attained for over half the subjects in the T/A 37.5/325 mg and PBO groups.

Duration of pain relief was not significantly different for T/A 75/650 and HYD/A and was significantly longer for both treatments when compared to PBO.

More T/A 37.5/325 mg and PBO patients (94%) needed supplemental medication compared to T/A 75/650 mg and HYD/A patients (78-84%); and the time to supplemental medication was significantly longer for T/A 75/650 mg, T/A 37.5/325 mg and HYD/A compared to PBO.

Subject's overall assessment of study medication was greater for all active treatments over PBO.

**CAPSS-241**

This was a single centre, randomised, DB, parallel group, active and PBO controlled, Phase IV study in 456 male and female patients with pain from an oral surgical procedure who randomly received one of three single-dose treatments (T/A 75/650 mg, T 100 mg, PBO). Subjects could receive a supplemental analgesic during the study.

## *Methods*

### *Objectives*

The objective of this study was to establish that Ultracet (T/A) is superior to Ultram (T) in analgesic efficacy for the treatment of pain following oral surgery.

### *Study Participants*

The study was conducted at one centre in the USA. Inclusion criteria were male or female (non pregnant, using adequate contraception) subjects, 18-75 years old, with at least moderate pain (PVA>50 mm and at least moderate pain on Pain Intensity Scale) within 5 h following an oral surgical procedure (extraction of 2 ipsilateral, or >2, impacted third molars; ≥2 requiring bone removal) and appropriate for pain management with an oral analgesic. Patients were excluded if they had a significant and/or unstable medical disease, significantly abnormal renal or hepatic function; or any condition that might affect ADME of the test medications or cause safety issues for the subject; or had received any analgesic within 24 h prior (other than short acting pre or intra operative anaesthetic agents) or after completion of the oral surgical procedure, or had received a long acting NSAID within 3 days of the study.

### *Treatments*

After screening, subjects were randomised to receive a single oral dose of Ultracet (T/A 75/650 mg), Ultram (T 100 mg) or PBO. Subjects were encouraged but not required to wait at least 1 h after dosing if there was no analgesic response or to wait till pain level returned to baseline if there was an analgesic response, for supplemental analgesic medication which could be requested at any time during the 6 h observation period.

### *Efficacy Variables and Outcomes*

The three primary efficacy variables were TOTPAR, SPID and SPRID, which were determined for the intervals 0-3 h, 3-6 h and 0-6 h.

Secondary efficacy variables were:

- PID, PAR
- time to onset of perceptible pain relief
- time to onset of meaningful pain relief
- incidence of use of supplemental pain medication
- time to use of supplemental pain medication
- overall medication assessment

Safety was assessed through AEs during the trial and vital signs.

### *Sample size*

Based on previous studies, using two-sided significance 0.05 with 90% power, 150 subjects per treatment group would demonstrate statistically significant benefits of Ultracet (T/A) over Ultram (T) for TOTPAR, SPID and SPRID over 0-8 h, with standard deviation (SD) of approximately 6.21.

### *Randomisation*

Computer generated randomisation lists were used with 1:1:1 ratios for the three treatments, in blocks of 6.

### *Blinding (masking)*

Patients received DB medications in separate containers per subject as single doses of two capsules. Blinding was achieved using matching PBO capsules. Individual treatment assignments could be unblinded in an emergency by opening a sealed envelope.

### *Statistical methods*

Primary analysis was an ANCOVA with baseline pain intensity as covariate and treatment as a qualitative independent factor on the primary efficacy variables, TOTPAR, SPID and SPRID for the interval 0-6, comparing Ultracet (T/A) and Ultram (T). Model sensitivity was considered established if either the T/A or T groups separated significantly ( $p \leq 0.05$ ) from the PBO group in the analysis of the primary outcomes.

Secondary endpoints were analysed using pair wise t-test, Kaplan-Meier estimate, log-rank test, logistic regression analysis or Wilcoxon-Mann-Whitney test.

### *Results*

#### *Participant flow*

Subjects were considered to have completed the study if they:

- completed the 6 h observation period without using supplemental analgesia
- had no analgesic response to study medication but completed  $\geq 30$  min of the 6 h observation period without using supplemental analgesia
- had an analgesic response to study medication, completed  $\geq 30$  min of the 6 h observation period and waited till pain intensity returned to baseline level before taking supplemental analgesic medication

Four hundred fifty-six patients were enrolled and randomised to DB treatment (153 T/A, 152 T, 151 PBO); 13 subjects (3%; 8 [5%] T/A, 3 [2%] T, 2 [1%] PBO) had an analgesic response but took supplemental medication before their pain intensity returned to baseline and were considered discontinued from the study, 2 subjects discontinued due to an AE (0%; 1 [1%] T/A, 1 [1%] T); and 441 subjects completed the study (97%). Of those completing the study, 334 (73%) took supplemental medication (76 [50%] T/A, 124 [82%] T, 134 [89%] PBO) and 106 (23%) completed the 6 h study without using supplemental analgesia (68 [44%] T/A, 24 [16%] T, 14 [9%] PBO).

#### *Recruitment*

CAPSS-241 was conducted from 8 November 2002 to 7 February 2003.

#### *Conduct of the study*

The study was conducted as planned. Additional exploratory analyses were conducted that would not affect the study in any significant manner.

#### *Baseline data*

The treatment groups were comparable for baseline demographics and characteristics: 33-39% male, 61-67% female; 88-90% White, 3-4% Black, 5-7% Asian, 1% Other; with a mean age of 21.5-22.1 years (range 18-49 years). The mean PVA baseline score was 72.1-72.4 mm; and 66-72% patients had moderate and 28-34% had severe baseline pain intensity (Table 14).

**Table 14. Baseline PVA score and baseline pain intensity, CAPSS-241**

		T/A	T	PBO	Total
<b>N</b>		153	152	151	456
<b>Baseline PVA (mm)</b>	<b>Mean±SD</b>	72.1±11.76	72.2±11.62	72.4±11.08	72.2±11.47
	<b>Range</b>	52-100	50-99	51-98	50-100
<b>Baseline Pain Intensity (n [%])</b>	<b>Moderate</b>	110 (71.9)	100 (65.8)	103 (68.2)	313 (68.6)
	<b>Severe</b>	43 (28.1)	52 (34.2)	48 (31.8)	143 (31.4)

*Numbers analysed*

All 456 subjects were analysed for efficacy and safety.

*Outcomes and estimation**Primary Efficacy Outcome*

With respect to TOTPAR SPID, and SPRID data and comparisons for the 0-3 h, 3-6 h and 0-6 h intervals; the pain relief provided by T/A 37.5/325 mg was statistically superior to that provided by T 50 mg and PBO for all variables for all time intervals ( $p < 0.001$ ); and T 50 mg was superior to PBO but not statistically significantly so for any comparisons.

*Other Efficacy Outcomes*

For T/A 37.5/325 mg the median time to onset of perceptible pain relief was 37.6 min and median time to onset of meaningful pain relief was 126.5 min; perceptible and meaningful pain relief were not attained for over half the subjects in the T 50 mg or PBO groups.

Fewer T/A 37.5/325 mg subjects (55%) needed supplemental medication compared to T 50 mg and PBO subjects (84-90%); and time to supplemental medication was significantly longer for T/A 75/650 mg compared to both T 50 mg and PBO.

Subject's overall assessment of study medication was significantly greater for T/A 37.5/325 mg than for T and PBO ( $p < 0.001$ ).

**CAPSS-216**

This was a multi centre, inpatient/outpatient, randomised, DB, parallel group, active and PBO controlled, Phase IIIb study in 596 male and female patients with acute musculoskeletal pain who randomly received T/A 37.5/325 mg, HYD/A 7.5/650 mg or PBO, (first dose x2; then x1-2 qid prn, max of 8/day), for 6 days. Subjects requiring an antiemetic during the first 4 h of the study or supplemental analgesia at any time were discontinued from the study.

*Methods**Objectives*

The objective was to compare the analgesic efficacy and safety of T/A versus HYD/A versus PBO for the treatment of acute musculoskeletal pain from an ankle sprain with a partial ligament tear.

*Study Participants*

The study was conducted in 47 centres in the USA. Inclusion criteria were male or female (non pregnant, using adequate contraception) subjects, 18-75 years old with at least moderate pain (PVA  $\geq$  50 mm and at least moderate pain on Pain Intensity Scale) at



baseline and immediately prior to first dose of study medication due to an acute ankle sprain with partial ligament tear (with pain on ambulation, swelling, and possible ecchymosis). Patients were excluded if the ankle injury was of greater severity or they had significant other associated trauma; if they had a significantly unstable medical disease, significantly abnormal renal or hepatic function, or any condition that might affect ADME of the test medications or cause safety issues for the subject; received other prescription or non prescription, short or long acting, medications or physical therapy that might have analgesic properties prior to or during the study.

#### *Study Treatments*

After screening, subjects were randomised to receive a single dose of T/A 75/650 mg, HYD/A 7.5/650 mg or PBO. Standard care of the sprain was permitted (with the exception of cold therapy for 30 min prior to each pain or activity evaluation [hly for 4 h post first dose]). Supplemental analgesic medication could be requested at any time during the 4 h observation period after the first dose; however subjects were encouraged but not required to wait at least 1 h after the dose and if either supplemental analgesia or an anti-emetic were taken in that initial 4 h period, the patient was to be discontinued from the study. Patients discharged after the 4 h observation period were to take 1-2 capsules of study medication (T/A 37.5/325 mg-75/650 mg, HYD/A 7.5/650 mg, or PBO) up to 4 times a day for 5 days. Supplemental analgesic medication could be taken at any time upon which the subject would be discontinued from the study.

#### *Efficacy Variables and Outcomes*

The primary efficacy variable was TOTPAR over the interval 0-4 h on Day 1 after the first dose of study medication.

Secondary efficacy variables were:

- Pain Intensity and PAR ratings 0-4 h
- daily Pain Intensity and Pain Relief rating scales
- Pain Intensity Rating scale at Final Visit
- Pain Relief rating scale at Final Visit
- Activity Impairment Assessment at Baseline and Final Visit
- subject's overall medication assessment
- efficacy failures

Safety was assessed through AEs, vital signs and physical examinations.

#### *Sample size*

Based on previous studies, using two-sided significance 0.05 and assuming a SD of 6.0 units, 600 subjects (200 per treatment group) would detect a difference in TOTPAR of 2.0 units between T/A and PBO groups with 90% power.

#### *Randomisation*

Computer generated randomisation lists were used with 1:1:1 ratio for the three treatments, in blocks of 6.

#### *Blinding (masking)*

Patients received DB medications in blister cards of 4 doses per day (2 columns per dose, to be taken in order as required), sufficient for 6 days (+2 extra days). Blinding was achieved using matching PBO capsules. Individual treatment assignments were concealed

on tear-off labels from the trial medication which were then attached to the subjects case report forms and could be unblinded in an emergency.

### *Statistical methods*

Primary analysis was an analysis of co variance (ANCOVA) with baseline pain intensity as covariate and treatment and centre as qualitative independent factors, on TOTPAR for the initial interval 0-4 h, to compare T/A and PBO, and T/A and HYD/A. Model sensitivity was considered established if the HYD/A group separated significantly ( $p \leq 0.05$ ) from the PBO group in the analysis of TOTPAR for the initial 0-4 h interval.

Secondary endpoints were analysed using ANCOVA, time plots, logistic regression analysis, Cochran-Mantel-Haenszel Test, Kaplan-Meier estimate, log-rank test or Fisher Exact Test.

### *Results*

#### *Participant flow*

Six hundred and three patients were randomised to DB treatment (192 T/A, 204 HYD/A, 207 PBO); 80 (13%) discontinued prematurely (26 [14%] T/A, 24 [12%] HYD/A, 30 [15%] PBO); 35 (6%) due to lack of efficacy (10 [5%] T/A, 4 [2%] HYD/A, 21 [10%] PBO), 22 (4%) due to AEs (10 [5%] T/A, 9 [4%] HYD/A, 3 [1%] PBO), 10 (2%) were lost to follow up (2 [1%] T/A, 4 [2%] HYD/A, 4 [2%] PBO); and 523 (87%) completed the study (166 [87%] T/A, 180 [88%] HYD/A, 177 [86%] PBO).

#### *Recruitment*

CAPSS-216 was conducted from 16 January 2003 to 27 October 2004.

#### *Conduct of the study*

The most significant change made to the protocol was to change the comparison of mean TOTPAR values between the T/A and HYD/A groups from a secondary efficacy analysis to a primary efficacy analysis (in addition to the comparison between the T/A and PBO groups). This change and other changes made for reasons of clarity and consistency were made prior to any patients being enrolled (5 December 2002) and in the evaluator's opinion would not have significantly affected the conduct of the study.

Two further changes made on 18 July 2003 after patients had been enrolled increased the time from ankle sprain to the first study related procedure from 24 to 48 h as an inclusion criterion and decreased the time for IBU use from 12 h to 6 h as an exclusion criterion. In the evaluator's opinion it would not be uncommon for someone with an ankle sprain to take a mild analgesic such as IBU and wait until the next day before deciding their ankle sprain was serious enough to warrant an X-ray and so these changes would increase the rate of enrolment in the study. The evaluator considers that the acute pain from a severe sprain experienced by a patient at 48 h is likely to be of an equally significant level as at 24 h and so these changes should not affect the study in any significant manner.

#### *Baseline data*

The treatment groups were generally comparable for baseline demographics and characteristics: 47-57% male, 43-53% female; 45-51% White, 32-38% Black, 1-3% Asian, 15-17% Other; with a mean age of 30.7-33.6 years (range 18-81 years). The injured ankle was the right for 53%; mean time from injury to first dose of study drug was 19.3 h and 19% subject had taken analgesic medication in the preceding 24 h. The mean PVA baseline score was 74.1-75.7 mm; and 37% had moderate activity impairment, 38% had severe activity impairment and 23% had complete activity impairment (Table 15).

*Numbers analysed*

Of the 603 randomised subjects, 601 were evaluable for intention-to-treat (ITT) efficacy, 596 were evaluable for modified ITT (mITT; ITT excluding patients who had an ankle X-ray after the 4 h observation period that showed more than a partial ligament tear) and 602 were evaluable for safety.

**Table 15. Baseline PVA score and baseline activity impairment, CAPSS-216**

		T/A	HYD/A	PBO	Total
<b>N</b>		190	201	205	596
<b>Baseline PVA (mm)</b>	<b>Mean±SD</b>	75.5±12.35	74.1±12.09	75.7±12.92	75.1±12.46
	<b>Range</b>	49.0-100.0	50.0-100.0	50.0-100.0	49.0-100.0
<b>Baseline Activity Impairment (n [%])</b>	<b>None</b>	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	<b>Mild</b>	4 (2.1)	3 (1.5)	3 (1.5)	10 (1.7)
	<b>Moderate</b>	67 (35.3)	77 (38.5)	77 (37.6)	221 (37.1)
	<b>Severe</b>	78 (41.1)	76 (38.0)	74 (36.1)	228 (38.3)
	<b>Complete</b>	41 (21.6)	44 (22.0)	51 (24.9)	136 (22.9)
	<b>Missing</b>	0	1	0	1

*Outcomes and estimation**Primary Efficacy Outcome*

The pain relief provided over 0-4 h by T/A and HYD/A were statistically significantly superior to that provided by PBO based on the TOTPAR score (6.6 and 6.8 versus 5.4, respectively;  $p < 0.001$ ); the difference between T/A and HYD/A in TOTPAR scores was not significant.

*Other Efficacy Outcomes*

The pain relief provided by T/A and HYD/A were statistically significantly better than that provided by PBO based on SPID (3.3 and 3.2 versus 2.7;  $p \leq 0.030$ ) and SPRID (9.9 and 10.0 versus 8.1;  $p \leq 0.001$ ) scores; and there were no significant differences between T/A and HYD/A.

Pain relief was statistically significantly greater with both T/A and HYD/A compared to PBO ( $p \leq 0.001$ ) but there was no significant difference between T/A and HYD/A for Pain Relief scores; and there were no significant differences between the 3 treatment groups for Pain Intensity scores.

There were no statistically significant differences between the 3 treatment groups for subject's final assessment of activity impairment.

More subjects rated study medication as 'good', 'very good' or 'excellent' with T/A (81%) and HYD/A (84%) than with PBO (69%).

There were significantly fewer efficacy failures with HYD/A (2.5%) than with PBO (11.2%); but the differences between HYD/A and T/A (6.3%), or T/A and PBO, were not significant.

## ***CAPSS-105***

This was a multi centre, outpatient, randomised, DB, parallel group, PBO controlled, Phase IIIb study to investigate analgesic efficacy and safety of T/A in 308 male and female patients with moderate or severe pain from a flare of osteoarthritis for 2-5 days and who were taking a stable daily dose of an NSAID or iCOX2 for  $\geq 30$  days, who randomly received T/A 37.5/325 mg (first dose x1 + x1 PBO), T/A 37.5/325 mg (first dose x2) or PBO (first dose x2), (first dose as stated, then x1-2 q4h-q6h, max 8/day) for 10 days in addition to the NSAID or iCOX2.

### *Methods*

#### *Objectives*

The objective was to investigate the analgesic efficacy and safety of T/A in the treatment of a painful flare of osteoarthritis.

#### *Study Participants*

The study was conducted in 30 centres in the USA. Inclusion criteria were male or female (non pregnant, using adequate contraception) subjects, 35-75 years old, with symptomatic osteoarthritis of the knee or hip  $\geq 1$  year (pain and osteophytes on X-ray taken in last year), who had been on a stable daily dose of an NSAID or iCOX2 for the past  $\geq 30$  days but had flare of osteoarthritis at the target joint 2-5 days prior to the study requiring additional relief (supplemental analgesic medication and/or increase in NSAID or iCOX2 dosage) and who had a PVA score  $\geq 50$  mm and at least moderate pain on a 4-point Pain Intensity Scale. Patients were excluded if they required imminent replacement of the target joint or had any other abnormality or disease that might affect the target joint; if they had a significant unstable medical disease, significantly abnormal renal and/or hepatic function or any condition that might affect ADME of the test medications or cause safety issues for the subject; or if they received physical therapy or other prescription or non prescription medications that might have analgesic properties, prior to or during the study.

#### *Study Treatments*

After screening, subjects were randomised to receive an initial dose of T/A 37.5/325 mg, T/A 75/650 mg or PBO, followed by T/A 37.5/325 mg (both T/A groups) or PBO (PBO group), x1-2 q4h-q6h, max 8/day, for 10 days in addition to their NSAID or iCOX2.

#### *Efficacy Variables and Outcomes*

The primary efficacy variables were the average daily Pain Intensity Scores (PIS) for Days 1-5 and the average daily Pain Relief scores for Days 1-5.

Secondary efficacy variables were:

- daily PIS and PAR scores
- PIS and PAR scores at Final Visit
- WOMAC Questionnaire scores
- physician/subject overall medication assessment scores at Final Visit
- discontinuation due to lack of efficacy.

Further efficacy measurements for the interval 0-4 h were:

- PID and PAR scores,
- TOTPAR, SPID, and SPRID.

Safety was assessed through AEs, physical examinations, vital signs and clinical laboratory tests.

#### *Sample size*

Based on previous studies, using two-sided significance 0.05 and assuming a SD of 5.0 units, 100 subjects per treatment group would detect a difference in TOTPAR score of 2.5 units between T/A and PBO groups, with >90% power.

#### *Randomisation*

Computer generated randomisation lists were used with 1:1:1 ratios for the three initial treatments, in blocks of 6.

#### *Blinding (masking)*

DB medications were supplied as a bottle of 2 tablets for the first dose and 2 bottles of 100 tablets for the remainder of the study. Blinding was achieved using matching PBO tablets. Individual treatment assignments were concealed on tear-off labels from the trial medication which were then attached to the subjects case report forms and could be unblinded in an emergency.

#### *Statistical methods*

Primary and secondary endpoints were analysed using ANCOVA models with baseline values as covariate and treatment and centre as qualitative factors, to compare T/A and PBO; Tamhane, Hochberg, and Dunnett step-down multiple testing procedure and time plots.

#### *Results*

##### *Participant flow*

Three hundred and eight patients enrolled and were randomised to DB treatment (102 T/A37.5/325, 95 T/A75/650, 111 PBO); 34 patients discontinued prematurely (11%; 12 [12%] T/A37.5/325, 16 [17%] T/A75/650, 6 [5%] PBO), 31 (10%) due to AEs (10 [10%] T/A37.5/325, 15 [16%] T/A75/650, 6 [5%] PBO) and 1 (0%) due to lack of efficacy (1 [1%] T/A37.5/325); and 274 (89%) completed the study (90 [88%] T/A37.5/325, 79 [83%] T/A75/650, 105 [95%] PBO).

##### *Recruitment*

CAPSS-105 was conducted from 6 December 1999 to 9 October 2000.

##### *Conduct of the study*

The study was conducted as planned; however, the analysis for lack of efficacy was not performed as only one patient discontinued for this reason.

##### *Baseline data*

There were some differences in baseline demographics and characteristics between the treatment groups but these were considered to be of no clinical relevance: 20-37% males, 63-80% females; 83-91% White, 8-17% Black, 0-1% Other; with a mean age 59.8-60.4 years (range 37-80 years). The target joint was the right knee for 34-47%, left knee for 30-45%, right hip for 5-19% and left hip for 4-14% of the subjects. The mean PVA baseline score was 72.6-73.8 mm; and 62% patients had moderate and 38% had severe baseline pain intensity (Table 16).

**Table 16. Baseline PVA score and baseline pain intensity, CAPSS-105**

		T/A			PBO	Total
		37.5/325	75/650	Combined		
<b>N</b>		102	95	197	111	308
<b>Baseline PVA (mm)</b>	<b>Mean±SD</b>	72.6±13.22	73.2±10.51	72.9±11.96	73.8±11.59	73.2±11.82
	<b>Range</b>	50.0, 99.0	50.0, 95.0	50.0, 99.0	45.5, 99.0	45.5, 99.0
<b>Baseline Pain Intensity n (%)</b>	<b>Moderate</b>	63 (61.8%)	59 (62.1%)	122 (61.9%)	69 (62.2%)	191 (62.0%)
	<b>Severe</b>	39 (38.2%)	36 (37.9%)	75 (38.1%)	42 (37.8%)	117 (38.0%)

*Numbers analysed*

All 308 subjects were analysed for ITT efficacy and safety.

*Outcomes and estimation**Primary Efficacy Outcome*

Pain Intensity scores at baseline were identical for T/A and PBO (2.4) and the average daily scores during Days 1-5 were significantly lower for T/A (1.39) than for PBO (1.66).

*Other Efficacy Outcomes*

The average Daily Pain Intensity scores were statistically significantly lower with T/A than with PBO during Days 1-5, during the OP Study Days and at the Final Visit.

The average Max Daily Pain Intensity scores were not statistically significantly different for T/A and PBO during Days 1-5, during the OP Study Days and at the Final Visit.

Average Daily Pain Relief scores were statistically significantly greater with T/A than with PBO during Days 1-5, during the OP Study Days and at the Final Visit.

For the interval 0-4 h the pain relief provided by T/A 75/650 mg was statistically significantly superior to that provided by PBO for SPID and SPRID ( $p \leq 0.037$ ) but not for T/A 37.5 mg compared to PBO; and not for TOTPAR for any comparisons of T/A to PBO.

The subject's and the investigator's overall assessment of study medication were similar for T/A (80-81% 'good' or 'very good') and PBO (56% 'good' or 'very good').

The WOMAC questionnaire scores were lower for T/A than for PBO; significantly so for Pain, Physical Function and Overall ( $p \leq 0.013$ ). One T/A 37.5/325 mg subject discontinued due to lack of efficacy on Day 1.

***Studies post-2001 in moderate to severe chronic pain:******A comparison of the analgesic efficacy and safety of T/A versus PBO for the treatment of the signs and symptoms of osteoarthritis in subjects receiving an iCOX2 (C-114)******CAPSS-114***

This was a multi centre, outpatient, randomised, DB, parallel group, PBO controlled, Phase III study in 306 male and female patients with symptomatic osteoarthritis who had been on a stable dose of an iCOX2 for  $\geq 2$  weeks and required additional pain relief and who in addition to the iCOX2 randomly received T/A 37.5/325 mg or PBO (titrated over 10 days to x1 qid or max tolerated; then x1-2 qid prn, min 2/day, max 8/day) for 91days.

## Methods

### Objectives

The objective of this study was to demonstrate the analgesic efficacy and safety of T/A 37.5/325 mg in the treatment of the pain of osteoarthritis in subjects receiving an iCOX2.

### Study Participants

The study was conducted in 28 centres in the USA. Inclusion criteria were male or female (non pregnant, using adequate contraception) subjects, 40-75 years old, with symptomatic osteoarthritis of the knee or hip for  $\geq 1$  year (pain and osteophytes on X-ray taken in last 2 years), who had been on a stable daily dose of an iCOX2 for  $\geq 2$  weeks but required additional relief from their osteoarthritis pain and who had a PVA score  $\geq 50$  mm at Visit 2. Patients were excluded if they required imminent replacement of the target joint or had had any other abnormality or disease that might affect the target joint; if they had a significantly unstable medical disease, significantly abnormal renal or hepatic function or any condition that might affect ADME of the test medications or that might cause safety issues for the subject; or received physical therapy or other prescription or non prescription medications that might have analgesic properties, prior to or during the study.

### Treatments

After screening and washout of any medication other than study drugs that might provide analgesia for up to 21 days, subjects were randomised to receive T/A 37.5/325 mg or PBO, for 91 days (titrated over 10 days to x1 qid, then 1-2 qid, max x8 per day, min x2 per day after Day 14), in addition to their iCOX2.

### Efficacy Variables and Outcomes

The primary efficacy variable was the Final PVA score; measured at each visit; (a 100 mm scale, 0 mm = no pain, 100 mm = extreme pain).

Secondary efficacy variables were:

- the WOMAC Osteoarthritis questionnaire; measured at each visit; a rating of pain, stiffness and physical function
- the pain relief rating (PRR) scale, measured at each visit from Visit 3; amount of pain relief relative to no medication
- the SF-36 Health Survey<sup>43</sup> scores; measured at Visit 2 and Final Visit; a 36-item survey to evaluate subject's physical, social and mental well-being
- investigator and subject overall assessments of the study medication; measured at Final Visit; rating of how study medication controlled subject's pain due to osteoarthritis, (-2 = very poor, 2 = very good)
- percentage of subjects who discontinued early from the study due to lack of efficacy

---

<sup>43</sup> The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

Safety was assessed through treatment emergent AEs (TEAEs) at each visit, vital signs, medical history, physical examination and laboratory tests.

#### *Sample size*

Using two-sided significance 0.05 and a SD of 30 mm, 143 subjects per treatment group (total 300 subjects) would detect a mean difference of 10 mm on the PVA scale between T/A and PBO groups with 80% power.

#### *Randomisation*

Computer generated randomisation lists were used with a 1:1 ratio for the two treatments, in blocks of 4.

#### *Blinding (masking)*

DB medications were supplied as bottles of 100 tablets at Visits 2, 3, 4, and 5. Blinding was achieved using matching PBO tablets. Individual treatment assignments were concealed on tear-off labels from the trial medication which were then attached to the subjects case report forms and could be unblinded in an emergency.

#### *Statistical methods*

Primary analysis was an ANCOVA of final PVA score with baseline score as covariate and treatment and centre as qualitative factors, to compare T/A and PBO.

Secondary endpoints were analysed using ANCOVA, Cox proportional hazards regression analysis, Kaplan-Meier estimate, log-rank test and logistic regression analysis.

### **Results**

#### *Participant flow*

Three hundred and seven patients enrolled and were randomised to DB treatment (153 T/A, 154 PBO). Eighty patients discontinued prematurely (26%; 41 [27%] T/A, 39 [25%] PBO), 39 due to insufficient pain relief (13%; 13 [9%] T/A, 26 [17%] PBO), 26 due to AEs (9%; 20 [13%] T/A, 6 [4%] PBO); and 227 (74%) completed the study (112 [73%] T/A, 115 [75%] PBO).

#### *Recruitment*

CAPSS-114 was conducted from 29 September 1999 to 12 October 2000.

#### *Conduct of the study*

Changes made to the protocol to allow for pharmacokinetic measurements would not in the evaluator's opinion have affected the study in any significant manner.

#### *Baseline data*

The treatment groups were comparable for baseline demographics and characteristics: 29-35% male, 65-71% female; 85-87% White, 12-14% Black, 1% Asian; with mean age of 60.1 years (range 36-80 years) for T/A and 61.8 years (range 35-77 years) for PBO. The target joint was right knee for 45% T/A, 40% PBO; left knee for 37% T/A, 33% PBO; right hip for 8% T/A, 17% PBO; and left hip for 11% T/A, 10% PBO. The mean PVA scores (primary efficacy variable) at baseline were similar for both groups (Table 17).



**Table 17. Baseline PVA score, CAPSS-114**

		T/A	PBO
<b>N</b>		153	153
<b>Baseline PVA (mm)</b>	Mean±SD	69.0±12.52	69.5±13.17
	Range	48-99	3-99

*Numbers analysed*

Of the 307 patients randomised, 306 subjects were evaluable for ITT efficacy and 306 patients were evaluable for safety.

*Outcomes and estimation**Primary Efficacy Outcome*

The mean PVA scores at the Final Visit were significantly lower for T/A (41.5 mm) than for PBO (48.3 mm;  $p=0.025$ ).

*Other Efficacy Outcomes*

Mean final PRR scores were significantly greater for T/A than for PBO groups (2.0 and 1.6, respectively;  $p=0.002$ ); more T/A subjects (42%) than PBO subjects 27% reported their final pain relief as 'complete' or 'a lot'.

WOMAC questionnaire scores were lower for T/A than for PBO but only significantly so for physical function (3.9 T/A, 4.5 PBO,  $p=0.049$ ).

Every subscale on the SF-36 Health Survey except General Health showed greater improvement for T/A compared to PBO by the Final Visit and the mean change was significant for the sub-scale of Role-physical ( $p=0.010$ ).

More T/A subjects reported an overall assessment of 'good' or 'very good' (68%) than PBO subjects (54%) and more investigators gave an overall assessment of T/A as 'good' or 'very good' (71%) compared to PBO (54%).

The incidence of efficacy failures was significantly lower for T/A than for PBO (9% versus 17%;  $p=0.029$ ); a lower discontinuation rate for T/A compared to PBO was obvious from Day 28 and the difference was significant for Day 84 ( $p=0.016$ ).

***Further studies in acute pain:***

***A comparison of the analgesic efficacy of Ultracet (T/A) versus A/COD versus PBO for the treatment of post-surgical pain (C-115);***

***A comparison of patient satisfaction with the association T (37.5 mg) plus APAP (325 mg) versus T (50 mg) for the treatment of subacute low back pain (GRTF-ZAL1);***

***A randomised, multi-centre, DB, double-dummy, parallel-group clinical study assessing the effectiveness and tolerability of oral T/A 37.5/325 mg compared with T 50 mg in day-care hand-surgery patients (ZAL-06)***

These were 3 additional randomised, DB, parallel group, Phase IIIb (C-115, GRTF-ZAL1) or IIIb/IV (ZAL-06) studies.

C-115, GRTF-ZAL1 and ZAL-06, were multi centre studies in male and female patients with pain from various models:

C-115 was an active and PBO controlled study to demonstrate the analgesic efficacy of Ultracet (T/A) in 305 patients with orthopaedic or abdominal post-surgical pain, who

randomly (with stratification according to procedure: orthopaedic/abdominal) received T/A 37.5/325 mg, A/COD 300/30 mg or PBO, (first dose: x2, then x1-2 qid prn, max 8/day) for 6 days; subjects requiring an antiemetic during the first 4 h of the study or supplemental analgesia at any time were to be discontinued.

GRTF-ZAL1 was an OP study to compare patient satisfaction of T/A versus T in 117 patients with subacute low back pain who randomly received T/A 37.5/325 mg or T 50 mg, (titrated from x1 qid Day 1 to x2 qid Day 5, then x2 qid) for 10 days; dose reduction was not permitted.

ZAL-06 compared effectiveness and tolerability of T/A and T in 261 patients with post operative pain from hand surgery who randomly received T/A 37.5/325 mg or T 50 mg (pre operative dose: x1; post operative dose in recovery: x1; then at home: x1 q6h [+x1 30min after each dose prn], max 8/day), for 2 days.

The primary efficacy variables were Pain Intensity and Pain Relief scores for the interval 0-4 h for C-115; and patient satisfaction with treatment for GRTF-ZAL1 and ZAL-06. Further efficacy variables common to all three studies were: measures of Pain Intensity and Pain Relief and efficacy failures/premature termination due to lack of efficacy. Additional efficacy endpoints involved an overall medication assessment (C-115, GRTF-ZAL1), the amount of medication taken daily (GRTF-ZAL1) and any re-medication/use of supplemental analgesic medications and anti-emetic medications (ZAL-06). For all the studies safety was assessed through AEs and vital signs as well as medical history and physical examination in C-115 and GRTF-ZAL1 and sedation assessment in ZAL-06.

#### *C-115*

Three hundred and six patients were randomised to DB treatment (98 T/A, 99 PBO, 109 A/COD); 142 patients discontinued prematurely (38 T/A, 53 PBO, 51 A/COD), 117 due to insufficient pain relief (28 T/A, 50 PBO, 39 A/COD), 22 due to AEs (8 T/A, 3 PBO, 11 A/COD); and 164 completed the study (60 T/A, 46 PBO, 58 A/COD). The treatment groups were comparable for baseline demographics and characteristics: 69-71% male, 29-31% female; 91-92% White, 7-8% Black, 0-1% Asian; 0-1% Other; with a mean age 46.2-48.9 years (range 18-79 years). Half of the patients had abdominal surgery and half had orthopaedic; and the mean PVA baseline score was 61.6-63.5 mm.

With respect to TOTPAR, SPID and SPRID data and comparisons for the interval 0-4 h; the pain relief provided by T/A 37.5/325 mg was statistically significantly superior to that provided by PBO ( $p \leq 0.033$ ) for all variables ( $p \leq 0.015$ ); A/COD is only statistically significantly superior to PBO for SPID and SPRID; and T/A 37.5/325 mg was not statistically superior to A/COD.

When the results were analysed according to surgical procedure; after an orthopaedic procedure the pain relief provided by T/A 37.5/325 mg was statistically significantly superior to that provided by PBO for all variables ( $p \leq 0.049$ ); A/COD was statistically significantly superior to PBO for all variables ( $p \leq 0.049$ ); and T/A 37.5/325 mg was not statistically superior to A/COD. After an abdominal procedure the pain relief provided by T/A 37.5/325 mg was not statistically significantly superior to that provided by A/COD or PBO and T/A 37.5/325 mg was not statistically superior to A/COD.

For further efficacy endpoints: Pain Intensity scores were lower and Pain Relief scores were higher with T/A than with PBO, overall and for orthopaedic and abdominal surgery. There were significantly more efficacy failures with PBO (40%) than with T/A or A/COD (24-26%) overall; with similar statistically significant findings for orthopaedic surgery but not for abdominal surgery. Subject's and investigator's overall assessment of study medication were similar for T/A (62-65% 'good' or 'very good'), A/COD (60-62% 'good' or 'very good') and PBO (45-46% 'good' or 'very good').

**GRTF-ZAL1**

One hundred and nineteen patients enrolled and were randomised to DB treatment (59 T/A, 60 T); 21 patients discontinued prematurely (6 T/A, 15 T), 17 due to AEs (4 T/A, 13 T); and 98 subjects completed the study (53 T/A, 45 T). The treatment groups were generally comparable for baseline demographics and characteristics: 36-50% male, 50-64% female; 81-83% Caucasian, 0-3% Black, 0-2% Asian, 0-2% Other, 14% Not Specified; with a mean age of 53.9-56.5 years (range 20-81 years).

*For the primary efficacy variable*, there was no statistically significant difference between last patient satisfaction scores for the T/A and T treatment groups.

*For secondary efficacy variables*, there were no significant differences between treatment groups for Pain Intensity, Pain Relief, Patient's assessment of efficacy, Patient's assessment of tolerance, Physician's assessment of medication, Frequency of and time until early discontinuation, frequency of efficacy failure and final dosage of medication. The overall assessment of medication by the physician was similar for both treatment groups and amount of final intake of medication was similar for both treatment groups, with most patients in both groups taking the lowest dose of 4units/day at end of study (EOS), and similar amounts of medication taken for each treatment group throughout the study. Pain intensity was decreased, with PVA score more than halved in both groups. PVA score, pain relief and global assessment of efficacy were slightly better for T than for T/A but the patient's assessment of tolerance and number of early discontinuations were slightly better for T/A. Frequency of efficacy failure was twice as high with T (12 [21%]) as with T/A (6 [10%]).

Overall, both T/A and T were similarly effective in treatment of subacute low back pain.

**ZAL-06**

Two hundred sixty-one patients were randomised to DB treatment (132 T/A, 129 T); 4 T/A and 1 T patients did not return, did not have an evaluation on the first post operative visit or had insufficient medication intake; 256 subjects completed the study (128 T/A, 128 T). The treatment groups were comparable for baseline demographics and characteristics: 36-41% male, 59-64% female; 98% Caucasian; with a mean age of 46.2-47.5 years (range 18-77 years).

*For the primary efficacy variable*: a subject was considered a responder if treatment satisfaction was 'good' or 'excellent' and no rescue or other analgesic medication was taken before 24.00 h on the first post operative day. The number of responders was greater with T/A (100 [78.1%]) than with T (92 [71.9%]) but the difference was not statistically significant. Therefore, treatment with T/A and T were considered comparable.

*For secondary efficacy variables*: The mean pain intensity was 2.6 with T/A and 2.8 with T on the evening of the day of surgery and 1.7 with both treatments on the evening of the first post operative day. The amount of study medication taken was comparable for both treatment groups, with most patients taking 4-8 tablets or capsules during the study. Average time to first study medication taken at home was 6.59 h with T/A and 6.73 h with T. Rescue medication was taken by 17.2% of T/A and 13.3% of T patients and average time to first intake of rescue medication was 25.6 h for both treatment groups; and anti-emetics were taken by 16% of T/A and 22% T of patients. There were no relevant differences between the groups for the time to discontinuation due to lack of efficacy (17 T/A patients discontinued after 12.8 h and 14 T patients discontinued after 10.2 h).

Overall there was no clear difference in response rates in pain management after hand surgery between T/A 32.5/325 mg and T 50 mg.

**Further studies in chronic pain:**

***A comparison of the analgesic efficacy and safety of T/A versus PBO for the symptomatic treatment of the pain and function of osteoarthritis (C-104);***

***A comparison of the analgesic efficacy of T/A versus PBO for the treatment of chronic lower back pain (C-112);***

***A comparison of the analgesic efficacy of T/A versus PBO for the treatment of chronic lower back pain (PRI/TRP-CAN-1);***

***A comparison of the analgesic efficacy of T/A versus PBO in subjects with the pain of fibromyalgia (C-113);***

***A randomised, multi-centre, DB, phase IIIb, parallel group study assessing the analgesic efficacy and safety of T/A 37.5/325 mg versus A/COD 500/30 mg in patients with chronic hip or knee-joint osteoarthritis (SP-ZAL-III-02)***

These were 5 additional multi centre multiple dose, OP, randomised, DB, parallel-group, Phase III (C-104, C-112, C-113), IIIb (PRI/TRP-CAN-1) or IV (SP-ZAL-III-02) studies.

C-104, C-112, C-113 and PRI/TRP-CAN-1 were PBO controlled trials to evaluate efficacy and safety of T/A in male and female patients with at least moderate pain (PVA $\geq$ 40 mm) from osteoarthritis (C-104), lower back pain (C-112, PRI/TRP-CAN-1) or fibromyalgia (C-113). In the studies, 318 patients who had been on a daily NSAID for  $\geq$  3months (C-104), 318 patients (C-112), 336 patients who had been on a daily analgesic for  $\geq$ 3 months (PRI/TRP-CAN-1) and 313 patients (C-113) entered washout phases during which all analgesics and drugs which reduce seizure thresholds were discontinued. They then randomly received T/A 37.5/325 mg or PBO (titrated over 10 days to x1 qid or max tolerated dose; then x1-2 qid prn, min 2-3/day, max 8/day) for 91 days. Supplementary analgesia (APAP 500 mg, max 4/day) was available if required only during the first 6 days when patients were taking up to 6 tablets/day of study medication.

SP-ZAL-III-02 was an active controlled trial to evaluate efficacy and safety of T/A compared to A/COD as a Step 2 analgesic treatment in 236 male and female patients with moderate or severe pain from knee or hip joint osteoarthritis, who were taking a daily dose of an NSAID or iCOX2 for  $\geq$ 1month. After 3-5 days washout during which all analgesics were discontinued, patients randomly received T/A 37.5/325 mg or A/COD 30/500 mg, (titrated over 6 days to x2 tid; if required then x2 qid; dose reduction was generally not permitted) for 84 days. Rescue analgesia was permitted throughout the study (diclofenac 50 mg, max 3/day).

For the first 4 studies the primary efficacy variables were: final PVA score (100 mm scale [0=no pain, 100=extreme pain]) for C-104; PVA score at each visit for C-112 and PRI/TRP-CAN-1; and time to discontinuation due to lack of efficacy for C-113. Further efficacy variables common to all the studies were: PRR scale, SF-36 Health Survey and efficacy failures. C-104, C-112, and PRI/TRP-CAN-1 also recorded the subject's and the study investigator's overall assessment of medication; C-104 and C-113 evaluated PVA scores at each visit; C-104 used the WOMAC Questionnaire; C-112 and PRI/TRP-CAN-1 used the McGill Pain Questionnaire and the RDQ; and C-113 used the Tender-point Evaluation (number out of 18 tender points painful on digital palpation), Myalgic Score (response to digital palpation by investigator), Fibromyalgia Impact Questionnaire (FIQ) Score and the Patient Assessment Sleep Questionnaire. In C-104 safety was assessed only through AEs during the trial. In the other 3 studies safety was assessed through TEAEs at each visit, vital signs, medical history, physical examination and clinical laboratory tests.

For SP-ZAL-III-02 the primary efficacy variable was change in Pain Intensity at motion while walking over a flat surface (100 mm horizontal VAS). Further efficacy variables were the WOMAC Questionnaire; the proportion of patients: attaining  $\geq$ 50% reduction in Pain

Intensity, with an absolute score of  $\leq 20$  mm of Pain Intensity, showing satisfactory Pain Relief, showing a response, or leaving the study due to lack of efficacy; SF-36 Health Survey; Nottingham Health Profile; consumption of rescue medication; patient's and investigator's global assessment of treatment, and of status of disease; and assessment of dependence after treatment cessation measured by opioid-dependence scale after withdrawal. Safety was assessed through AEs and vital signs.

### **C-104**

Three hundred twenty-one patients enrolled and were randomised to DB treatment (162 T/A, 159 PBO). One hundred sixty-three patients discontinued prematurely (83 T/A, 80 PBO), 116 due to insufficient pain relief (47 T/A, 69 PBO), 28 due to AEs (24 T/A, 4 PBO); and 158 completed the study (79 T/A, 79 PBO). The treatment groups were comparable for baseline demographics and characteristics: 35-36% male, 64-65% female; 89-91% White, 8% Black, 0-1% Asian; 1-2% Other; with a mean age of 61.0 years (range 35-80 years) for T/A and 61.6 years (range 40-87 years) for PBO. The target knee was the left for 47% T/A and 54% PBO patients.

For the primary efficacy outcome, mean PVA scores at baseline were comparable for the two treatment groups (80.09 mm T/A, 79.92 mm PBO) and at the Final Visit they were lower for T/A (49.38) than for PBO (54.13). Although a significant difference in PVA scores between T/A and PBO groups was seen for the Day 21-41 Visit Window ( $p=0.002$ ), the difference between treatment groups for the Final Visit (which included scores for all subjects who discontinued the study) was not significant ( $p=0.160$ ).

For further efficacy outcomes: Mean final PRRs were significantly greater for T/A than for PBO groups (1.5 and 1.2, respectively;  $p=0.020$ ); 56% T/A and 43% PBO patients rated their pain relief at Final Visit as 'a lot' or 'moderate'; while 25% T/A and 40% PBO patients rated their pain relief as 'none' or 'worse'. WOMAC questionnaire scores were comparable between treatment groups for each Visit Window; for both groups the mean scores for amount of pain, joint stiffness, physical function, and overall, decreased from baseline to Final Visit. SF-36 Health Survey scores and changes from baseline were comparable between treatment groups; the quality of life (QOL) assessments and physical and mental component scores were comparable between the groups at baseline and at the Final Visit. The subject's and study investigator's overall assessment of study medication were similar for T/A and PBO, with no clear patterns of assessment scores seen. The cumulative percentage of patients discontinuing the study due to lack of efficacy was statistically significantly greater for PBO compared to T/A at all times after Day 7 ( $p=0.054$ ).

### **C-112**

Three hundred twenty-two patients enrolled and were randomised to DB treatment (162 T/A, 160 PBO). One hundred fifty-seven patients discontinued prematurely (71 T/A, 86 PBO), 90 due to insufficient pain relief (31 T/A, 59 PBO), 39 due to AEs (30 T/A, 9 PBO); and 165 completed the study (91 T/A, 74 PBO). The treatment groups were generally comparable for baseline demographics and characteristics: 33-41% male, 59-67% female; 89-92% White, 8-11% Black, 0-1% Asian; with a mean age of 53.6 years (range 22-74 years) for T/A and 54.1 years (range 25-75 years) for PBO. The baseline PVA score was 71.1 mm (range 41-100 mm) for T/A and 68.8 mm (range 40-100 mm) for PBO.

For the primary efficacy endpoint, mean PVA scores at the Final Visit were significantly lower for T/A (44.4 mm) than for PBO (52.3 mm;  $p=0.015$ ).

For secondary efficacy endpoints, the mean final PRRs were significantly greater for the T/A group than for the PBO group (1.8 and 1.1, respectively;  $p<0.001$ ); more T/A (40%) than PBO (20%) subjects rated their pain relief at their Final Visit as 'complete' or 'a lot'. The incidence of efficacy failures was significantly lower for T/A than for PBO (19%



versus 38%;  $p < 0.001$ ); a lower discontinuation rate for T/A compared to PBO was obvious from Day 14 and the difference was significant for Day 84 ( $p < 0.001$ ).

Mean baseline scores for Sensory and Affective components of the McGill Pain Questionnaire and Total Score and Present Pain Index, were similar for T/A and PBO groups; mean changes of all components improved for T/A compared to PBO and were significant for the Sensory component ( $p = 0.011$ ), Total Score ( $p = 0.021$ ) and Present Pain Index ( $p = 0.011$ ). Mean baseline scores for Total Score and Bothersomeness Score of the RDQ were similar for the T/A and PBO groups but were significantly improved for T/A compared to PBO by the Final Visit ( $p = 0.023$  and  $p = 0.027$ , respectively). Every subscale on the SF-36 Health Survey showed greater improvement for T/A compared to PBO by Final Visit and the mean changes were significant for the sub-scales of Role-physical ( $p = 0.005$ ), Bodily Pain ( $p = 0.046$ ), Role-emotional ( $p = 0.001$ ), Mental Health ( $p = 0.026$ ) and Reported Health Transition ( $p = 0.038$ ), as well as for the Mental Component Summary ( $p = 0.008$ ). The subject's and the study investigator's gave similar ratings in their overall assessments of study medication, with mean overall rating scores significantly greater for T/A (both 0.6) than for PBO (-0.1 to 0.1;  $p \leq 0.002$ ).

### ***PRI/TRP-CAN-1***

Three hundred thirty-eight patients were enrolled and randomised to DB treatment (167 T/A, 171 PBO). One hundred ninety-one patients discontinued prematurely (81 T/A, 110 PBO), 112 due to insufficient pain relief (30 T/A, 82 PBO), 60 due to AEs (47 T/A, 13 PBO) and 147 completed the study (86 T/A, 61 PBO). The treatment groups were comparable for baseline demographics and characteristics: 36-39% male, 61-64% female; 94-95% White, 0-2% Black, 0-1% Asian, 1% Hispanic, 4% Other; with a mean age of 57.5 years (range 29-80 years) for T/A and 57.5 years (range 25-82 years) for PBO. The mean PVA scores at baseline were similar for both groups (67.9 mm T/A, 67.6 mm PBO).

For the primary efficacy endpoint: mean PVA scores at the Final Visit were significantly lower for T/A (47.4 mm) than for PBO (62.9 mm;  $p < 0.001$ ).

For secondary efficacy endpoints, the mean final PRRs were significantly greater for the T/A group than for the PBO group (1.8 and 0.7, respectively;  $p < 0.001$ ); 40% of T/A and 13% of PBO patients rated their pain relief at the Final Visit as 'complete' or 'a lot'; while 23% of T/A and 58% of PBO patients rated their pain relief as 'none' or 'worse'. The incidence of efficacy failures was significantly lower for T/A than for PBO (18% versus 49%;  $p < 0.001$ ); a lower discontinuation rate for T/A compared to PBO was obvious from Day 14 and the difference was significant for Day 84 ( $p < 0.001$ ).

Mean baseline scores for Sensory and Affective components of the McGill Pain Questionnaire and Total Score and Present Pain Index were similar for T/A and PBO groups; mean changes of all components improved for T/A compared to PBO and were significant for the Sensory component ( $p = 0.009$ ), Total Score ( $p = 0.011$ ) and Present Pain Index ( $p < 0.001$ ). The mean baseline Total Score and Bothersomeness Score of the RDQ were similar for the T/A and PBO groups but were significantly improved for T/A compared to PBO by the Final Visit ( $p = 0.043$  and  $p < 0.001$ , respectively). Every subscale on the SF-36 Health Survey showed greater improvement for the T/A group compared to the PBO group by the Final Visit and the mean changes were significant for the sub-scales of Physical functioning ( $p = 0.017$ ), Bodily Pain ( $p < 0.001$ ) and Mental Health ( $p = 0.023$ ) as well as for the Physical Component Summary ( $p = 0.018$ ). The subjects and the study investigators gave similar ratings in their overall assessments of study medication, with mean overall rating scores significantly greater for T/A (0.6-0.7) than for PBO (-0.4 to -0.3;  $p < 0.001$ ).

**C-113**

Three hundred fifteen patients were enrolled and randomised to DB treatment (158 T/A, 157 PBO). One hundred seventy-five patients discontinued prematurely (77 T/A, 98 PBO), 111 due to insufficient pain relief (39 T/A, 72 PBO), 47 due to AEs (29 T/A, 18 PBO) and 140 completed the study (81 T/A, 59 PBO). The treatment groups were generally comparable for baseline demographics and characteristics: 5-7% male, 93-95% female; 94-97% White, 3-6% Black, 0-1% Asian; with a mean age of 48.9 years (range 19-73 years) for T/A and 50.5 years (range 21-75 years) for PBO. The baseline PVA score was 72.4 mm (range 26-100 mm) for T/A and 71.5 mm (range 40-100 mm) for PBO.

For the primary efficacy endpoint, a lower discontinuation rate for the T/A group compared to the PBO group was obvious from Day 14 and the difference was significant for Day 84 ( $p < 0.001$ ). The incidence of efficacy failures was significantly lower for the T/A group (39 [25.0%]) than for the PBO group (72 [45.9%];  $p < 0.001$ ).

For secondary efficacy endpoints, in the evaluable-for-efficacy population, similarly to the ITT population, a lower discontinuation rate for the T/A group compared to the PBO group was obvious from Day 14 and the difference was significant for Day 84 ( $p < 0.001$ ). The incidence of efficacy failures was significantly lower for the T/A group (39 [25.7%]) than for the PBO group (68 [45.6%];  $p < 0.001$ ). Mean PVA scores at the Final Visit were significantly lower for the T/A (53.4 mm) than for the PBO group (65.1 mm;  $p < 0.001$ ). Mean PRR scores at the Final Visit were significantly greater for T/A than for PBO (1.7 versus 0.8;  $p < 0.001$ ).

The mean Tender Point Score at Final Visit was significantly lower for T/A than for PBO (13.3 versus 14.1; 0.040). The mean Myalgic Score at Final Visit was lower for T/A than for PBO (1.3 versus 1.5) but not significantly so. All parameters within the FIQ showed improvement for T/A compared to PBO by the Final Visit and the mean changes were significant for the parameters of Physical Impairment ( $p = 0.024$ ), Feel Good ( $p = 0.001$ ), Do Job ( $p = 0.044$ ), Pain ( $p = 0.015$ ), Stiffness ( $p = 0.008$ ) and Anxiety ( $p = 0.032$ ) as well as for Total Score ( $p = 0.008$ ). Every subscale on the SF-36 Health Survey showed greater improvement for T/A compared to PBO by the Final Visit and the mean changes were significant for the sub-scales of Physical Functioning ( $p = 0.005$ ), Role-physical ( $p = 0.001$ ), Bodily Pain ( $p = 0.002$ ), Reported Health Transition ( $p = 0.029$ ) and Physical Component Summary ( $p = 0.001$ ). All aspects of the Sleep Questionnaire were similar for T/A and PBO, with Sleep Index 6 ( $p = 0.776$ ) and Sleep Index 9 ( $p = 0.744$ ) comparable for the Final Visit.

**SP-ZAL-III-02**

Two hundred thirty-seven patients were randomised to DB treatment (117 T/A, 119 A/COD, 1 did not receive treatment). Ninety-one patients discontinued prematurely (46 T/A, 45 A/COD), 64 due to AEs (32 T/A, 32 A/COD), 7 due to lack of efficacy (5 T/A, 2 A/COD) and 145 completed the study (71 T/A, 74 A/COD). The treatment groups were comparable for baseline demographics and characteristics: 15-18% male, 82-85% female; 100% Spanish; with a mean age of 63.8 years (range 40-75 years) for T/A and 63.2 years (range 38-75 years) for A/COD. The baseline pain intensity score was 60.8 mm for T/A and 62.4 mm for A/COD.

For the primary efficacy endpoint, the mean PVA scores at baseline were comparable for the two treatment groups (63.57 mm T/A, 61.41 mm A/COD) and at the Final Visit they were lower for A/COD (27.12) than for T/A (35.54). The decreases in pain intensity from baseline were clinically significant for both groups but the difference between the groups was not statistically significant ( $p = 0.073$ ) and non-inferiority of T/A to A/COD could not be confirmed.

For the secondary efficacy endpoints, the changes from baseline in WOMAC pain domain and WOMAC stiffness domain were not significantly different between the T/A and A/COD

groups but non-inferiority of T/A to A/COD could not be confirmed. In contrast, the change from baseline in WOMAC physical function domain was not significantly different between T/A and A/COD and non-inferiority testing was significant for both the Per protocol (PP) and the ITT populations. The proportion of patients showing a 50% reduction in pain intensity from baseline was not significantly different for T/A and A/COD. Differences in pain intensity from baseline at each visit were similar for both treatments. SF-36 Health Survey scores and changes from baseline were comparable between treatment groups. The Nottingham health profile scores were comparable between treatment groups. Subjects generally gave better overall assessment scores to T/A than A/COD and the study investigators gave better scores to A/COD than T/A. A similar amount of rescue medication was taken in each treatment group during the study.

### **Evaluator's overall conclusions on clinical efficacy**

#### ***For the pivotal studies (T-A-010, T-A-012, T-A-013):***

- single dose T/A provided statistically significantly greater pain relief than PBO or equivalent component doses of T and APAP over 8 h for the treatment of moderate and severe acute pain
- the onset of analgesia of T/A was comparable to that of APAP
- the duration of analgesia of T/A was comparable to that of T

#### ***For the supportive studies:***

##### *Early studies*

- The early single-dose studies, T-A-002, T-A-003, T-A-011, T-A-004 and T-A-005, all assisted in helping to determine the design (best pain model, severity of baseline pain, and sample size) for the pivotal studies to demonstrate efficacy of T/A in acute pain.
- Similarly multi dose studies T-A-008 and T-A-009 assisted in determining what type of studies would best demonstrate the efficacy of T/A in chronic pain.

##### *Long-term data*

- T-A-006-OL and T-A-015 showed that T/A was effective in controlling chronic, non malignant pain for up to 27 months without development of tolerance.

##### *Acute pain*

- C-128 found that single dose T/A was effective in a dose dependent fashion and C-241 found single-dose T/A 37.5/325 mg was superior to single dose T 50 mg in the treatment of moderate-severe pain after an oral surgical procedure.
- C-216 found that short term T/A and HYD/A gave comparable efficacy in the treatment of moderate-severe musculoskeletal pain from an ankle sprain.
- C-105 found that short term T/A was effective in the treatment of moderate-severe pain from a painful flare of osteoarthritis.
- C-115 found that short term T/A and A/COD gave comparable efficacy in the treatment of post-surgical pain.
- GRTF-ZAL1 and ZAL-06 found that short term T/A 37.5/325 mg and T 50 mg gave comparable efficacy in the treatment of subacute low back pain and pain after hand surgery, however ZAL-06 failed to demonstrate superiority of T/A over T.



*Chronic pain*

- C-114 found that T/A was effective when used in addition to an iCOX2 in the treatment of moderate to severe pain from osteoarthritis.
- T-A-008 and T-A-009 found that T/A and IBU gave comparable efficacy in the treatment of osteoarthritis of the hip or knee, or in low back pain.
- T-A-006 and SP-ZAL-III-02 found that T/A and A/COD gave comparable efficacy in the treatment of chronic pain of benign origin, or of osteoarthritis of the hip or knee; however SP-ZAL-III-02 failed to demonstrate non-inferiority of T/A to A/COD.
- C-104 failed to differentiate T/A from PBO in the treatment of pain from osteoarthritis.
- C-112 and PRI/TRP-CAN-1 found T/A was effective in the treatment of chronic lower back pain.
- C-113 found T/A was effective in the treatment of pain from fibromyalgia.

The studies provided with the current submission are in keeping with the TGA adopted EU guidelines for evaluation of medications for treatment of nociceptive pain<sup>44</sup>, in that:

- A variety of randomised, parallel-group studies were conducted including PBO controlled, active comparator and multi arm study drug/active comparator/PBO studies; using appropriate active comparator drugs and rescue medications.
- Appropriate to the indication of generalised treatment of pain there was variety in the studies included with the current submission:
  - PBO controlled studies, active comparator studies and multi arm studies of study drug/active comparator/PBO
  - various appropriate active comparator drugs
  - IP and OP studies
  - studies in a variety of models of both acute and chronic pain
  - single dose studies; and short term, long term and multiple dose studies
  - various measures and endpoints of pain are used for primary and secondary efficacy variables (the TGA guideline list is also extensive and does not single out any one measure or endpoint as the best)
- The study populations were largely representative of the target population. However:
  - There were no patients in the 12-16 year old age bracket included in any study. The evaluator does not consider this a cause for concern from an efficacy point of view as the component medications T and APAP are both marketed to the population  $\geq 12$  years and no PK interactions were demonstrated between T and APAP.
- Exploratory studies were multiple, single and multiple dose and were used to determine the best dosage/regimen, pain model and sample sizes to demonstrate efficacy and safety of T/A.
- Confirmatory studies covered acute and chronic pain of benign origin and somatic and visceral pain models but not oncologic pain models; with moderate and severe levels of pain intensity and pre defined primary efficacy endpoints were attained.

---

<sup>44</sup> Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain, EMEA/CPMP/EWP/612/00, pp4-5

Comment: In the TGA guidelines it is stated: that the inclusion of somatic (major orthopaedic) and visceral (abdominal, gynaecologic, or thoracic surgery) populations supports the broader indication of 'acute pain management in general (moderate to severe pain)'; that efficacy of a drug in cancer related pain can usually be extrapolated to non-cancer pain with the same pain-generating mechanisms, although there is no comment on whether efficacy in non cancer pain drugs can be extrapolated to cancer pain drugs; and that a general pain indication is possible if studies include acute severe pain, chronic pain in visceral and somatic models and cancer pain. The guidelines also indicate that pain models using osteoarthritis and low back pain only replicate chronic pain of mild to moderate intensity, and that pain models of cancer are required to replicate chronic pain of moderate to severe intensity.

However, the tools used to measure baseline levels of pain in the studies submitted are generally accepted and indicate pain levels of moderate to severe intensity despite no cancer pain studies having been included.

Considering these statements from the TGA guidelines, the fact that intensity of pain from both malignant and non-malignant sources can range from mild to severe and that neither T nor APAP are limited to use only in patients with non malignant pain, it can be argued that the use of T/A should not be limited to only patients with non malignant pain.

The current submission provides adequate evidence to justify the indication for treatment of moderate to severe acute pain and mild to moderate chronic pain. The evidence to justify the indication for treatment of moderate to severe chronic pain is less compelling, largely due to the TGA guideline requirements for studies using oncologic pain models. Regardless of the final wording of the indication, there should be a statement under the '*Clinical Trials*' section in the PI that states clearly that efficacy of T/A in the treatment of pain from cancer has not been studied.

The studies provided with the current submission are also in keeping with the TGA adopted guidelines for fixed combination medicinal products in that:

- justification for the fixed combination is that it offers
  - an improvement of the benefit/risk (equal or improved efficacy, together with decreased AEs, as a result of lower daily doses of each component drug when taken as a combination), and
  - a simplification of therapy (a single fixed dose tablet to be taken as 1 or 2 qid, compared to 2 separate medications to be taken according to 2 completely different and unconnected timetables)
- all three pivotal efficacy studies (parallel group comparisons with component drugs, PBO and a reference drug) established that both components (T and APAP) contribute to the analgesic effect of the combination drug T/A.

## Safety

### Introduction

Safety data for T/A was contained in 5 Phase I studies (TRAM-PHI-001, T-P-001, T-P-002, T-P-003, HPZALDEFF/01), 3 Phase II studies (CA, CB, T-A-007), 18 Phase III studies (T-A-002, T-A-003, T-A-004, T-A-005, T-A-006, T-A-008, T-A-009, T-A-010, T-A-011, T-A-012, T-A-013, T-A-015, C-104, C-112, C-113, C-114, C-128) and 8 Phase IIIb/IV studies (C-105, C-115, C-216, C-241, PRI/TRP-CAN-1, GRTF-ZAL1, SP-ZAL-III-02, ZAL-06).

To maintain consistency with previous applications, the sponsors presented the safety information as data became available for various periods: up till 2001, 2001-2004, 2004-2006 and 2006-2010. For this report the data was reviewed for the 12 primary source studies (using the proposed commercial fixed dose combination of T/A) that were presented with the initial 2001 application, the 21 supportive studies (using other ratios of T/A, and PK and PD studies) and the various pooled data and meta- analyses and reports.

### **Patient exposure**

Safety data regarding T/A in the treatment of moderate to severe pain was presented in the initial 2001 application and was found in 12 primary source studies: 8 single-dose (T-A-002, T-A-003, T-A-004, T-A-005, T-A-010, T-A-011, T-A-012, T-A-013) and 4 multi-dose studies (T-A-006, T-A-008, T-A-009, T-A-015), summarised in Table 18.

Additional safety data up until 2010 came from supportive studies including 5 OL studies in healthy subjects (TRAM-PHI-001, T-P-001, T-P-002, T-P-003, HPZLDEFF/01), a dose-ranging study (T-A-007) and 2 pilot studies (CA, CB), 5 multiple-dose studies in chronic pain (C-104, C-112, C-113, C-114, PRI/TRP-CAN-1), a single dose study (C-128) and 2 multi dose studies (C-105, C-115) in acute pain and 5 post marketing studies (C-216, C-241, ZAL-06, SP-ZAL-III-02, GRTF-ZAL1). All studies are summarised in Table 19.

In the primary source studies, 1846 of 3726 patients (age range 16-91 years; 2206 had baseline pain reported as moderate and 1015 had base line data reported as severe) with pain from surgery, osteoarthritis or of benign origin were exposed to T/A 37.5/325 mg tablets: 472 to single doses of 2-3 tablets and 1374 to multiple doses of up to 10 tablets a day for up to 8 weeks (270), 6 months (369) or 24 months (309).

For long term treatment, 327 patients (age range 20-91 years) completed 6 months treatment and 120 patients completed 12 months treatment.

In the supporting studies, 1968 of 4761 patients (age range 16-87 years) with pain from surgery, osteoarthritis, fibromyalgia of musculoskeletal origin or of benign origin and 119 of 124 healthy subjects, were exposed to T/A: 1894 to 37.5/325 mg tablets and 193 to other combinations (25/500 mg, 25/650 mg, 50/650 mg, 100/500 mg). Of those receiving 37.5/325 mg tablets, 165 had single doses of 1-3 tablets; 732 had multiple doses to a max of 10 tablets per day for 1-10 days and 844 had multiple doses to a max of 8 tablets per day for 84-91 days.

Overall, with the exception of T-A-007, CA and CB, all the studies used a tablet with dose combination as proposed for marketing (37.5/325 mg) and dosages within or close to the proposed range (initial dose x2 tablets, then prn q6h for pain, max 8 tablets per day), although 3 studies gave a single dose of x3 tablets, 6 studies allowed the min dosing interval to be q4h and 5 studies allowed a max of 10 tablets per day. Only one study, HPZLDEFF/01, used a 37.5/325 mg effervescent tablet of T/A as is proposed for marketing.

**Table 18. Summary of patient exposure, primary source studies (up until 2001)**

		Enrolled	Exposed to T/A	Exposed to proposed dose range	Long-term safety data
PC and AC	T-A-002	250: oral surgery •203 mod pain •47 severe pain	50 T/A 75/650 mg	50 T/A 75/650 mg	
	T-A-003	250: oral surgery •167 mod pain/ •83 severe pain	50 T/A 75/650 mg	50 T/A 75/650 mg	
	T-A-010	400: oral surgery •275 mod pain •125 severe pain	80 T/A 75/650 mg	80 T/A 75/650 mg	
	T-A-011	156: oral surgery •120 mod pain •36 severe pain	31 T/A 75/650 mg	31 T/A 75/650 mg	
	T-A-012	400: oral surgery •264 mod pain •136 severe pain	80 T/A 75/650 mg	80 T/A 75/650 mg	
	T-A-013	400: oral surgery •281 mod pain •119 severe pain	80 T/A 75/650 mg	80 T/A 75/650 mg	
PC	T-A-004	200: gynaecologic surgery •31 mod pain •168 severe pain •1 unknown level of pain	51 T/A 112.5/975 mg		
	T-A-005	200: orthopaedic surgery •158 mod pain •42 severe pain	50 T/A 112.5/975 mg		
AC	T-A-008	313: osteoarthritis •8 mild pain •199 mod pain •100 severe pain •6 unknown level of pain	OL: 312 T/A 37.5/325 mg, x1-2 qid x1wk DB: 119 T/A 37.5/325 mg, max 10/day x8wks	OL: 312 T/A 37.5/325 mg, x1-2 qid x1wk DB: 119 T/A 37.5/325 mg, max 10/day x8wks	
	T-A-009	388: benign low back pain •9 mild pain •267 mod pain •91 severe pain •18 unknown level of pain	OL: 388 T/A 37.5/325 mg, x1-2 qid x1wk DB:151 T/A 37.5/325 mg, max 10/day x8wks	OL: 388 T/A 37.5/325 mg, x1-2 qid x1wk DB:151 T/A 37.5/325 mg, max 10/day x8wks	
OL and AC	T-A-006	403: benign chronic pain •1 no pain •86 mild pain •241 mod pain •68 severe pain •7 unknown level of pain	309 T/A 37.5/325 mg, max 10/day x4wks, then x24months	309 T/A 37.5/325 mg, max 10/day x4wks, then x24months	Exposure >180days continuously: x148 Exposure >360days continuously: x120
OL	T-A-015	366: benign chronic pain	365 T/A 37.5/325 mg, max 10/day x6months	365 T/A 37.5/325 mg, max 10/day x6months	Exposure >180days continuously:x179

**Table 19. Summary of patient exposure, supportive studies (up until 2010). Table continued across two pages.**

		Enrolled	Exposed to T/A	Exposed to proposed dose range
PC and AC	C-115	306: post-surgical pain orthopaedic or abdominal surgery	98 T/A 37.5/325 mg, first dose x2, then max 8/day for 6days	98 T/A 37.5/325 mg, first dose x2, then max 8/day for 6days
	C-128	200: oral surgery •175 mod pain •25 severe pain	50 T/A 75/650 mg 50 T/A 37.5/325 mg	50 T/A 75/650 mg 50 T/A 37.5/325 mg
PC	C-104	317: osteoarthritis	161 T/A 37.5/325 mg, 3-8/day x91days	161 T/A 37.5/325 mg, 3-8/day x91days
	C-105	308: osteoarthritis + NSAID/iCOX2	102 T/A 37.5/325 mg, first dose x1, then max 8/day x10days	102 T/A 37.5/325 mg, first dose x1, then max 8/day x10days
			95 T/A 37.5/325 mg, first dose x2, then max 8/day x10days	95 T/A 37.5/325 mg, first dose x2, then max 8/day x10days
	C-112	318: chronic low back pain	152 T/A 37.5/325 mg, 3-8/day x91days	152 T/A 37.5/325 mg, 3-8/day x91days
	C-113	312: fibromyalgia	152 T/A 37.5/325 mg, 2-8/day x91days	152 T/A 37.5/325 mg, 2-8/day x91days
	C-114	306: osteoarthritis + iCOX2	153 T/A 37.5/325 mg, 2-8/day x91days	153 T/A 37.5/325 mg, 2-8/day x91days
	PRI / TRP-CAN-1	336: chronic low back pain	167 T/A 37.5/325 mg, 3-8/day, x91days	167 T/A 37.5/325 mg, 3-8/day, x91days
	T-A-007	300: oral surgery •175 mod pain •125 severe pain	50 T/A 50/650 mg 50 T/A 25/650 mg	
	CA	215: oral surgery	53 T/A 100/500 mg	
CB	160: Caesarean section	40 T/A 25/500 mg		
OL	TRAM-PHI-001	12: healthy	12 T/A 37.5/325 mg	12 T/A 37.5/325 mg
	T-P-001	32: healthy	28 T/A 37.5/325 mg max 10/day x7days 1 T/A 37.5/325 mg max 9/day x2days 1 T/A 37.5/325 mg max 5/day x1day	28 T/A 37.5/325 mg max 10/day x7days 1 T/A 37.5/325 mg max 9/day x2days 1 T/A 37.5/325 mg max 5/day x1day
	T-P-002	24: healthy	21 T/A 37.5/325 mg x3	
T-P-003	24: healthy	23 T/A 37.5/325 mg x2 x2days 1 T/A 37.5/325 mg x2 x1day	23 T/A 37.5/325 mg x2 x2days 1 T/A 37.5/325 mg x2 x1day	
PM	P C a	C-216	602: musculoskeletal pain	192 T/A 37.5/325 mg, first dose x2, then max 8/day x6days

		Enrolled	Exposed to T/A	Exposed to proposed dose range	
	n d  A C				
	P C	C-241	456: oral surgery	153 T/A 75/650 mg	153 T/A 75/650 mg
		ZAL-06	261: hand surgery	132 T/A 37.5/325 mg, x1 preop, x1 post-op, then max 8/day for 2days	132 T/A 37.5/325 mg, x1 preop, x1 post-op, then max 8/day for 2days
	AC	SP-ZAL-III-02	236: osteoarthritis	46 T/A 37.5/325 mg, max 8/day for 84days	46 T/A 37.5/325 mg, max 8/day for 84days
		GRTF-ZAL1	119: low back pain	59 T/A 37.5/325 mg max 8/day x10days	59 T/A 37.5/325 mg max 8/day x10days
Effervescent tablet:					
OL	HPZLDEFF/01	32: healthy	31 T/A 37.5/325 mg effervescent tablet dissolved in 200mL water + T/A 37.5/325 mg FCT  1 T/A 37.5/325 mg FCT	31 T/A 37.5/325 mg effervescent tablet dissolved in 200mL water + T/A 37.5/325 mg FCT  1 T/A 37.5/325 mg FCT	

PC = placebo-controlled; AC = active-controlled; OL = open-label; PM = post-marketing; FCT = film coated tablet.

### Adverse events

For the DB phase of the multiple dose studies, AEs occurred to a similar degree with T/A (66-71%) and the comparators A/COD (76%) and IBU (56-61%). AEs most commonly affected the Gastrointestinal (GI) or Nervous systems or were Psychiatric AEs. The most frequent AEs seen across the studies were nausea, constipation, somnolence, dizziness and headache. In each study, nausea, dizziness and headache occurred at a similar rate for T/A (3-17%) and the comparators (7-19%); whilst constipation and somnolence were both less frequent with T/A (11-17%) than with A/COD (21-24%) but more frequent than with IBU (2-6%).

The sponsors also compared safety data for T/A with that of T alone. As none of the multiple dose studies used T as a treatment group, comparison was made to historical T data from three studies, TKB<sup>45</sup>, TL2<sup>46</sup>, and TKM, which had similar designs and subject populations as T-A-006, T-A-008, T-A-009 and T-A-015. From these three studies and post marketing data it was found that the average daily dose of T when given as combination T/A 37.5/325 was 131-176 mg and the average daily dose of T when given alone as T50 was 250-260 mg. A dose response was seen for AEs with statistically significantly greater incidences of most AEs with T compared to T/A and this effect was also seen in the elderly population ( $\geq 65$  years old) in which some of these AEs might be expected to have more dire effects (such as dizziness and somnolence may lead to increased falls, constipation and nausea may decrease QOL).

For the OL long-term phases of the multiple dose studies (T-A-006, 015), a similar profile of AEs was seen for T/A with the most frequent being nausea (21-22%), dizziness (15-16%), somnolence (11-16%), headache (13-15%) and constipation (14%) and the overall rate of AEs was 83-88%. There was some variation of incidences of AEs over time but no apparent increases in frequency with time for any individual AE.

Similarly for the single dose studies in patients with oral dental, orthopaedic or gynaecological post operative pain (T-A-002, T-A-003, T-A-004, T-A-005, T-A-010, T-A-011, T-A-012, T-A-013), AEs tended to occur at a similar incidence with T/A and T and both had a greater incidence greater than PBO; the most frequent AEs being nausea (10-33% T/A, 12-39% T, 2-19% PBO), somnolence (14-35% T/A, 13-20% T, 6-14% PBO), vomiting (3-23% T/A, 0-26% T, 2-13% PBO), dizziness (5-13% T/A, 6-10% T, 0-8% PBO) and headache (3-8% T/A, 9-12% T, 10-13% PBO). The overall rates of AEs in the single dose studies were 20-48% with T/A, 22-46% with T, 4-46% with A, 5-26% with IBU and 4-33% with PBO.

A meta-analysis of 7 of the single dose trials (T-A-002, T-A-003, T-A-010, T-A-012, T-A-013, T-A-004, T-A-005) found that in dental pain studies the number-needed-to-harm (NNH) for any AE was 5.4 for T/A (1 AE expected for every 6 patients taking a single dose of T/A instead of PBO) compared to 5.0 for T 75 mg but that in post surgical pain studies there was no statistically significant difference in NNH between study treatments.

An update of the meta-analysis to include 18 studies of similar design in patients receiving T 50-150 mg found that the AE profile of T was the same regardless of whether the medication was given alone or in combination with APAP. Subgroup analysis found more females than males had  $\geq 1$  AE overall and more females (especially those weighing  $< 55$  kg) than males experienced the individual AE of nausea; however no effect was seen on incidence or profile of AEs with baseline pain intensity, race, or extent of exposure.

Most AEs were of mild or moderate severity.

Across the combined 12 studies the most frequent AEs of incidence  $\geq 1\%$  considered at least possibly related to study medication were: Body as a whole (asthenia, fatigue, hot flushes), Central and peripheral nervous system (C&PNS; dizziness, headache, tremor), GI system (abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting), Psychiatric disorders (anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence), Skin and appendages (pruritus, rash, increased sweating).

In each of the 12 studies, specific AEs with a potential association with either of the components of the combination medication were examined.

---

<sup>45</sup> Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain, EMEA/CPMP/EWP/612/00, pp3-9

<sup>46</sup> Guideline on clinical development of fixed combination medicinal products, EMEA/CHMP/EWP/240/95 Rev. 1, pp7-8

- The incidences of AEs related to convulsions/seizures, liver function and renal function were found to be low in patients treated with T/A.
- No subjects had anaphylactoid/anaphylactic reactions or anaphylactoid shock; however AEs associated with less severe allergic reactions occurred (such as pruritus, rash, contact dermatitis or urticaria)
- The incidences of dependence/abuse and withdrawal symptoms were found to be low in patients treated with T/A

*In the OL PK studies in healthy subjects:*

AEs were mostly from the Central Nervous System (CNS) and GI system and most were of mild severity. The incidence of AEs was slightly lower in patients after eating (26%) compared to after fasting (38%).

Note: HPZLDEFF/01 was the only study that used the T/A effervescent tablet for marketing (in 31 subjects)

*In the dose-ranging study (T-A-007):*

AEs occurred to a greater extent with T/A 50 mg, T/A 25 mg, T 50 mg and T 25 mg (8-18%) than with APAP and PBO (2-4%). Most AEs were in the GI system.

*In the five multi-dose studies in chronic pain (C-104, C-112, C-113, C-114, PRI/TRP-CAN-1):*

The overall incidence of AEs with T/A was 572/797 (72%) compared to 387/792 (49%) with PBO. The most frequent AEs (incidence  $\geq 5\%$ ) were nausea (17% T/A, 6% PBO), constipation (13% T/A, 4% PBO), headache (13% T/A, 9% PBO), somnolence (11% T/A, 3% PBO), dizziness (10% T/A, 4% PBO), pruritus (7% T/A, 2% PBO), fatigue (6% T/A, 2% PBO), dry mouth (6% T/A, 1% PBO) and upper respiratory tract infection (URTI; 5% T/A 6% PBO)<sup>47</sup>. Most AEs were of mild or moderate intensity and were doubtfully or possibly related to study medication.

A meta-analysis of 4 studies of T/A (C-104, C-112, C-113, C-114) and 4 studies of T (C-051, TPS OA, TPS BP, TPS FM) found that in patients with chronic pain the most frequent AEs with T/A were constipation, dizziness, drowsiness, dry mouth, headache and nausea; the same AEs but also vomiting were reported for T. With IBU the most frequent AEs were constipation, drowsiness/sleepiness, headache and nausea; and with PBO the most frequent were constipation, headache and nausea only in the T/A trials. In one trial over 91 days, patients discontinued due to AEs to a greater extent with T/A than with PBO (NNH 9.3) but in another trial over 91 days the difference between patients discontinuing due to AEs with T and PBO was not significant. In another trial over 39 days, patients discontinued due to AEs to a greater extent with T than with IBU (NNH 3.4); and in yet another trial over 91 days, analgesic efficacy of T/A improved with co administration of an iCOX2 without a significant increase in the rate of discontinuations due to AEs (NNH 12).

---

<sup>47</sup> Single-dose oral tramadol and tramadol plus paracetamol in acute postoperative pain: an updated meta-analysis



*For single dose (C-128 and post marketing study C-241) and multiple dose (C-105, C-115, and post marketing study GRTF-ZAL1) studies in patients in acute pain:*

The most frequent AE seen with T/A was nausea; and dizziness, vomiting and headache were the next most frequent in the first four studies but somnolence and dry mouth were the next most frequent in GRTF-ZAL1. Both nausea and vomiting occurred to a greater degree with HYD/A and headache was more common with PBO than with T/A or T in C-128. Headache was also more common with PBO than with the analgesic T/A in C-241 and C-105 but occurred at the same rate in C-115. In all the studies nausea was greatest with a higher dose of T (significantly so for C-241 and GRTF-ZAL1), so combining T with A appears to allow for a lower T dose and hence less nausea.

In both single dose C-241 and multiple dose GRTF-ZAL1 studies, the overall incidence of AEs was less with T/A (51-54%) than with T50 (64-73%), that is a dose response was evident for the incidence of AEs with dose of T. In the single dose Study C-128, fewer AEs occurred with both dosages of T/A (30-34%) compared to HYD/A (56%) or PBO (48%). In the multiple dose Study C-105, AEs occurred to a greater extent with T/A (45%) than with PBO (23%); but in the multiple dose Study C-115, AEs occurred at the same rate for T/A and PBO (39-40%) and both less than with A/COD (51%). Most AEs were of mild or moderate intensity and were not considered related to study medication.

When data was combined for the 12 primary source studies, 4 studies in chronic pain (C-104, C-112, C-113, C-114) and 2 in acute pain (C-105, C-128), the overall incidence of AEs with T/A was 1765/2836 (62%) with the most frequent AEs (incidence  $\geq 5\%$ ) being nausea (18%), dizziness (12%), somnolence (10%), constipation (8%), headache (8%), vomiting (7%), URTI (5%) and pruritus (5%). Most AEs were of mild or moderate intensity and were doubtfully or possibly related to study medication. The only change for the combined 18 studies to the combined 12 primary source studies in terms of most frequent AEs of incidence  $\geq 1\%$  considered at least possibly related to study medication was that 'Psychiatric disorder (euphoria)' was no longer included.

*In the three other post marketing studies (C-216, ZAL-06, SP-ZAL-III-02):*

In C-216, the overall incidence of AEs was greater with T/A (83 [43%]) than with HYD/A (74 [37%]) and PBO (40 [19%]); and were considered likely related to study medication for 41% T/A, 36% HYD/A, and 14% PBO patients. The majority of the most frequent ( $>4.5\%$ ) AEs occurred at a similar rate with T/A (somnolence [17%], nausea [15%], dizziness [9%], vomiting [7%]) and HYD/A (somnolence [16%], nausea [14%], dizziness [9%], vomiting [4%]); whilst the most frequent AE with PBO was somnolence (7%). Most AEs were mild or moderate in intensity.

In SP-ZAL-III-02, AEs occurred to a greater extent with A/COD (75%) than with T/A (63%); with the most frequent being constipation (much greater with A/COD [38%] than with T/A [18%]), nausea (14% T/A, 12% A/COD) and dizziness (11% T/A, 10% A/COD).

In ZAL-06, AEs occurred more with higher T dose (57% with T50, 41% with T/A); and the most frequent ( $\geq 5\%$ ) AEs were nausea (26% T/A, 36% T), dizziness (16% T/A, 19% T), somnolence (9% T/A, 14% T), vomiting (7% T/A, 12% T) and increased sweating (5% T/A, 7% T).

## **Serious adverse events and deaths**

### ***Deaths***

*For the 12 primary source studies:* There were no deaths amongst the single dose studies and 3 deaths in the multi dose studies (2x myocardial infarction [one after screening but prior to study medication; one after 16 months T/A], 1x cancer [6 months after discontinuing from T/A]; all were considered unlikely to be related to study medication).

For the 21 supportive studies: There were no deaths.

### **SAEs**

*For the 12 primary source studies:* The incidence of non fatal serious AEs (SAEs) was low (62/3726 [1.7%]) and similar for T/A and the active comparators (A/COD, IBU). There were 4 SAEs reported in the single dose studies (none with T/A, all considered unlikely to be related to study medication). There were 58 SAEs reported in the multi dose studies: 2 certainly/very likely related to study medication (both with T/A: overdose due to elderly subject misunderstanding dosing, withdrawal symptoms at end of study (EOS)), 6 possibly related to study medication (5 with T/A: convulsions, abdominal pain, diarrhoea, drug abuse, anxiety; 1 with IBU: constipation) and the remainder doubtfully/unlikely to be related to study medication. All SAEs resolved except one case of human immunodeficiency virus and one case of facial nerve palsy.

*For the 21 supportive studies:* The incidence of non fatal SAEs was low. There were no SAEs in the 5 OL studies in healthy subjects (TRAM-PHI-001, T-P-001, T-P-002, T-P-003, HPZLDEFF/01), in the dose ranging study (T-A-007) or in the 2 pilot studies (CA, CB).

SAEs occurred in each of the 5 multi dose studies in patients with chronic pain (C-104, C-112, C-113, C-114, PRI/TRP-CAN-1). Overall, SAEs occurred in 1.3% (21/1589) of the patients; 20 SAEs in 17 patients with T/A and 5 SAEs in 4 patients with PBO and all were considered unrelated to study drug.

There were no SAEs in the single dose study in patients with acute pain (C-128) but in the 2 multi dose studies (C-105, C-115) SAEs occurred in 0.7% (4/614) of patients; 3 with PBO and 1 with A/COD (the constipation seen with A/COD was the only SAE considered related to study medication).

SAEs occurred in 2 of the 5 post marketing studies: in SP-ZAL-III-02, 3 SAEs occurred in 2 [1.7%] subjects with T/A, and 5 SAEs occurred in 3 [2.1%] subjects with A/COD (only 'transient global amnesia' with T/A was considered related to study drug); while in ZAL-06, 2 SAEs were seen in 1 subject with T/A (nausea and hypotension, both likely related to study drug).

### **Laboratory findings**

*For the 12 primary source studies:*

No safety laboratory parameters were measured in any of the single dose studies.

In the multi dose studies, liver function tests (LFTs) were specifically investigated due to the APAP component of T/A. There were no clinically significant mean changes from baseline for any laboratory parameters in the DB or OL phases of the studies for T/A, A/COD or IBU. Markedly abnormal laboratory values were seen in individual patients from all treatment groups for biochemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], blood urea nitrogen [BUN], creatinine, sodium, potassium, chloride, calcium, glucose, total protein, lactate dehydrogenase [LDH]) and haematology (white cells and count and platelets) parameters but incidences were low and there were no associations between abnormalities and TEAEs or other patterns evident.

*For the 21 supportive studies:*

No safety laboratory parameters were measured in the dose ranging study (T-A-007), the two pilot studies (CA, CB), the single dose study and a multi-dose study in acute pain (C-128, C-115) or any of the 5 post marketing studies.

In one OL study in healthy subjects (T-P-001), 9 subjects had increased AST and ALT and 10 subjects had increased potassium. These changes were of unknown clinical significance and there were no changes of clinical significance seen in laboratory parameters in any of the other OL studies in healthy subjects (TRAM-PHI-001, T-P-002, T-P-003, HPZLDEFF/01).

In the 5 multi dose studies in chronic pain and 1 multi dose study in acute pain (C-105), no clinically significant mean changes from baseline occurred for any laboratory parameters with T/A or PBO. Markedly abnormal laboratory values were seen in individual patients from both treatment groups for biochemistry (AST, ALT, alkaline phosphatase [AP], total bilirubin, albumin, BUN, creatinine, sodium, potassium, chloride, calcium, glucose, total protein, uric acid) and haematology (white cells and count, red blood cell count [RBCs], haematocrit, haemoglobin and platelets) parameters but incidences were low and there were no associations between abnormalities and TEAEs or other patterns evident.

No clinically significant changes occurred in any vital sign parameters or physical examinations in any treatment groups in any of the studies.

### **Safety in special populations**

Specific studies of T/A in special populations were not conducted. However, elderly patients were included in many of the studies submitted. As the PKs of T and APAP were not significantly affected by co administration with each other, the safety of T/A in special populations was expected to reflect the safety of the component drugs in the same populations. Therefore:

*Children:* Treatment with T/A is not recommended in children under the age of 12 years.

*Elderly:* No dose adjustment is required for T/A in the elderly. The elimination half life of oral T is increased by 17% in patients >75 years of age so it is recommended that the minimum dosing interval for T should be 6 h. The min dosing interval for T/A is already 6 h (and not 4 h as for T), so no adjustment of dose or dosing interval is required for T/A in patients >75 years old.

*Renal insufficiency:* Treatment with T/A is not recommended in patients with severe renal insufficiency ( $CL_{CR} < 10$  mL/min); the minimum dosing interval should be 12 h in patients with moderate renal insufficiency ( $CL_{CR}$  10-30 mL/min). Post dialysis administration of T/A to maintain analgesia is not required as T is removed only slowly by haemodialysis or haemofiltration.

*Hepatic insufficiency:* Treatment with T/A is not recommended in patients with severe hepatic impairment. Consideration should be given to increasing the minimum dosing interval in patients with moderate hepatic insufficiency.

### **Safety related to drug-drug interactions and other interactions**

No interaction studies were performed for the combination T/A tablet with concomitant medications. Since the PKs of T and APAP were not significantly affected when administered together, any drug interactions with T/A are expected to reflect those of the component drugs. Therefore:

Concomitant use of T/A is contradicted with:

- Monoamine oxidase (MAO) inhibitors (non-selective, selective-A, selective-B): due to risk of serotonergic syndrome. MAO inhibitors should be ceased 2 weeks prior to beginning treatment with T/A.

Concomitant use of T/A is not recommended with:

- carbamazepine and other enzyme inducers: due to risk of decreased efficacy and decreased duration from decreased plasma concentrations of T
- opioid agonist-antagonists (buprenorphine, nalbuphine, pentazocine): due to decreased analgesic effect from competitive blocking of receptors and risk of withdrawal syndrome.

Care should be exercised if T/A is to be given with:

- serotonergic medicines (selective serotonin reuptake inhibitors [SSRIs], triptans): due to isolated cases with T of serotonin syndrome
- opioid derivatives (including anti-tussive drugs, substitutive treatments), benzodiazepines and barbiturates: due to increased risk of respiratory depression
- CNS depressants (opioid derivatives [including anti-tussive drugs, substitutive treatments], barbiturates, benzodiazepines, anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide, baclofen: due to increased central depression which may affect ability to drive vehicles and use machines
- Warfarin like compounds: due to reports of increased international normalized ratio (INR<sup>48</sup>); prothrombin time should be monitored
- CYP3A4 inhibitors (ketoconazole, erythromycin): due to possible inhibition of metabolism of T (N-demethylation) and possible inhibition of metabolism of active O-demethylated metabolite
- drugs that reduce seizure threshold (bupropion, SSRIs, tricyclic antidepressants, neuroleptics): due to increased risk of seizures; and speed of absorption of APAP possibly increased by metoclopramide or domperidone or possibly decreased by cholestyramine.

### **Discontinuation due to adverse events (DAEs)**

*For the 12 primary source studies:* In the 8 single dose trials: the incidence of discontinuations due to AEs (DAEs) was low and similar for all treatment groups (0-3 withdrawals for any one treatment group [T/A, T, A, IBU and PBO]), with the most frequent reasons for discontinuation being nausea, vomiting or headache.

In the 4 multiple dose trials: DAEs occurred to a similar degree in the DB phases of T-A-006, T-A-008 and T-A-009, regardless of treatment (12-15% with T/A, 14% with A/COD, 12-15% with IBU). Nausea was the main cause for discontinuation in all studies and all treatment groups (3-4% T/A, 5% A/COD, 3-4% IBU). Incidence of DAEs increased with length of the trial but was similar for both OL long-term studies (T-A-006, T-A-015; 24-27%), with the most frequent reasons for withdrawing being nausea (5-9%), dizziness (2-6%), somnolence (3-4%) and vomiting (2-4%).

*For the 21 supportive studies:*

In the 5 OL studies in healthy subjects, the dose ranging study and the two pilot studies, the incidence of DAEs was low (0-3 per study) with vomiting the only AE occurring in more than one subject (2 with T/A, 2 with T, 1 with A).

---

<sup>48</sup> For people taking the blood-thinning medication warfarin pro thrombin test results are given as a number that represents a ratio called the international normalized ratio (INR). The INR is a calculation (ratio) of a measured prothrombin time test result to a normal value for a prothrombin time test taken in a specific laboratory.

*In the 5 multi-dose studies in chronic pain subjects:* The incidence of DAEs with T/A was greater in PRI/TRP-CAN-1 (28.7%) than in the other studies (13.1-18.6%); and in all the studies, DAEs occurred with T/A to a greater degree than with PBO (2.5-11.5%). The most frequent AEs causing withdrawal were nausea (3.9-9.0% with T/A, 0-4.5% with PBO), vomiting (1.9-6.0% with T/A, 0-1.2% with PBO), dizziness (1.9-6.0% with T/A, 0-2.4% with PBO), headache (3.8-4.2% with T/A, 1.3-1.8% with PBO) and somnolence (0.6-3.0% with T/A, 1-1.3% with PBO), with nausea and somnolence both causing at least one DAE in each of the 5 studies.

There were no DAEs in the single dose study in acute pain (C-128) but in the 2 multi dose studies (C-105, C-115), DAEs occurred in 8.2-13% of T/A subjects, 3-5% of PBO subjects and 10.1% of A/COD, with the most frequent causes being nausea (3.1-8.6% T/A, 0.9-1.0% PBO, 3.7% A/COD), vomiting (4.1-5.6% T/A, 0.9-1.0% PBO, 3.7% A/COD) and dizziness (1.0-4.6% T/A, 0-0.9% PBO, 0% A/COD).

In the post marketing studies in patients with acute pain, the incidence of DAEs was similar for patients taking T/A (5.2%) and HYD/A (4.4%) in C-216 but greater for those taking T (22%) compared to those taking T/A (8%) in GRTF-ZAL1. In C-241 there was 1 DAE each with T/A and T. In SP-ZAL-III-02, similar numbers discontinued due to AEs with T/A (27.4%) and A/COD (26.9%), with the most frequent AEs being nausea (6.0% T/A, 7.6% A/COD), vomiting (4.3% T/A, 5.0% A/COD) and dizziness (4.3% T/A, 4.2% A/COD). In ZAL-06 there were more DAEs with T (6.3%) than with T/A (4.7%), with the most frequent being nausea (3 T/A subjects, 4 T subjects), vomiting (2 T/A subjects, 3 T subjects) and dizziness (2 T/A subjects, 3 T subjects).

### **Post marketing experience**

T/A was first approved in the USA on 15 August 2001 and later in Europe (5 April 2002). Periodic safety update reports (PSURs) were provided up til 14 August 2010. The cumulative patient exposure to T/A from 15 August 2001 to 14 August 2010 is approximately between 1059 and 2118 million patient-treatment-days.

The PSUR for 5 April 2003-4 October 2003 identified a possible safety risk due to an atypical withdrawal reaction having been noted for T. The sponsor determined to add to the safety information in the PI for T/A to the effect of, "Other symptoms, that have been seen very rarely with T discontinuation include: panic attacks, severe anxiety, hallucinations, paraesthesias, tinnitus, and unusual CNS symptoms."

All other PSURs confirmed the favourable safety profile of T/A, with no new drug risks identified and no change to the benefit-risk ratio.

### **Evaluator's overall conclusions on clinical safety**

Safety assessment involved assessment of AEs, SAEs, DAEs, deaths, specific AEs (AEs related to convulsions/seizures, liver function, renal function; anaphylactoid/anaphylactic reactions or anaphylactoid shock; dependence/abuse and withdrawal symptoms), vital signs and physical examinations. Safety data was reviewed for the 12 primary source studies (including the 3 pivotal studies) and for the 21 supportive studies. The total safety population from all studies in the submission included 8478 patients with pain (4756 acute pain, 3722 chronic pain; 2556 with pain specified as moderate, 1165 with pain specified as severe) and 124 healthy subjects.

### **Exposure**

Overall, 3814 patients with pain and 119 healthy subjects were exposed to T/A 37.5/325 mg tablets (age range 16-91 years old): 637 to single doses of 1-3 tablets and 2950 to multiple doses of up to 10 tablets per day. Of those patients receiving T/A 37.5/325 mg,

327 received the study drug for >180 days and 120 received the study drug for >360 days, fulfilling the TGA requirements for safety data in 300-600 patients for 6 months or longer.

### ***AE profile***

The AE profile for T/A remained consistent across the range of studies in patients with acute and chronic pain. The overall incidence and types of AEs were similar for T/A and the comparators A/COD and IBU, however, the incidence of constipation was greater for A/COD. The most frequent AEs with T/A occurred in the GI system and CNS or were Psychiatric AEs and consisted of nausea, dizziness, somnolence, constipation, headache, and vomiting. Length of treatment with T/A did not affect the frequency of any AEs. Specific AEs related to convulsions/seizures, liver function, renal function, dependence/abuse and withdrawal, occurred with a low incidence and there were no reports of anaphylactoid/anaphylactic reactions or anaphylactoid shock. AEs were generally mild to moderate.

When T/A data was compared to historical T data the average daily dose of T with T/A 37.5/325 mg was 131-176 mg, while the average daily dose of T with T 50 mg was 250 mg. There was a clear dose response, with the incidence of AEs increasing with the dose of T. This was also evident for the elderly population  $\geq 65$  years of age.

The incidence of deaths was low and all deaths associated with T/A were considered unlikely to be related to study medication. The incidence of non-fatal SAEs with T/A was low and similar to the A/COD and IBU treatment groups. The incidence of DAEs was similar for the T/A to A/COD, IBU and HYD/A treatment groups and greater for T compared to T/A. There were no clinically relevant consistent abnormal laboratory findings or abnormalities of vital signs or physical examination.

The AE profile of T/A was consistent with the known profiles of the component medications, T and APAP, with no new or unexpected safety issues identified.

### ***Effervescent tablet***

Since PK BE of the two tablets has been established, the AE safety data from the T/A FCT can be extrapolated to the equivalent dose effervescent T/A tablet. However, the evaluator has identified three formulation specific potential safety concerns that may not have presented on evaluation of the FCT formulation:

1. Effervescent tablets often contain high sodium and/or potassium levels, making them a poorer choice for elderly patients or patients with renal insufficiency.
2. There is a warning under *Precautions* in the PI for T/A, in a paragraph regarding the effervescent tablet. However it may be well to also add a warning to the paragraph(s) pertaining to the groups of patients that may be affected, that is under the headings 'Use in the elderly' and/or 'Impaired renal function', to the effect that it is better not to use the effervescent tablet in these groups or to state that studies have not been done with the effervescent tablet in these patient groups.
3. The potential for abuse may be greater when a drug is available in liquid form, as is the case with the effervescent tablet.
4. There is a lack of actual efficacy/safety data with the film-coated tablet in the group of patients aged 12-16 years.



Although the data in the submission and post marketing experience with T suggest a low likelihood of abuse with the FCT of T/A, it may be that a liquid form of the drug would present an easier form of ingestion, and 'an easy drug to ingest' may be particularly relevant to this age group when looking at risk taking behaviour. Counter to this, the reasons identified for the low likelihood of abuse with the FCT would apply to the effervescent tablet as well: being a prescription drug decreases general availability of the tablet and increases accountability of the person purchasing the drug, the dose of T is lower in the combination tablet than in the monotherapy tablet, and T is nausea inducing in a dose dependent manner. Overall, the evaluator thought that the likelihood of abuse with the effervescent tablet was low and this will be monitored through the PSURs.

### ***Overdose***

Overdose may lead to symptoms and signs of toxicity of either or both of T and APAP.

Symptoms and signs of toxicity of T include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Symptoms and signs of toxicity of APAP include pallor, nausea, vomiting, anorexia, abdominal pain, liver damage up to hepatic failure, encephalopathy, coma, death, acute renal failure, cardiac arrhythmias and pancreatitis.

Immediate treatment in a hospital is required.

### ***Abuse/withdrawal***

The submitted studies and postmarketing experience with T indicate that the likelihood of abuse and withdrawal symptoms with T/A is low.

## **Clinical summary and conclusions**

### **Benefit risk assessment**

#### ***Benefits***

- There was no PK interaction of T and APAP when given in combination, as single or multiple doses (T-P-001, T-P-002, T-P-003), therefore PKs of T/A can be predicted from those of T and APAP.
- Food did not affect the BA of T or APAP when given as T/A (T-P-003).
- There was no clinically relevant effect on the PKs of T or APAP that would require a dose adjustment of either, from gender, race, body weight,  $CL_{CR}$ , smoking, CYP2D6 genotype, age or concomitant oestrogen medication (DM98313, DM98311).

In the analgesic treatment of pain:

- Three randomised, DB active and PBO controlled, pivotal studies (T-A-010, T-A-012, T-A-013) found that T/A:
  - In single doses provided statistically significantly greater pain relief than PBO or either component T or APAP, over 8 h in the treatment of 'moderate to severe' acute pain
  - had an onset of analgesia comparable to that of APAP
  - had a duration of analgesia comparable to that of T

- was effective in controlling chronic non malignant pain for up to 27 months without the development of tolerance (T-A-006-OL, T-A-015).
- was effective in the treatment of both 'moderate to severe' and 'mild to moderate' acute pain from oral and post surgical procedures, a flare of osteoarthritis, subacute low back pain and musculoskeletal pain (C-128, C-241, C-216, C-105, C-115, GRTF-ZAL1, ZAL-06).
- had comparable efficacy to HYD/A in the treatment of 'moderate to severe' acute musculoskeletal pain from an ankle sprain (C-216)
- gave comparable efficacy to A/COD in the treatment of 'mild to moderate' post surgical pain (C-115)
- 37.5/325 mg gave comparable or superior efficacy to T 50 mg in the treatment of 'moderate to severe' and 'mild to moderate' acute pain (C-241, GRTF-ZAL1, ZAL-06)
- was effective when used as adjunctive treatment to iCOX2 in the treatment of 'moderate to severe' chronic pain from osteoarthritis (C-114).
- was effective in the treatment of 'mild to moderate' chronic pain of benign origin, pain from osteoarthritis, low back pain and pain from fibromyalgia (T-A-008, T-A-009, T-A-006, SP-ZAL-III-02, C-112, C-113).
- gave comparable efficacy to IBU and A/COD in the treatment of chronic pain (T-A-008, T-A-009, T-A-006, SP-ZAL-III-02).

### **Risks**

T/A:

- was generally well tolerated in the target population.
- has not been studied in patients with renal impairment.
- has not been studied in patients with hepatic impairment.
- has not been evaluated in cancer-related pain.
- the effervescent T/A tablet has not been evaluated directly.

### **Balance**

Efficacy of T/A in the treatment of moderate to severe acute pain and mild to moderate chronic pain was demonstrated as equal to or better than the component drugs, T and APAP, and comparable analgesics; together with an AE profile comparable to that of the component drugs. However, as the AEs of T are dose dependent and the daily doses of the component drugs are significantly decreased when taken as a combination medication, the AE profile of T/A is improved over that of T and comparable medications. The analgesic benefits of T/A therefore outweigh the potential risks. T/A provides a useful 'Step 2' drug that combines the speed of analgesia of APAP with the increased duration and strength of analgesia of T.

The efficacy and safety data from the T/A FCT can be extrapolated for the effervescent T/A tablet due to the demonstration of PK BE of the two tablets.

T/A was not studied in cancer pain directly but was studied in both visceral and somatic pain and both of the individual components, T and APAP, have general pain indications. The indication for T/A needs to reflect the lack of cancer pain studies, either by being

*'For pain in general. T/A has not been studied in cancer-related pain.'*

or by more specifically limiting the indication to



*'Moderate to severe acute pain and mild to moderate chronic pain'.*

The drug fulfils criteria for a fixed combination medication as both T and APAP contribute to the analgesic effect of T/A (quick-acting APAP, and longer/stronger acting T), the combination gives an improvement in the benefit/risk ratio (by giving equal or improved efficacy with decreased AEs, as a result of lower daily doses of component drugs) and the treatment regime is simplified and compliance is expected to improve as a result.

## **Conclusions**

It was recommended that the application to register two dosage forms of the combination medication Zaldiar (tramadol hydrochloride/acetaminophen; 37.5/325 mg), a film-coated tablet and an effervescent tablet, for the symptomatic treatment of moderate to severe acute pain and mild to moderate chronic pain be approved, with consideration of the suggested changes to the wording of the indication and draft PI.

## **V. Pharmacovigilance findings**

An RMP was not required for this application.

## **VI. Overall conclusion and risk/benefit assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

There were no objections in respect of quality (chemistry, manufacturing and controls) to registration of Zaldiar film-coated and effervescent tablets. The quality evaluator was satisfied with the bioavailability studies and noted that the effervescent and film-coated tablets are bioequivalent. The rate of absorption of both drug substances is reduced by food but the extent of absorption is not affected. Bioavailability of each of the component actives is not altered by the presence of the other active. Absorption of both components after oral administration is high.

### **Nonclinical**

There were no objections on nonclinical grounds to the registration of Zaldiar. Efficacy studies in rodents supported clinical data demonstrating supra additive analgesic and anti-hyperalgesic effects of combination dosing with tramadol and paracetamol. No secondary effects particular to the combination were identified. No genotoxicity or carcinogenicity data were submitted for the combination. Previous assessments have noted paracetamol genotoxicity after long exposures at hepatotoxic doses (unlikely with normal therapeutic use) and liver and bladder tumours have been reported at very high, cytotoxic doses of paracetamol. Taking into account the evidence of a threshold effect, it is considered that paracetamol is non genotoxic and non carcinogenic at therapeutic doses. Tramadol (100 µg/mL) was genotoxic in the mouse lymphoma assay in the presence of metabolic activation but negative in all other tests.

Carcinogenicity studies showed a dose related increase in hepatocellular adenoma in males and an increases incidence of pulmonary adenomas in female mice (common tumours in aged mice) that was not dose dependent. The genotoxic and carcinogenic

liabilities of paracetamol and tramadol individually are considered to be low at therapeutic doses and a similar conclusion for the combination was considered reasonable.

No metabolic inhibitory activity between paracetamol and tramadol was detected in liver microsomes at therapeutic concentrations. Tramadol metabolism primarily involves CYP2D6, CYP2B6 and CYP3A4/5; paracetamol metabolism involves CYP2E1, CYP1A2, CYP3A4 and CYP2D6.

Reproductive toxicity studies with the combination were limited to one embryofetal development study in rats. Observations were similar to corresponding tramadol alone studies. The reproductive toxicity profiles of tramadol and paracetamol individually were generally unremarkable, with adverse embryofetal/offspring effects likely to be secondary to maternotoxicity. There was no evidence of teratogenicity in mice, rats or rabbits.

## Clinical

### Pharmacology

There were no pharmacodynamic studies included in this submission.

As noted in the PIs for products containing tramadol: after oral administration of two 50 mg capsules, the mean absolute bioavailability (f<sub>abs</sub>) is 68-72% and the peak serum level (C<sub>max</sub>) is reached two hs (range one to three) after administration. After repeated oral administration of 50 mg and 100 mg tramadol capsules at six hly intervals, steady state is reached 30 to 36 hs after the first administration and the bioavailability is greater than 90%. The plasma concentrations at steady state exceeded by 52% and 36% those extrapolated from the single dose administration studies with 50 mg and 100 mg capsules respectively. This can be explained by first pass metabolic saturation.

The PIs for products containing paracetamol note that it is absorbed rapidly and completely from the small intestine after oral administration. Peak plasma paracetamol concentrations occur 30 to 120 minutes after oral administration. It is uniformly distributed throughout most body fluids with an apparent volume of distribution of 1 to 1.2 L/kg. Plasma protein binding is negligible at the usual therapeutic concentrations but increases with increasing plasma concentrations. Approximately 90 to 95% of a dose of paracetamol is metabolised by the hepatic microsomal system. In adults at therapeutic doses paracetamol is mainly conjugated with glucuronide (45-55%) or sulphate (20-30%).

Five pharmacokinetic studies of Zaldiar in healthy subjects were included in the submission. C<sub>max</sub>, T<sub>max</sub> and AUC for tramadol and paracetamol from Zaldiar were compared with dose normalised PK data from tramadol and paracetamol given as oral solutions in previous studies. Results are summarised in the clinical evaluation. The T<sub>max</sub> values for both tramadol and paracetamol were longer when given as Zaldiar compared with the oral solutions whereas mean AUC was comparable. Food has no clinically significant effect on absorption of either tramadol or paracetamol from Zaldiar tablets. The effervescent tablet was bioequivalent to the film-coated tablet with respect to AUC and C<sub>max</sub>. Potential drug-drug interactions were not explored with the sponsor claiming these could be predicted from knowledge of the individual active constituents.

Two population PK analyses were submitted. These analyses considered the effects of sex, body weight, renal function, race, smoking and CYP2D6 Poor Metaboliser status. The first analysis included only 84 healthy adult subjects with a necessarily narrow range of body weights and renal function and only 6 CYP2D6 Poor Metabolisers. This analysis showed no PK effects for any of the tramadol components or for paracetamol that were not already known for the individual active components. A larger population PK analysis was

performed with 236 patients from the efficacy/ safety studies. That analysis also showed no unexpected PK effects.

### **Efficacy**

Three randomised, double blind, single dose studies in patients with moderate to severe pain were identified as pivotal. All involved patients with pain after oral surgery. There were 8 other single dose studies, including 3 dose-finding studies and 18 multiple dose studies that were considered supportive.

Three summary efficacy variables were used in the pivotal studies to indicate overall analgesic effect and are derived from measures of:

- pain relief (PAR; 0=none, 1=a little, 2=some, 3=a lot, 4=complete),
- pain intensity difference (PID; difference between current pain intensity [0=none, 1=mild, 2=moderate, 3=severe] and baseline pain intensity [2=moderate or 3=severe]); and
- the sum of the two (PRID [PAR+PID]).

The summary efficacy variables determined for a time interval were:

- total PAR (TOTPAR; the sum of hly PAR scores),
- sum of PID (SPID; the sum of hly PID scores), and
- sum of PRID (SPRID; sum of hly PAR and PID [PRID] scores).

These variables are commonly used as efficacy endpoints in pain studies. For each variable, higher values reflect greater analgesic effect.

*Dose finding* was assessed in 3 studies. *Study T-A-007* was a dose response study that compared 6 single dose treatments: T/A 25/650 mg, T/A 50/650 mg, T 25 mg, T 50 mg, A 650 mg and PBO. Subjects could receive a supplemental analgesic during the study. The objectives were to evaluate and compare analgesic efficacy and safety of the six single dose treatments over 8 h in subjects with at least moderate post operative dental pain from mandibular third molar extraction.

Fifty subjects were enrolled in each treatment group. Statistical comparisons for each of the 5 active regimens against placebo and the T/A 50/650 and T/A 25/650 combinations versus each component for TOTPAR, SPID and SPRID for the 0-8 h post treatment time interval have been summarised in the clinical evaluation.

*Study CA* compared T/A 100/500 mg with placebo, T 100 mg and A 500 mg given separately in patients undergoing molar extraction.

*Study CB* compared T/A 25/500 mg with placebo, T 25 mg and A 500 mg given separately to patients after caesarean section. Results for these studies are shown in the clinical evaluation. These studies showed generally favourable comparisons for the 2 T/A combinations assessed against tramadol and paracetamol given alone at the same doses but most comparisons of the combination with each active given separately did not reach statistical significance. These studies informed the design and size of the pivotal studies and also affected the composition of the proposed combination. The 650 mg dose of paracetamol was chosen for the final combination because it was considered that there was no evidence of a linear dose response curve of paracetamol and the maximally effective single oral dose of 650 mg of paracetamol, according to the available evidence, has been tested versus the combination (sponsor's Clinical Overview).

*The pivotal studies (T-A-010, T-A-012, T-A-013)* had the same design and are discussed together in the clinical evaluation report (CER) above. These were single centre,

randomised, double blind active and placebo controlled studies with a factorial design. The objective was to evaluate efficacy and safety of combination T 75 mg with A 650 mg in subjects experiencing pain from an oral surgical procedure and to demonstrate the contribution of each component to the analgesic effect of the combination.

A total of 1200 subjects (400/study) aged over 16 years with moderate or severe pain following an oral surgical procedure (extraction of 2 ipsilateral, or >2, third molars requiring bone removal) were enrolled. Subjects were stratified by baseline pain severity: moderate or severe and received one of 5 single dose treatments (T/A 75 mg/650 mg, T 75 mg, A 650 mg, IBU 400 mg or PBO). Subjects could receive a supplemental analgesic during the studies. If a subject took rescue medication or discontinued prematurely, remaining observation points were filled using the last observation carried forward (LOCF) method. The protocols did not specify what type of rescue medications was to be used should the analgesic effect of study medication be insufficient, other than that the rescue medication not contain paracetamol or tramadol.

Across the studies most subjects were female (55-63%) and Caucasian (75-93%). The mean age was 21.1-21.7 years (range 16-46 years). Baseline pain was consistent across the studies (moderate for 66-70%, severe for 30-34%; mean rating (6.1-6.2); and the majority of subjects had 4 molars removed (64-83%). Table 11 presents the primary summary efficacy variables (TOTPAR, SPID, and SPRID) and statistical comparisons for the intervals 0-4 h, 4-8 h and 0-8 h for each of the pivotal studies.

In each study, IBU was superior to placebo for each of the primary efficacy measures ( $p < 0.001$ ) demonstrating sensitivity of the models. Table 11 also provides statistical comparisons for T/A 75/650 mg against T 75 mg and A 650 mg in the 3 pivotal studies. For the majority of efficacy endpoints T/A 75/650 mg was superior to T 75 mg and A 650 mg alone. For all three studies there were no statistically significant differences for TOTPAR, SPID and SPRID scores for subjects reporting moderate baseline pain intensity compared to those reporting severe baseline pain intensity. No comparison of T/A 75/650 mg with IBU 400 mg was performed but in general the mean measures of pain relief were greater for IBU than for T/A 75/650 mg.

Table 12 shows the cumulative number of subjects requiring rescue medication each h post dose for the three pivotal studies. In *Studies T-A-010* and *T-A-012*, the T/A groups had a greater number of subjects not requiring rescue medication at any time during the study (26-36%) compared to T (14-18%), A (10-18%) and PBO (5-9%). In *Study T-A-013*, the T/A and T groups had a similar number of subjects not requiring re-medication at any time during the study (28-29%), greater than for A (15%) and PBO (9%), that is, 64% to 74% of subjects given T/A 75/650 in the pivotal studies required additional analgesia at least once during the study.

A further 5 studies of similar design were conducted. Two pain models were investigated in the early development program of T/A: *T-A-002*, *T-A-003* and *T-A-011* (all non-supportive) were single dose studies in acute pain from oral surgery. *Studies T-A-004* and *T-A-005* were single dose studies in acute pain from gynaecologic and orthopaedic surgery respectively. They did not use the proposed dose regimen and were also non supportive. In these early single dose trials, tramadol/paracetamol was always numerically superior to each of its components alone but failed to reach the level of statistical significance, primarily compared with paracetamol in the dental pain model and tramadol in the postsurgical model. The sponsor postulated that uncomplicated third molar extraction in the early dental pain trials was not sufficient enough to allow the effect of paracetamol to wear off and permit discrimination of the combination from paracetamol, particularly once the peak plasma level of paracetamol was achieved and that the higher doses used in the postsurgical model resulted in a dose of tramadol that reduced the sensitivity of this

model to discriminate between the combination and tramadol (sponsor's Clinical Overview).

A meta analysis of Studies T-A-002, 003, 004, 005, 010, 012 and 013 (single dose studies in dental pain) and 18 studies from an earlier sponsor (Grünenthal) were re-analysed in an updated meta analysis taking into account baseline pain intensity. That analysis was reported as showing that 48/109 patients with severe pain given T/A reported improvement in pain compared with 2/94 patients given placebo in the same studies. For patients with severe pain at baseline the NNT for a 50% reduction in pain was 2.4 (1.9 to 3.1) at 6 h post dose compared with 3.3 (2.1 to 8.0) for T alone and 3.5 (2.2 to 9.6) for A alone.

There were 3 multi centre, multiple dose, Phase III studies in subjects with moderate or severe chronic pain conducted prior to 2001: *T-A-008*, *T-A-009* and *T-A-006* were randomised, DB, parallel group, active controlled studies to evaluate relative potency and safety of T/A compared to IBU (*T-A-008*, *T-A-009*) or paracetamol/ codeine 300/30 mg (*T-A-006*). Studies *T-A-008* and *T-A-009* also provided information on the average dosing requirements of such treatment. In Studies *T-A-008* and *T-A-009* subjects received T/A 37.5/325 mg or IBU 200 mg, (x1-2 q4h-q6h, max 10/day [8/day if >75 year]) for 56 days. Supplementary analgesia was available if required (containing PBO [for T/A treatment group] or IBU 200 mg [for IBU treatment group], x1 prn, max 6/day).

These studies were not designed to demonstrate equivalence or apparently superiority of one treatment over another. The clinical evaluation showed the TOTPAR, SPID and SPRID 0-6 h scores for Studies *T-A-008* and *T-A-009* respectively. The difference of mean pain scores for T/A 37.5/325 mg and IBU 200 mg were given but there was no discussion of what would constitute a meaningful difference between treatments and no statistical efficacy data were presented. Supplementary analgesia was given, with the majority of patients in both the T/A and IBU groups in both studies.

Ten additional safety/efficacy studies in either acute or chronic pain were completed after the initial marketing authorisation for T/A was submitted in the EU. A total of 2,992 subjects were enrolled into these ten studies. They are discussed briefly by the clinical evaluator. Five of these studies were placebo controlled, multiple dose studies in patients with chronic pain conducted over 3 months (CAPSS-104, 112, 113, 114 and PRI/TRP/CAN1). Subjects were primarily 40-75 years of age and were taking a stable daily dose of an NSAID for at least three months before study entry. In CAPSS-114, subjects who had been taking a COX-2 selective inhibitor for pain relief were permitted to continue taking it while in the trial. All subjects had at least moderate baseline pain (mean pain severity ranged from 67.8 mm to 80.1 mm, on a standard PVA scale, 0-10 mm). Study drug was titrated from one (tramadol 37.5 mg with paracetamol 325 mg) to 4 tablets/day over the first 10 days, followed by a regimen of 1 or 2 tablets every 4 to 6 hs as needed. The maximum dose allowed was 8 tablets/day (tramadol 300 mg with paracetamol 2600 mg) (sponsor's Clinical Overview).

T/A was statistically superior to placebo in lowering the PVA score in PRI/TRP/CAN1 and CAPSS-112 and CAPSS-114 and in increasing the time to discontinuation due to efficacy failure in CAPSS-113 and PRI/TRP/CAN1. Statistical significance in lowering the PVA score was not demonstrated in CAPSS-104. A meta analysis of chronic pain studies was conducted using data from Studies CAPSS-104, 112, 113 and 114. In that meta analysis T/A was superior to placebo for chronic pain. The meta analysis also compared T/A in the above studies with T alone given at a higher dose in other studies. For that comparison the authors of the analysis concluded that efficacy of T/A was similar to that of T alone.

There were 3 randomised, double blind, controlled multi dose studies conducted after 2001 in patients with acute pain (CAPSS-105, 115, and GRTF-ZAL1). These studies examined efficacy and safety of T/A over 6-10 days in subjects with acute pain of at least

moderate intensity from osteoarthritis (CAPSS-105), low back pain (GRTF-ZAL1) and surgery (CAPSS-115), respectively. GRTF-ZAL1 was a comparison of patient satisfaction with the association tramadol (37.5 mg) plus paracetamol (325 mg) versus tramadol (50 mg) for the treatment of subacute low back pain. It was a small study with 60 patients in each group and failed to show a statistically significant difference between the 2 treatment groups. Study CAPSS-105 subjects required a minimum PVA score of 50 mm (on a 100 mm scale) and in CAPSS-115 the minimum pain score was 40 mm. In both these studies T/A was superior to placebo over a period up to 10 days.

## **Safety**

Across the 12 trials initial studies safety data were evaluated from the 1,909 subjects who were treated with tramadol/paracetamol, 306 of whom were treated with the combination for at least six months.

Additional patients were studied in the 21 studies performed subsequent to the initial marketing authorisation being granted. Post marketing spontaneous adverse event reports were also available with an estimated exposure from August 2011 to August 2010 of from 1059 to 2118 million patient-days.

The safety profiles of tramadol and paracetamol are well known and the dose regimens for each component allow for less than the current maximum recommended dose of each component given as monotherapy. The sponsor's Clinical Overview showed results of a combined analysis of adverse drug reactions (ADRs) reported in double blind or open label studies clinical studies where T/A was compared with T alone (at either the same dose as T/A or higher).

These showed reduced constipation, nausea, vomiting and dizziness associated with T/A compared with T alone. Given the generally lower dose of T in T/A these lower ADR incidences were not unexpected as those ADRs are dose related. No new safety concerns were apparent from the clinical trial program. Safety was assessed over a maximum duration of 6 months. This is acceptable given the extensive data on long term use of each component.

No drug interaction studies were performed and this product relies on interaction data available for each of the active components. Dependency and withdrawal effects were not examined. It is anticipated this product would have similar propensities for dependency and withdrawal effects as tramadol. Its use in overdose would result in a combination of the toxicities of tramadol and paracetamol.

The clinical evaluator noted the sodium (7.8 mmol, that is, 179.4 mg/ dose) content of the effervescent tablet. In patients with sodium restriction this should be taken into account and should be adequately reflected in the information to prescriber and consumers.

## **Risk Management Plan**

An RMP was not required for this submission.

---

## Risk-benefit analysis

### Delegate considerations

#### Discussion

The mean  $t_{1/2}$  of paracetamol was 2.54 h compared with 5.14 h for (+)-T and 4.67 h for (-)-T, 7.78 h for (+)M1 and 6.18 h for (-)M1. The mean  $T_{max}$  was 0.9 h for paracetamol compared with 1.8 h for (+)-T and (-)-T and 2.1 h for (=)-M1 and 2.2 h for (-)-M1. This suggests that the initial analgesic effect from the combination would be due primarily to the paracetamol component and the effect towards the end of the 6 h dose period to be primarily due to tramadol. This may cause some variation in degree of analgesia throughout the dosing period but this occurs with analgesics in any case as the concentration of active rises and falls during the dose period.

The minimum time between doses of 6 h is longer than the dose duration of 4 to 6 h recommended for tramadol or paracetamol alone. As with dosing of the individual actives, dose adjustment is not required for sex, race, body weight, smoking or CYP2D6 phenotype. The effect of renal impairment on the PK of the component actives has not been adequately explored. Subjects with renal impairment were not included in the clinical trials or in the population PK analyses.

The initial dose finding studies examined T/A combinations of 50/ 650 mg and 25/ 650 mg but not the 70/ 650 mg combination proposed as the usual dose regimen for Zaldiar. All the dose finding studies were underpowered to determine differences between active regimens. Nevertheless, the T/A combinations generally performed better than either the 25 mg or the 50 mg dose of tramadol given alone. The 650 mg dose of paracetamol was comparable in analgesic effect to the T/A 25/650 mg combination, suggesting a higher dose of tramadol was required in the combination product. Also of interest was that 650 mg paracetamol consistently performed better than 50 mg tramadol, though no statistical comparisons of these regimens were submitted.

The current 1000 mg single dose of paracetamol, which is the recommended dose for adults in Australia was not compared with any of the T/A combinations in the dose finding or the efficacy studies, nor was a T/A combination that included 1000 paracetamol examined. It is not clear from the data submitted that the chosen ratio for tramadol and paracetamol is optimal or that the dose regimen is optimal.

The pivotal studies in acute pain demonstrated that the proposed combination, given at the proposed dose was superior to either component given alone. The majority of subjects in these studies had moderate pain with mean baseline pain rating 6.1 or 6.2 in each of the 3 studies. The proportion of subjects with severe pain at baseline who required additional analgesia in each study was not presented.

The conditions examined were not those generally chosen for assessment of efficacy in severe pain, in particular there was no assessment of efficacy in patients with pain associated with malignancy. Studies performed after the initial marketing authorisation was given also did not clearly assess efficacy of the combination in patients with severe pain.

Some 64 to 74% of subjects in the pivotal acute pain studies given T/A 75/650 mg required additional analgesia. Time to re-medication was longer for T/A 50/650 mg (257 min) than for T 50 mg (120 min) and paracetamol (195 min). This does not support the proposed dose interval of 6 h (360 min). Onset of pain relief was statistically significantly faster for both T/A combinations than component T doses ( $p \leq 0.041$ ) but not for paracetamol. Mean duration of pain relief was statistically significantly longer for T/A

50/650 mg (257min) than for T 50 mg (120 min; p) and paracetamol 650 mg (195 min). Again this does not support the proposed dose interval of 6 h (360 min). It may be however that the combination provides insufficient analgesia in the majority of cases of severe pain, leading to these patients requesting additional analgesia prior to the end of a dose interval. This would then appear as if the chosen dose interval was too long.

The meta analysis of acute dental pain studies and 18 earlier studies did not show a statistically significant difference between T and A given alone and T/A for patients with severe pain in single dose studies at 6 hs post dose.

Use of Zaldiar in patients with chronic pain has not been thoroughly examined. Most evidence for efficacy was obtained in 5 studies where T/A was given every 4 – 6 h rather than at a maximum of every 6 h as proposed. There is no comparison of Zaldiar with its active components in patients with chronic pain. When given every 4 - 6 h Zaldiar was demonstrated to be superior to placebo in the majority of 12 weeks studies conducted after 2001. Earlier studies appeared to be exploratory only.

There is very limited assessment of the use of Zaldiar with other analgesics. It should not be used with opioid analgesics. Limited data suggest use no major changes to efficacy if Zaldiar is given in conjunction with an NSAID.

The Delegate did not consider that the study program had adequately assessed efficacy of Zaldiar in patients with severe pain. Given the proportion of patients in the pivotal studies who required additional analgesia and the lack of planned analyses in the subgroup of patients with severe pain The Delegate was not satisfied that Zaldiar provides sufficient analgesia for patients with severe pain. The Delegate did not propose to approve this product for use in patients with severe pain. Given the superiority of the proposed combination and dose regimen over each of the components given alone in the pivotal studies the Delegate proposed to approve Zaldiar at its proposed dose regimen for patients with moderate pain. This creates somewhat of an inconsistency given that tramadol alone is indicated for treatment of both moderate and severe pain, though with a higher daily dose of tramadol than the proposed combination product. The duration of assessment has been adequate given the indications for each component active ingredient.

The sponsor had proposed as an additional statement in the indications that *the use of Zaldiar should be restricted to patients whose moderate to severe pain is considered to require a combination of tramadol and paracetamol (see Pharmacology)*. The Delegate considered this an unnecessary statement that is likely to confuse potential prescribers. This product is one of many products likely to have similar analgesic properties and it has not been demonstrated that this particular combination product is required for the management of any degree of pain; it has only been shown that it has efficacy that is superior to each of its components given separately.

Use in children aged from 12 years has been proposed and is permitted for both tramadol and paracetamol given alone but no pharmacokinetic data for use in patients aged from 12 to 16 years were presented. In the absence of either PK or efficacy data the Delegate did not propose to approve use in adolescents aged from 12 to 16 years.

### **Conclusion and recommendation**

The Delegate proposed to approve Zaldiar film-coated tablets and effervescent tablets, each dose form containing 37.5 mg tramadol and 325 mg paracetamol for *the relief of moderate pain*. This proposed indication is consistent, as far as possible, with the available evidence and with the current indication for tramadol. The dose regimen should be as proposed by the sponsor.



The advice of the Advisory Committee on Prescription Medicines (ACPM) was specifically requested on the following:

- Should the sponsor be required to provide comparative efficacy data for Zaldiar with the standard maximum doses of tramadol and paracetamol that are recommended in Australia for either single or multi dose studies?
- Has efficacy of Zaldiar in the relief of severe pain been adequately demonstrated to support an indication that includes relief of severe pain?
- Should the indication for Zaldiar be limited to acute pain only due to the lack of comparative data for Zaldiar with its active components in patients with chronic pain?
- Should use of Zaldiar be limited to patients aged from 16 years rather than from 12 years as requested by the sponsor given the absence of PK and efficacy data in patients aged 12 to 16 years?

Definition of the Pain Intensity Score are outlined below:

- **PID:** Pain intensity difference is defined as the difference between the current pain intensity (that is, that experienced during the 8 h observation period; 0=none, 1=mild, 2=moderate, 3=severe) and baseline pain intensity (either moderate [2] or severe [3]). For individual subjects, hly PID scores range from -1 (indicating a change of moderate baseline pain to severe pain on therapy) to 3 (indicating a change from severe baseline pain to no pain on therapy).
- **PRID:** Pain relief combined with pain intensity difference in an hly pain assessment variable derived from combining hly pain relief and PID scores of individual subjects. For individual subjects, hly PRID scores range from -1 (a combination of 0 [no pain relief] and -1 PID score [indicating a change of moderate baseline pain to severe pain on therapy]) to 7 (a combination of 4 [complete pain relief] and 3 PID score [indicating a change from severe baseline pain to no pain on therapy]).
- **TOTPAR:** Summary efficacy variable that provides an indication of overall analgesic effect. This variable is calculated by summing over the appropriate hly pain relief evaluations. Hourly pain relief assessments are based on a rating scale of 0 (no relief) to 4 (complete relief); thus, summed over the entire eight-h observation period, TOTPAR results range from 0 (indicating no relief at any timepoint) to 32 (indicating complete relief at every time point).
- **SPID:** Summary efficacy variable that provides an indication of overall analgesic effect. This variable is calculated by summing over the appropriate hly PID scores. Thus, summed over an eight-h observation period, SPID results range from -8 (indicating an increase from moderate baseline pain to severe pain at each time point) to 24 (change from severe baseline pain to complete relief at each time point).

### Response from Sponsor

This Pre ACPM response document is based on the TGA Delegate's Overview dated 12 December 2011 that included a Request for ACPM advice and Review of the Product Information for Zaldiar. This response document provides comment in relation to the TGA Delegate's Request for ACPM advice.

The sponsor's main objection relates to the TGA Delegate's proposal "to approve Zaldiar film-coated tablets and effervescent tablets each dose form containing 37.5 mg tramadol and 325 mg paracetamol for the relief of moderate pain. This proposed indication is consistent as far as possible with the available evidence and with the current indication

for tramadol. The dose regimen should be as proposed by the sponsor.” The sponsor’s objection is detailed in Section 2.2 below.

### ***Request for ACPM advice***

In this section the sponsor comments on the questions for which the TGA Delegate has requested ACPM advice (see dot points above):

In considering this response, the sponsor asked the ACPM to take into account the long history of clinical use and established efficacy and safety of the individual components of this fixed combination product, namely tramadol and paracetamol, in the indication proposed by the sponsor. This history was acknowledged by the TGA in their presubmission approval of a Literature-based Submission for some components of the submission. The sponsor believes that the use of the fixed combination Zaldiar should be consistent with the established clinical use of its individual components in Australia and worldwide.

### *Comparison against maximum standard doses*

#### **Delegate’s request for ACPM advice:**

*Should the sponsor be required to provide comparative efficacy data for Zaldiar with the standard maximum doses of tramadol and paracetamol that are recommended in Australia for either single or multi-dose studies?*

### *Sponsor’s Position:*

Zaldiar was developed in accordance with applicable guidelines that were valid at the time of its clinical development, that is the European Union (EU) CPMP *Guidance for Fixed Combination Medicinal Products* (1996)<sup>49</sup> and the US FDA *Guideline for the Clinical Evaluation of Analgesic Drugs* (1992)<sup>50</sup>. Neither of these guidelines required comparison of the combination against the maximum or standard doses or both of its active components.

The above mentioned EU guideline states that a fixed combination product is justified if it results in “a level of efficacy similar to the one achievable by each active substance used alone at higher doses than in combination, but associated with a better safety profile”. This is fulfilled by Zaldiar because acute pain studies demonstrated that Zaldiar is superior to each component at a dose identical to each component’s dose in the combination and Zaldiar was superior in efficacy in a study comparing two tablets of Zaldiar to 100 mg of tramadol<sup>51</sup>.

Clinical studies<sup>51</sup> (Zal-06) demonstrate that higher doses of each of the individual active components of Zaldiar are needed to reach an efficacy similar to that of Zaldiar, in fact suggesting that for example 50 mg tramadol are equianalgesic to one tablet of Zaldiar. As elaborated in the sponsor’s Clinical Overview, the combination product has been shown to improve the safety profile relative to the individual compounds when administered at equianalgesic dosages.

In studies in chronic pain with Zaldiar, patients were instructed to adjust their dose of analgesic study medication to their personal optimum or to use their analgesic study medication as needed. This so called flexible dosing is a common feature of clinical trials in chronic pain. Its purpose (as compared to a fixed dose regimen) is to prevent that patients

<sup>49</sup> <http://www.tga.gov.au/pdf/euguide/ewp024095enfin.pdf>

<sup>50</sup> US Department of Health and Human Services FDA, *Guideline for the Clinical Evaluation of analgesic drugs*, 1992, Part IV/Volume 59/Page 75-106

<sup>51</sup> Fricke Jr. James R; Hewitt David J., Jordan Donna M., Fisher Alan, Rosenthal Norman R, A double-blind placebo-controlled comparison of tramadol/acetaminophen and tramadol in patients with postoperative dental pain; *Pain* 109 (2004) 250-257

withdraw due to side effects caused by a dose that is higher than needed for sufficient analgesia and/or which is soliciting intolerable adverse effects. The mean (SD) daily number of Zaldiar tablets taken in the Studies CAPSS-104, CAPSS-112, CAPSS-113, CAPSS-114 and PRI-TRP-CAN-1 were 3.9 (1.56), 4.2 (1.84), 4.0 (1.77), 4.1 (1.6) and 4.2 (1.7), respectively. This average dosing is confirmed by data from post marketing surveillance studies<sup>52,53</sup> which revealed an average number of 3.8 (1.1) and 3.8 (1.4) tablets taken per day, respectively.

This shows that on average patients took doses clearly lower than the maximum daily allowance of 8 tablets per day (which would be equianalgesic to the standard maximum dose of tramadol recommended in Australia based on the study results mentioned above).

Consequently, a study in chronic pain comparing Zaldiar against tramadol alone at the maximum daily dose using a fixed dose regimen would not reflect clinical practice and would bear an inherent risk not to provide valid results because a substantial part of the trial population would receive higher doses than actually needed.

In conclusion, studies comparing Zaldiar with its individual active components at maximum standard doses are not required by the guidelines and are considered unlikely to produce meaningful results. (For further discussion on the need for comparative data see below.)

*Information supporting the use of Zaldiar for relief of severe pain*

**Delegate's Request for ACPM Advice**

*Has efficacy of Zaldiar in the relief of severe pain been adequately demonstrated to support an indication that includes relief of severe pain?*

*Sponsor's Position:*

As outlined in the following the sponsor is of the opinion that the efficacy of Zaldiar has indeed been adequately demonstrated in both, moderate and severe, pain:

*Studies with Zaldiar supporting claim for moderate to severe pain*

For several single dose clinical trials the relative analgesic efficacy of the tramadol/paracetamol combination to its components and to placebo was evaluated as a function of baseline pain intensity. Data from three single dose efficacy trials were combined for these subgroup analyses and the analyses were performed on all efficacy variables. 379 of the 1,197 subjects evaluable for efficacy across the three pivotal single-dose trials (TRAMAP-ANAG-001, 002 and 003) rated their pain as severe before administering study medication compared to 818 who rated their baseline pain as moderate. Efficacy results are summarised by treatment group and baseline pain severity in Table 20. Baseline pain intensity had no apparent influence on the analgesic efficacy of the tramadol/paracetamol combination. In both pain severity subgroups, mean pain relief and pain intensity difference scores (PAR, PID, PRID) were consistently greater following a single dose of tramadol/paracetamol than following placebo or tramadol 75 mg at each observation point, and were superior to those in the paracetamol 650 mg group from Hour 2 through Hour 8. For the three summary efficacy variables, TOTPAR, SPID and SPRID, tramadol/paracetamol provided statistically superior pain relief compared with placebo,

<sup>52</sup> Serrie A, Jouve E, Creuse A, et al. Efficacy and safety of paracetamol (325 mg) – tramadol (37.5 mg) combination (PTC) in elderly patients: a PMS in general practice. *European Journal of Pain; (Suppl. 1),2009, S179*

<sup>53</sup> Mejjad O, Serrie A, Ganry H. Epidemiological data, efficacy and safety of a paracetamol–tramadol fixed combination in the treatment of moderate-to-severe pain. *SALZA: a post-marketing study in general practice. Curr Med Res Opin* 2011; 27 (5): 1013-1020.

tramadol 75 mg and paracetamol 650 mg over the 0-4 h, 4-8 h and 0-8 h intervals (two-sample t-test,  $p \leq 0.020$ ) in both the moderate and severe baseline pain subgroups (Table 21). In both subgroups, the median time to perceptible or meaningful pain relief was faster following administration of tramadol/paracetamol than following a single dose of placebo or tramadol 75 mg, while the estimated median duration of pain relief was longer for the combination than for either of its components. Thus, the tramadol/paracetamol combination has been shown to provide superior pain relief to either of its components in subjects suffering from moderate or severe dental pain.

**Table 20. Efficacy variables for 0-8 h interval in subjects with moderate or severe baseline pain: Combined pivotal single dose trials.**

Variable	Baseline Pain Intensity	TRAM/APAP	TRAM 75 mg	APAP 650 mg	Ibuprofen $\bar{x}$	Placebo
Number of Subjects <sup>a</sup>	Moderate	165	162	164	164	163
	Severe	75	76	76	76	76
Mean TOTPAR (0-8 hr)	Moderate	12.4	6.9	8.9	13.7	3.5
	Severe	11.4	6.2	7.7	13.4	2.8
Mean SPID (0-8 hr)	Moderate	3.3	-0.6	1.6	4.1	-3.1
	Severe	7.7	4.3	5.1	9.7	1.6
Mean SPRID (0-8 hr)	Moderate	15.7	6.3	10.5	18.0	0.4
	Severe	19.1	10.6	12.9	23.1	4.5
Median Time to Perceptible PR (min)	Moderate	25.0	54.1	26.9	39.9	81.5
	Severe	25.6	37.9	25.0	31.4	-- <sup>b</sup>
Median Time to Meaningful PR (min)	Moderate	59.9	-- <sup>b</sup>	60.1	106.7	-- <sup>b</sup>
	Severe	93.3	-- <sup>b</sup>	108.3	88.3	-- <sup>b</sup>
Estimated Median Duration of PR (min) <sup>c</sup>	Moderate	302.0	122.5	187.5	362.0	122.0
	Severe	266.0	122.0	180.5	388.5	96.0
Overall Assessment: % Rating Study Drug Excellent/Very good	Moderate	45%	21%	29%	46%	9%
	Severe	33%	16%	26%	43%	5%

<sup>a</sup> Number of subjects included in analysis of three summary variables; actual number of subjects with evaluable data for remaining efficacy parameters was same or fewer by one to three subjects in certain treatment groups.

<sup>b</sup> Not estimable.

<sup>c</sup> Same as median time to remedication.

**Table 21. Baseline Intensity. TRAM/APAP Comparison.**

Summary Variable/ Baseline Pain Intensity	Model Sensitivity <sup>a</sup>	TRAM/APAP Comparison <sup>b</sup>		
		vs. Placebo	vs. TRAM 75 mg	vs. APAP 650 mg
TOTPAR (0-8 hr)				
Moderate	<0.001	<0.001	<0.001	<0.001
Severe	<0.001	<0.001	<0.001	0.005
SPID (0-8 hr)				
Moderate	<0.001	<0.001	<0.001	0.005
Severe	<0.001	<0.001	<0.001	0.005
SPRID (0-8 hr)				
Moderate	<0.001	<0.001	<0.001	<0.001
Severe	<0.001	<0.001	<0.001	0.004

<sup>a</sup> P-value for statistical comparison of ibuprofen 400 mg vs. placebo, one-sided t-test.

<sup>b</sup> P-value for statistical comparison of Tramadol/APAP vs. placebo and each component, two-sample t-tests.

In addition, a meta-analysis of five dental pain trials (TRAMAP-ANAG-002, 003, 010, 012, 013) and two postsurgical pain trials (TRAMAP-ANAG-004, 005) along with 18 tramadol trials showed that baseline pain intensity (moderate or severe) made no difference on the NNT (see Table 22). This further supports the efficacy of the tramadol/paracetamol combination in moderate as well as severe pain.

**Table 22. Relative Benefit Number. Needed to treat for single dose pain trials by baseline pain. Intensity: Pain relief scores.**

Treatment	Baseline Pain Intensity	Improved on Active	Improved on Placebo	Relative Benefit (95% CI) <sup>a</sup>	NNT (95% CI)
<b>Dental Pain at 6 hours</b>					
TRAM/PARA	Moderate	97/231	12/245	8.6 (4.8 to 15)	2.7 (2.3 to 3.3)
TRAM 75 mg		35/238	12/245	3.0 (1.6 to 5.6)	10 (6.6 to 22)
PARA 650 mg		80/238	12/245	6.9 (3.8 to 12)	3.5 (2.8 to 4.5)
Ibuprofen 400 mg		111/234	12/245	9.7 (5.5 to 17)	2.4 (2.0 to 2.8)
TRAM/PARA	Severe	48/109	2/94	21 (5.2 to 83)	2.4 (1.9 to 3.1)
TRAM 75 mg		13/99	2/94	6.2 (1.4 to 27)	9.1 (5.5 to 27)
PARA 650 mg		28/102	2/94	13 (3.2 to 53)	4.0 (2.9 to 6.2)
Ibuprofen 400 mg		52/105	2/94	23 (5.8 to 93)	2.1 (1.7 to 2.7)
<b>Postsurgical Pain at 6 hours</b>					
TRAM/PARA	Moderate	28/53	11/48	2.3 (1.3 to 4.1)	3.3 (2.1 to 8.4)
TRAM 112.5 mg		15/44	11/48	1.5 (0.8 to 2.9) <sup>b</sup>	9.0 (3.4 to -14)
PARA 975 mg		13/44	11/48	1.3 (0.7 to 2.6) <sup>b</sup>	15 (4.1 to -8.8)
TRAM/PARA	Severe	32/48	15/52	2.4 (1.5 to 3.8)	2.5 (1.7 to 4.6)
TRAM 112.5 mg		32/54	15/52	2.1 (1.3 to 3.3)	3.3 (2.1 to 8.0)
PARA 975 mg		32/56	15/52	2.0 (1.2 to 3.2)	3.5 (2.2 to 9.6)

<sup>a</sup> A statistically significant benefit of active treatment over placebo was assumed when the lower limit of the 95% CI for relative benefit was >1.

<sup>b</sup> No significant difference between active and placebo.

Note: Improved = number of subjects with at least 50% pain relief and NNT = number-needed-to-treat for at least 50% pain relief over six hours.

Mean pain intensity was also evaluated in controlled multiple dose trials of three months duration in patients in whom chronic pain from osteoarthritis (CAPSS-104 and 114), low back pain (CAPSS-112 and PRI/TRP-CAN1) and fibromyalgia (CAPSS-113) ranged from moderate to severe pain (67.8 mm to 80.01 mm, on a standard Pain Visual Analogue scale, 0-100 mm; see Table 23). Available literature suggests that pain intensity above 54 mm on this instrument is likely to be severe pain<sup>54</sup>. An evaluation of the relative analgesic efficacy of the tramadol/paracetamol combination as a function of baseline pain intensity was not performed in these studies as the superiority of the combination to each component alone in moderate or severe pain was sufficiently proven in factorial designed single dose clinical trials. However, except for CAPSS-104, all of these trials showed a statistically significant superiority of Zaldiar over placebo which clearly demonstrates efficacy of Zaldiar in patients with moderate to severe chronic pain.

A meta-analysis based on NNTs calculated from chronic pain trials CAPSS-104, CAPSS-112, CAPSS-113 and CAPSS-114 concluded that the efficacy of Zaldiar is superior to that of placebo. This meta-analysis also found that NNTs for Zaldiar were similar to the NNTs found in a meta-analysis of trials with tramadol in chronic pain (sponsor's Clinical Overview). Hence, the sponsor believes that it is reasonable to conclude that Zaldiar and tramadol have similar efficacy in chronic pain. This justifies an indication for Zaldiar similar to the one for tramadol; "for the relief of moderate to severe pain".

<sup>54</sup> Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimeters? Pain 1997;72:95-97

**Table 23: Summary of baseline pain VAS<sup>3</sup> (mm), Intent to Treat Population.**

	Tramadol/Paraceta mol	Placebo	Total
<b>CAPSS-104</b>			
n	155	156	311
Mean	80.09	79.92	80.01
Median	81.0	82.0	81.0
SD	13.03	13.29	13.16
(Min,Max)	(47,100)	(45,100)	(45,100)
<b>CAPSS-112</b>			
n	161	157	318
Mean	71.1	68.8	70.0
Median	72.0	71.0	71.0
SD	14.54	14.87	14.72
(Min,Max)	(41,100)	(40,100)	(40,100)
<b>CAPSS-113</b>			
n	156	157	313
Mean	72.4	71.5	72.0
Median	75.0	72.0	74.0
SD	14.34	14.58	14.45
(Min,Max)	(26,100)	(40,100)	(26,100)
<b>CAPSS-114</b>			
n	151	151	302
Mean	69.0	69.5	69.3
Median	67.0	68.0	68.0
SD	12.52	13.17	12.85
(Min,Max)	(48,99)	(3,99)	(3,99)
<b>PRI/TRP-CAN1</b>			
n	167	169	336
Mean	67.9	67.6	67.8
Median	66.0	67.0	67.0
SD	14.95	15.53	15.22
(Min,Max)	(40,100)	(40,100)	(40,100)

a The Pain Visual Analog (PVA) Score was measured on a 100 mm scale (0=no pain; 100=extreme pain)

Furthermore post marketing surveillance studies confirm the good efficacy and tolerability profile of Zaldiar established in clinical trials in everyday clinical practice. For example, the two recently published post marketing surveillance studies<sup>55,53</sup> included 5495 and 2663 patients, respectively, with moderate to severe pain at baseline. In the study of Serrie et al.<sup>52</sup> mean pain intensity on the day of inclusion was  $6.3 \pm 1.9$  measured on NRS from 0 to 10. In these patients the most severe pain intensity over the last 8 days had been  $7.2 \pm 2.0$ . In the study of Mejjad et al.<sup>53</sup> the mean pain intensity on inclusion was  $6.1 \pm 1.6$  on the 11-point NRS. The maximum pain intensity over the previous 8 days was  $7.0 \pm 1.6$ .

These exemplary data from post marketing surveillance studies strongly suggest that the results from the clinical trials with Zaldiar can be transferred into clinical practice and further support the notion that Zaldiar is effective in both moderate and severe pain.

*Further data supporting the claim for moderate to severe pain*

It is important to mention that both active substances of Zaldiar are well established and have been used alone and in combination already for many years. The efficacy of both components is well known and documented. Additionally, it has been shown in clinical studies at clinically relevant doses (TRAMAP-PHI-001 and 002) that the two components do not interact with each other in terms of pharmacokinetics. Therefore, both components stay in the fixed combination as effective and safe as they are known to be as single substances. Thus, tramadol, despite being given in combination with paracetamol, retains its effectiveness in its well established indications of acute and chronic moderate to severe pain (please refer also to discussion above).

<sup>55</sup> Serrie A, Jouve E, Creuse A, et al. Efficacy and safety of paracetamol (325 mg) – tramadol (37.5 mg) combination (PTC) in elderly patients: a PMS in general practice. European Journal of Pain; (Suppl. 1),2009, S179

Tramadol is the stronger analgesic of the combination with an established profile in the management of chronic pain of malignant as well as non malignant origin<sup>56</sup>. The sponsor therefore believes that the indication of the fixed combination has to be kept in line with the indication of medicinal products consisting of tramadol alone.

For tramadol, the indication approved in Australia and many other countries worldwide, such as the EU, is “treatment of moderate to severe pain”. In the WHO 3 step Analgesic Ladder tramadol is characterised as a Step II compound. Consequently, the fixed tramadol/paracetamol combination should also be ranked as a Step II compound.

### *Conclusion*

In conclusion, an indication for Zaldiar that includes relief of severe pain would be consistent with the indication of Zaldiar in European countries and with the indication of tramadol in Australia and is supported by the available clinical trial data on acute as well as chronic severe pain.

Thus, for Zaldiar an indication for the treatment of moderate to severe pain should be granted.

*Should Zaldiar be indicated for chronic pain?*

**Delegate’s Request for ACPM Advice** *Should the indication for Zaldiar be limited to acute pain only due to the lack of comparative data for Zaldiar with its active components in patients with chronic pain?*

### *Sponsor’s Position:*

It is true that there is no direct comparative data for Zaldiar with its single active components in chronic pain. However, based on applicable regulatory guidance documents the sponsor believes that such a comparison is not a prerequisite for approval of this combination product.

The clinical trials in support of the proposed indication in moderate to severe pain for tramadol/paracetamol were conducted in accordance with the clinical guidelines available at the time of development, that is, the EU CPMP *Guidance for Fixed Combination Medicinal Products* (1996)<sup>46</sup> and the US FDA *Guideline for the Clinical Evaluation of Analgesic Drugs* (1992)<sup>50</sup>. Both guidelines indeed required comparative data to the individual components to a combination product. However, according to the FDA guideline, demonstration of the efficacy of the combination analgesic product is best derived from single dose studies using a factorial design, in which the combination is compared to the individual components, to placebo and to a standard analgesic(s) that adequately delineates the assay sensitivity of the model. As a consequence a factorial design in dental pain was used for the pivotal studies (TRAMAP-ANAG-010, TRAMAP-ANAG-012, TRAMAP-ANAG-013).

The multiple dose trials in chronic painful conditions, such as osteoarthritis, low back pain and fibromyalgia (CAPSS-104, -112, -113, -114 and PRP/TRP/CAN1 [with a duration of three months]) were controlled studies designed to ensure that tramadol/paracetamol was safe when used within the recommended dose range over an extended period of time and showed that the analgesic effect persists on repeated, as needed dosing. Additionally, two open label studies have been carried out (TRAMAP-ANAG-006 [double-blind study with a switch to open label extension after four weeks and then extended up to 23 months], TRAMAP-ANAG-015 [open label trial up to 6 months]).

<sup>56</sup> Grond Stefan, Sablotzki Armin, Clinical Pharmacology of Tramadol, Clin Pharmacokinet 2004, 43 (13): 879-923 0312-5963/04/00013-0879/S31.00/0

The EU guideline also allows the inclusion of data on the individual substances to further support the combination. In this respect it should be highlighted that extensive experience is available for the single components tramadol and paracetamol. Various studies have demonstrated the analgesic efficacy and safety of oral tramadol in the treatment chronic pain (see review of Grond et al.<sup>56</sup> and Table 24).

**Table 24. Controlled trials of oral tramadol in chronic pain**

Study	Type of pain	Study design	N	Duration	Analgesic drug	Dosage (mg/day)	Analgesic efficacy	Adverse events
<b>Cancer pain</b>								
Bono et al.	Cancer	db, co	60	2 x 1 week	IR TRM BP	300 0.6	TRM=BP	TRM<BP
Brema et al.	Cancer	no	131	1-6 month	SR TRM BP	200-300 0.6-0.8	TRM>BP	TRM=BP
Grond et al.	Cancer	no	1658	1-967 days	IR or SC TRM IR MOR	300-600 10-60	TRM=MOR	TRM<MOR
Osipova et al.	Cancer	no	124	4-12 weeks	IR TRM SR MOR	368 69-96	TRM<MOR	TRM<MOR
Tawfic et al.	Cancer	db	64	8 weeks	IR TRM SR MOR	217 50	TRM<MOR	TRM<MOR
Wilder-Smith et al.	Cancer	db, co	20	2 x 4 days	IR TRM IR MOR	375 101	TRM=MOR	TRM<MOR
<b>Chronic pain</b>								
Adler et al.	Osteoarthritis	db	279	1 month	SR TRM IR TRM	150-400 150-400	SR-TRM= IR-TRM	SR-TRM= IR-TRM
Bird et al.	Osteoarthritis	db, co	40	2 x 2 weeks	IR TRM PTZ	200 prn	TRM>PTZ	TRM<PTZ
Goroll	Chronic	db	84	1 week	IR TRM TIL/NAL	300 Pm	TRM> TIL/NAL	NR
Jensen et al.	Osteoarthritis	db	264	2 weeks	IR TRM DXP	300 164	TRM>DXP	TRM>DXP
Pavelka et al.	Osteoarthritis	db, co	60	2 x 4 weeks	IR TRM DIC	87 244	TRM=DIC	TRM>DIC
Rauck et al.	Chronic	db	390	4 weeks	IR TRM PAR/COD	1407/140 250	TRM= PAR/COD	TRM= PAR/COD
Roth	Osteoarthritis	db	63	13 days	IR TRM+NSAID PL+NSAID	250 200-400	TRM>PL	NR
Schnitzer et al.	Low back pain	db	254	4 weeks	IR TRM PL	150-300/ 1300/2600	TRM>PL	TRM>PL
Sorge et al.	Low back pain	db	205	3 weeks	SR TRM IR TRM	200 200	SR-TRM= IR-TRM	SR- TRM=IR- TRM
Wilder-Smith et al.	Osteoarthritis	db	60	1 moth	SR TRM SR DC	200 120	T > DC	T > DC

BP = buprenorphine; co = crossover; DXP = dextropropoxyphene; db= double-blind; DC = dihydrocodeine; DIC = diclofenac; IR = immediate release; MOR = morphine; NAL = naloxone; no = nonrandomised open; NR = not reported; PAR = paracetamol; PTZ = pentazocine; PL = placebo; prn = as needed; SC = subcutaneous; SR = sustained release; TRM = tramadol; TIL = tilidine; > indicates superior to; = indicates equivalent to; < indicates inferior to.

Likewise the long-term safety and efficacy in chronic pain of paracetamol has been evaluated in clinical trials of up to 2 years<sup>57,58,59</sup>. Based on these data on the individual substances it is possible to assess long term use of the combination product comparatively. A meta-analysis using data from clinical trials CAPSS-104, CAPSS-112, CAPSS-113 and CAPSS-114 calculated NNTs for Zaldiar in chronic pain. These NNTs were similar to the NNTs found in a meta-analysis for tramadol in chronic pain trials (sponsor's Clinical Overview).

<sup>57</sup> Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of osteoarthritis of the knee. *N Engl J Med* 1991; 325 (2): 87-91

<sup>58</sup> Williams HJ, Ward JR, Egger MJ, Neuner R, Brooks RH, Clegg DO, Field EH, Skosey JL, Alarcon GS, Willkens RF, Paulus HE, Russell IJ, Sharp JT. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum* 1993; 36 (9): 1196-1206.

<sup>59</sup> Pincus T, Koch GG. A randomized, double-blind, cross-over clinical trial of diclofenac plus. *Rheum* 2001; 44: 1587-1598.



The sponsor was of the opinion that the fixed combination tramadol/paracetamol has sufficiently been characterised with respect to safety and efficacy especially taking into account the principles laid down in the EU guideline.

Overall, the clinical development program for tramadol/paracetamol followed a logical progression, according to the existing guidelines culminating in the design and conduct of three single dose clinical trials that unequivocally demonstrated the incremental analgesic efficacy of the tramadol/paracetamol combination relative to its components alone, and trials that clearly demonstrated the effectiveness and/or safety of the combination with repeated, as needed dosing over an extended period of time. In the sponsor's view this justified an indication of Zaldiar for both acute and chronic pain.

#### *Use of Zaldiar in adolescents*

##### **Delegate's Request for ACPM Advice:**

*Should use of Zaldiar be limited to patients aged from 16 years rather than from 12 years as requested by the sponsor given the absence of PK and efficacy data in patients aged 12 to 16 years?*

#### *Sponsor's Position:*

It is true that the application submitted in Australia does not contain any PK and efficacy data for Zaldiar in patients aged 12 to 16 years. However, as outlined in the following, the sponsor is of the opinion that the use of Zaldiar by adolescent patients from the age of 12 years is justified even in the absence of such data.

For subjects above the age of 12 years the PK of both tramadol and paracetamol is independent of age<sup>60, 61, 62, 63</sup>. Relevant PK interactions between the two compounds have not been observed (Study TRAMAP-PHI-002).

The efficacy and safety of tramadol in children and adolescents is recognised and reflected in national Product Information by lower age limits for its use varying from 1 year to 12 years depending on the country. The Australian PI of tramadol supports the use of tramadol in subjects above the age of 12 years with an approved maximum single dose of 100 mg and a maximum daily dose of 400 mg, both of which are higher than the tramadol doses administered according to the recommended dosing regimen for Zaldiar.

Paracetamol is one of the most widely used of all drugs, with a wealth of experience clearly establishing it as the standard antipyretic and analgesic for mild to moderate pain states<sup>64</sup>. Paracetamol is used worldwide in paediatric subjects of all ages including preterm children. In Australia, the TGA's Medicines Evaluation Committee<sup>65</sup> recommends a dosing scheme of 500 to 1000 mg every four to six hs as necessary not exceeding 4 g in 24 hs for adults and children 12 years and over. Again these doses are higher than the paracetamol doses administered according to the recommended dosing regimen for Zaldiar.

<sup>60</sup>Anderson BJ, Franca, FFicanzca, What we don't know about paracetamol in children, Paediatric Anaesthesia 1998, 8: 451-460

<sup>61</sup> Anderson BJ, Pons G, Autret-Leca E, Allegaert K, Boccard E. Pediatric intravenous paracetamol (propacetamol) pharmacokinetics: a population analysis. Pediatric Anesthesia 2005;15:282-292

<sup>62</sup> Miller, Roberts, Fischer, The Toxicology Center, Department of Pharmacology, and the Division of Pediatric Clinical Pharmacology, College of Medicine, University of Iowa; Acetaminophen elimination kinetics in neonates, children, and adults; 1976, Volume 19 Number 3.

<sup>63</sup> Wilson JT, Jeroudi M, Rodarte A, Kearns G, Liao S, Medve R. Disposition of tramadol in children. Br J Clin Pharmacol 2000; 140.

<sup>64</sup>Prescott LF. Paracetamol: past, present, and future. Am J Ther.2000 Mar;7(2):143-7.

<sup>65</sup> see <http://www.tga.gov.au/pdf/archive/review-analgesics-030411.pdf> <http://www.tga.gov.au/pdf/otc-argom-110906.pdf>

For the reasons discussed above the sponsor is of the opinion that the use of Zaldiar by adolescent patients above the age of 12 years is justified.

### **Advisory Committee Considerations**

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered this product has a positive benefit-risk profile for the indication.

*Zaldiar is indicated for the treatment of moderate pain.*

In making this recommendation, the ACPM considered the guidelines for fixed dose combination products and noted the nonclinical evidence supporting the supra additive effect of the combination and therefore the reduced dosage for the component actives. The ACPM also noted that the guidelines do not require comparative maximal dose efficacy data. It is not clear that the proposed dosing interval of 6 h is optimal and this interval was not mandated in the pivotal clinical trials. The ACPM noted that there is no safety or efficacy evidence to support long term use in chronic pain.

The ACPM noted that evidence from the safety and efficacy studies does not support use of Zaldiar for severe pain, despite the current registration for the tramadol component for this indication. The proposed maximum doses of the components of Zaldiar are lower than those already approved for the components given separately. There was a lack of safety and efficacy data for adolescents aged from 12 to 16 years; however, given approval of the components for use in this population Zaldiar should not be precluded in adolescents.

The committee supported the amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI).

There were no specific conditions of registration advised by the ACPM.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

### **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of Zaldiar [Tramadol hydrochloride and Paracetamol] film-coated tablets and effervescent tablets, respectively (37.5/325 mg) for oral administration, indicated for:

*Zaldiar is indicated for the treatment of moderate pain.*

## **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at .

---

## **Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia  
Email: [info@tga.gov.au](mailto:info@tga.gov.au) Phone: 1800 020 653 Fax: 02 6232 8605

[www.tga.gov.au](http://www.tga.gov.au)

Reference/Publication #

## PRODUCT INFORMATION

### NAME OF THE MEDICINE

ZALDIAR<sup>®</sup> 37.5 mg/325 mg, Film coated tablets

ZALDIAR<sup>®</sup> 37.5 mg/325 mg, Effervescent tablets

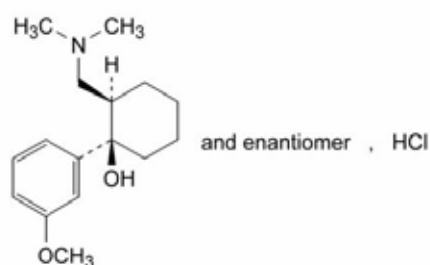
### DESCRIPTION

*Film-coated tablet:* Pale yellow film-coated tablet, marked with the manufacturer's logo  $\square$  on one side and 'T5' on the other side.

*Effervescent tablet:* Off white to slightly rosy coloured with some coloured speckles, of round shape, flat with bevelled edges

### Tramadol hydrochloride

(1R,2R)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride



Molecular formula:

C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub> · HCl

Relative molecular mass

Mr = 299.8

Chemical Abstracts Service (CAS) registry number

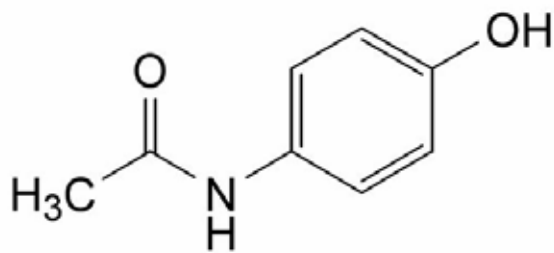
36282-47-0

White or almost white, crystalline powder; freely soluble in water and methanol, very slightly soluble in acetone

pKa of 9.41. The n-octanol/water log partition coefficient (logP) is 1.35 at pH 7.

### Paracetamol

N-(4-Hydroxyphenyl)acetamide



Molecular formula

C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>

Relative molecular mass

Mr = 151.2

Chemical Abstracts Service (CAS) registry number:

103-90-2

White or almost white, crystalline powder; sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride (15-25°C)

pKa of 9.5 at 25°C . Partition coefficient (logP) of 0.51.

One film-coated or effervescent tablet contains 37.5 mg tramadol hydrochloride and 325 mg paracetamol

## **PHARMACOLOGY**

Pharmacotherapeutic group: Tramadol, combinations

ATC code: N02A X 52

Pharmacodynamics:

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non-selective agonist of the  $\mu$ ,  $\delta$ , and  $\kappa$  opioid receptors with a higher affinity for the  $\mu$  receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an anti-tussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect . The effect of tramadol on gastro-intestinal motility is lower than with pure opioid analgesics. At therapeutic doses, tramadol has no clinically significant effect on left ventricular function or cardiac index. Orthostatic changes in blood pressure have been observed. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

Antagonism studies demonstrated that both opioid and non-opioid properties of tramadol contribute to its analgesic activity.

Apart from analgesia, tramadol may produce other symptoms similar to that of opioids including: dizziness, somnolence, nausea, constipation, sweating and pruritus

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

ZALDIAR FCT and EFF Tablets: Product information V2.4 (Final) 29 Feb 2012

2 of 18

ZALDIAR is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

#### Pharmacokinetics:

Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

After a single oral administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/mL [(+)-tramadol/(-)-tramadol] and 4.2 µg/mL (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives  $t_{1/2}$  are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2.5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of ZALDIAR, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

#### Absorption:

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75 %. After repeated administration, the bioavailability is increased and reaches approximately 90 %.

After administration of ZALDIAR, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of ZALDIAR with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that ZALDIAR can be taken independently of meal times.

#### Distribution:

Tramadol has a high tissue affinity ( $V_{d,\beta}=203 \pm 40$  l). It has a plasma protein binding of about 20%.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

#### Biotransformation:

Tramadol is extensively metabolized after oral administration. About 30 % of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Tramadol is metabolised through *O*-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through *N*-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through *N*-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect is unlikely to change on multiple dosing.

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P 450 to an active intermediate (the *N*-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

#### Elimination:

Tramadol and its metabolites are eliminated mainly by the kidneys. The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9 % of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

#### Use in the elderly

Population PK and dedicated PK studies using tramadol alone did not reveal a relevant effect of age on the PK of tramadol up to the age of 75 years. Above the age of 75 years the elimination half-life of tramadol was slightly prolonged by about 15% and exposure (AUC) increased by about 50% in comparison to subjects aged between 65 – 75 years.

#### Use in children

The pharmacokinetics of ZALDIAR has not been studied in children or adolescents aged under 16 years.

#### Use in renal impairment

The pharmacokinetics of ZALDIAR has not been studied in patients with renal impairment. Based on studies using tramadol alone, excretion of tramadol and its metabolite M1 is reduced in patients with CKD stages 4 or 5.

#### Use in hepatic impairment

The pharmacokinetics of ZALDIAR has not been studied in patients with hepatic impairment. Tramadol and paracetamol are both extensively metabolized by the liver. In patients with severe hepatic impairment ZALDIAR should not be used.

## CLINICAL TRIALS

### Acute Pain

A total of 1200 subjects (400 / study) aged over 16 years with moderate or severe pain following an oral surgical procedure (extraction of 2 ipsilateral, or > 2, third molars requiring bone removal) were enrolled. Subjects were stratified by baseline pain severity: moderate or severe, and received one of 5 single-dose treatments (tramadol / paracetamol 75 mg / 650 mg, tramadol 75 mg, paracetamol 650 mg, ibuprofen 400 mg or placebo). Subjects could receive a supplemental analgesic during the studies. If a subject took rescue medication or discontinued prematurely, remaining observations points were filled using the last observation carried forward (LOCF) method.

Across the studies most subjects were female (55-63%) and Caucasian (75-93%). Mean age was 21.1 – 21.7 years (range 16-46 years). Baseline pain intensity was consistent across the studies (moderate for 66-70%, severe for 30-34%); mean rating (6.1-6.2); and the majority of subjects had 4 molars removed (64-83%). 64% to 74% of subjects given T/A 75/650 in the pivotal studies required additional analgesia at least once during the study. Table 1 presents the primary summary efficacy variables (TOTPAR, SPID, and SPRID) and statistical comparisons for the intervals, 0-4 hours, and 0-8 hours, for each of these studies.

**Table 1: Primary summary efficacy variables: TOTPAR, SPID and SPRID scores, pivotal studies: T-A-010, T-A-012, T-A-013, efficacy analysis groups**

Variable	Treatment	N	0 – 4h			0 – 8 h		
			Mean (SD)	T/A vs component	Active vs PBO	Mean (SD)	T/A vs component	Active vs PBO
Study T-A-010								
TOTPAR	T/A	80	7.7(4.12)		<0.001	13.7(8.19)		<0.001
	T75	78	4.3(4.26)	<0.001	0.001	8.1(8.45)	<0.001	<0.001
	APAP650	80	6.5(4.11)	0.032	<0.001	10.1(7.13)	0.002	<0.001
	IBU400	80	7.6(4.69)		<0.001	13.6(9.09)		<0.001
	PBO	79	2.2(3.02)			3.7(6.02)		
SPID	T/A	80	3.1(2.94)		<0.001	5.0(5.95)		<0.001
	T75	78	1.1(3.17)	<0.001	0.001	1.8(6.48)	<0.001	0.001
	APAP650	80	2.4(2.81)	0.066	<0.001	3.1(5.00)	0.017	<0.001
	IBU400	80	3.3(3.39)		<0.001	5.6(6.42)		<0.001
	PBO	79	-0.3(2.20)			-1.1(4.53)		
SPRID	T/A	80	10.8(6.75)		<0.001	18.7(13.47)		<0.001
	T75	78	5.3(7.10)	<0.001	0.001	10.0(14.22)	<0.001	<0.001
	APAP650	80	8.9(6.67)	0.037	<0.001	13.1(11.53)	0.003	<0.001
	IBU400	80	10.9(7.80)		<0.001	19.2(14.89)		<0.001
	PBO	79	1.8(4.86)			2.6(9.73)		
Study T-A-012								
TOTPAR	T/A	80	6.8(4.92)		<0.001	11.1(9.72)		<0.001
	T75	80	2.7(3.85)	<0.001	0.031	5.0(8.31)	<0.001	0.024
	APAP650	80	5.4(4.11)	0.019	<0.001	7.5(7.35)	0.003	<0.001
	IBU400	80	6.9(4.89)		<0.001	12.7(9.80)		<0.001
	PBO	80	1.5(2.70)			2.4(5.43)		
SPID	T/A	80	2.9(3.19)		<0.001	4.7(6.46)		<0.001
	T75	80	0.4(2.66)	<0.001	0.028	0.4(5.82)	<0.001	0.018
	APAP650	80	2.3(2.66)	0.096	<0.001	2.9(4.75)	0.026	<0.001



	IBU400	80	2.9(3.61)		<0.001	5.2(6.91)		<0.001
	PBO	80	-0.5(2.42)			-1.5(4.91)		
SPRID	T/A	80	9.6(7.86)		<0.001	15.8(15.72)		<0.001
	T75	80	3.1(6.23)	<0.001	0.025	5.4(13.52)	<0.001	0.017
	APAP650	80	7.7(6.51)	0.033	<0.001	10.4(11.63)	0.006	<0.001
	IBU400	80	9.8(8.23)		<0.001	17.9(16.12)		<0.001
	PBO	80	0.9(4.75)			0.8(9.50)		
Study T-A-013								
TOTPAR	T/A	80	7.0(5.01)		<0.001	11.4(10.44)		<0.001
	T75	80	3.3(4.40)	<0.001	0.066	7.0(10.03)	0.002	0.020
	APAP650	80	5.6(5.12)	0.033	<0.001	8.2(9.53)	0.020	0.002
	IBU400	80	8.2(5.15)		<0.001	14.6(10.85)		<0.001
	PBO	80	2.2(3.96)			3.8(7.85)		
SPID	T/A	80	2.9(3.61)		<0.001	4.4(7.50)		<0.001
	T75	80	0.2(3.52)	<0.001	0.034	0.6(7.64)	<0.001	0.012
	APAP650	80	2.0(3.71)	0.046	<0.001	2.2(7.07)	0.032	<0.001
	IBU400	80	3.8(3.67)		<0.001	6.7(7.82)		<0.001
	PBO	80	-0.8(3.15)			-2.1(6.70)		
SPRID	T/A	80	9.9(8.38)		<0.001	15.8(17.47)		<0.001
	T75	80	3.5(7.65)	<0.001	0.045	7.5(17.14)	<0.001	0.013
	APAP650	80	7.6(8.58)	0.034	<0.001	10.4(15.98)	0.021	<0.001
	IBU400	80	12.0(8.58)		<0.001	21.3(18.20)		<0.001
	PBO	80	1.3(6.82)			1.7(13.94)		

## Chronic Pain

Efficacy of ZALDIAR in the relief of chronic pain has not been examined in comparison to tramadol and / or paracetamol given alone. Efficacy and safety of ZALDIAR in patients with chronic pain was examined in 5 placebo-controlled, multiple-dose studies conducted over 3 months (CAPSS-104, CAPSS-112, CAPSS-113, CAPSS-114 and PRI/TRP/CAN1). Subjects were primarily 40-75 years of age and taking a stable daily dose of an NSAID for at least 3 months before study entry. In CAPSS-114, subjects who had been taking a COX-2 selective inhibitor for pain relief were permitted to continue taking it while in the trial. Mean pain severity ranged from 67.8 mm to 80.1 mm, on a standard pain visual analogue (PVA) scale, 0-10 mm. Study drug was titrated from one (tramadol HCl 37.5 mg with paracetamol 325 mg) to 4 tablets / day over the first 10 days, followed by a regimen of 1 or 2 tablets every 4 to 6 hours, as needed. The maximum dose allowed was 8 tablets / day (tramadol HCl 300 mg with paracetamol 2600 mg).

ZALDIAR was statistically superior to placebo in lowering the PVA score in PRI/TRP/CAN1 and CAPSS-112 and CAPSS-114, and in increasing the time to discontinuation due to efficacy failure in CAPSS-113 and PRI/TRP/CAN1. Statistical significance in lowering the PVA score was not demonstrated in CAPSS-114.

The efficacy of ZALDIAR in the treatment of patients with cancer has not been investigated in clinical trials.

## INDICATIONS

ZALDIAR is indicated for the treatment of moderate pain.

## CONTRAINDICATIONS

- hypersensitivity to tramadol, paracetamol or to any of the excipients, including the colouring agent sunset yellow E110, listed at the end of this document,
- acute intoxication with alcohol, hypnotic drugs, centrally-acting analgesics, opioids or psychotropic drugs,
- ZALDIAR should not be administered to patients who are receiving monoamine oxidase inhibitors or within two weeks of their withdrawal (see *Interactions with other Medicines*),
- in cases of severe hepatocellular insufficiency
- in patients with hepatic failure or decompensated active liver disease,
- epilepsy not controlled by treatment (see *Precautions*).

## PRECAUTIONS

### *Maximum daily dose*

In adults and adolescents 12 years and older, the maximum daily dose of 8 tablets of ZALDIAR should not be exceeded. In order to avoid inadvertent overdose, patients should be advised not to exceed the recommended dose and not to use any other paracetamol (including over the counter) or tramadol hydrochloride containing products concurrently without the advice of a physician.

ZALDIAR contains tramadol HCl and paracetamol. Paracetamol has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of paracetamol at doses that exceed 4,000 milligrams per day, and often involve more than one paracetamol-containing product.

### *Use in renal impairment*

Because of the presence of tramadol, the use of ZALDIAR is not recommended in patients with CKD stage 5. In cases of CKD stage 4, the dosing should be increased to 12-hourly intervals. As tramadol is removed only very slowly by haemodialysis or by haemofiltration, post dialysis administration to maintain analgesia is not usually required.

ZALDIAR Effervescent Tablets also contain 7.8 mmol (or 179.4 mg) sodium per dose which should be taken into consideration by patients on a controlled sodium diet.

### ***Use in hepatic impairment***

The pharmacokinetics of ZALDIAR have not been studied in patients with hepatic impairment. Tramadol and paracetamol are both extensively metabolized by the liver.

ZALDIAR contains tramadol HCl and paracetamol and is not recommended for use in patients with severe hepatic impairment.

#### **Tramadol HCl:**

The relationship between degree of hepatic impairment and half-life of tramadol has not been extensively studied to provide a dosing recommendation for tramadol; instead, an individual dosing regimen based on the patient's needs is proposed. A dose interval prolongation should be carefully considered.

#### **Paracetamol:**

In patients with chronic or active hepatic disease, especially those with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration, the paracetamol dose should not exceed 3g/day. . It is of note that the maximum daily dose of Zaldiar (8 tablets) is equivalent to 2.6 g paracetamol.

### ***Use in patients with respiratory insufficiency***

ZALDIAR should be administered cautiously in patients at risk of respiratory depression. When large doses of tramadol are administered with anaesthetic medications or alcohol, respiratory depression may result.

### ***Opioid- dependent patients***

Tramadol is not recommended as a substitute in opioid-dependent patients. Although tramadol is an opioid-agonist, it cannot suppress opioid withdrawal symptoms. Animal experiments have shown that under certain circumstances the administration of tramadol may provoke a withdrawal syndrome in opioid dependent monkeys.

Because of the difficulty in assessing dependence in patients who have previously received substantial amounts of opioid medications, caution should be used in the administration of ZALDIAR to such patients. In patients with tendency for drug abuse or dependence, treatment with ZALDIAR should only be carried out for short periods under strict medical supervision. Cases of dependence and abuse of tramadol have been reported rarely.

Concomitant use of opioid agonists-antagonists (buprenorphine, pentazocine) is not recommended (see *Drug Interactions*)

### ***Increased intracranial pressure, head trauma, shock or reduced levels of consciousness***

ZALDIAR should be used with caution in patients with increased intracranial pressure, head injury, shock or a reduced level of consciousness of uncertain origin. Pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating mental status in these patients if they are receiving ZALDIAR.

### ***Misuse, Abuse and Diversion***

Tramadol has mu-opioid agonist activity. ZALDIAR, a tramadol-containing product, can be sought by drug abusers and people with addiction disorders and may be subject to criminal diversion. The possibility of illegal or illicit use should be considered when prescribing or dispensing ZALDIAR in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Misuse or abuse poses a significant risk to the abuser that could result in overdose and death.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

### ***Withdrawal symptoms***

Withdrawal symptoms may occur if ZALDIAR is discontinued. Reported symptoms have included anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been reported less frequently with ZALDIAR discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering ZALDIAR at the time of discontinuation.

### ***Risk of seizures***

Convulsions have been reported in tramadol-treated patients susceptible to seizures or taking other medications that lower the seizure threshold, especially selective serotonin re-uptake inhibitors, tricyclic antidepressants, antipsychotics, centrally acting analgesics or local anaesthesia. Epileptic patients controlled by a treatment or patients susceptible to seizures should be treated with ZALDIAR only if there are compelling circumstances. Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol exceed the recommended upper dose limit.

### ***Use during anaesthesia***

In one study, use of tramadol during general anaesthesia with enflurane and nitrous oxide was reported to enhance intra-operative recall. Until further information is available, use of tramadol during light planes of anaesthesia should be avoided.

ZALDIAR Effervescent Tablets contain colorant Sunset yellow E110 which may cause allergic reactions. ZALDIAR Effervescent Tablets also contain 7.8 mmol (or 179.4 mg) sodium per dose which should be taken into consideration by patients on a controlled sodium diet.

ZALDIAR Film-coated tablets contain a small amount of lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### ***Use in children***

The effective and safe use of ZALDIAR has not been established in children below the age of 12 years. Treatment is therefore not recommended in this population.

ZALDIAR should not be given to children aged less than 12 years or to those who weigh less than 37.5kg. Dose reduction is required for patients with body weight less than 50kg (*see Dosage and Administration*)

#### ***Use in elderly patients***

The usual dosages may be used although it should be noted that in volunteers aged over 75 years the elimination half life of tramadol was increased by 15% following oral administration. In patients over 75 years old, it is recommended that the minimum interval between doses of not less than 6 hours should be strictly adhered to, due to the presence of tramadol.

#### ***Genotoxicity***

Genotoxicity studies with the fixed combination (tramadol and paracetamol) have not been performed. There was no evidence of genotoxicity with tramadol in a standard battery of *in vitro* and *in vivo* tests. Paracetamol can cause chromosomal damage *in vitro* and *in vivo*, but only at high concentrations or at large doses associated with hepatotoxicity.

#### ***Carcinogenicity***

Carcinogenicity studies with the fixed combination (tramadol and paracetamol) have not been performed..

Results of carcinogenicity tests do not suggest a potential risk of tramadol for man.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

#### ***Use in Pregnancy (Pregnancy Category C)***

Since ZALDIAR is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy.

- Data regarding paracetamol: Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol used in the recommended dosages.
- Data regarding tramadol: Tramadol should not be used during pregnancy as there is inadequate evidence available to assess the safety of tramadol in pregnant women. Tramadol administered before or during birth does not affect uterine contractility. In neonates it may induce changes in the respiratory rate which are usually not clinically relevant. Long-term treatment during pregnancy may lead to withdrawal symptoms in the newborn after birth, as a consequence of habituation.

Fertility studies with the fixed combination (tramadol and paracetamol) have not been performed. No effect on fertility has been observed after oral administration of tramadol to male and female rats at respective doses up to 50 and 75 mg/kg/day. Mice continuously exposed to paracetamol 1430 mg/kg/day in the diet showed effects in offspring (fewer pups, retarded growth, increased abnormal sperm). The clinical significance of these findings is unknown.

Oral administration of the tramadol/paracetamol combination to rats during the period of organogenesis elicited embryofetal toxicity at materno-toxic doses (at 50/434

mg/kg tramadol/paracetamol or 1.5 times the maximal recommended clinical dose on a mg/m<sup>2</sup> basis), but no teratogenicity was observed. Oral administration of tramadol alone during organogenesis to rats (up to 75 mg/kg/day) and rabbits (up to 175 mg/kg/day) was associated with embryofetal toxicity (reduced fetal and placental weight, delayed ossification) along with maternal toxicity. Mice continuously exposed to paracetamol alone (1430 mg/kg/day in the diet) showed offspring effects (fewer pups, retarded growth, increased abnormal sperm) but no teratogenicity was observed in these studies.

### ***Use in Lactation***

Since ZALDIAR is a fixed combination of active ingredients including tramadol, it should not be ingested during breast feeding.

- Data regarding paracetamol: Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breast feeding by women using single ingredient medicinal products containing only paracetamol.
- Data regarding tramadol: Tramadol and its metabolites are found in small amounts in human breast milk. An infant could ingest about 0.1% of the dose given to the mother. Tramadol should not be ingested during breast feeding.

Animal studies with fixed combination (tramadol and paracetamol) have not been performed. Oral administration of tramadol to rats from late gestation to weaning at 80 mg/kg/day (2.5 times the maximal recommended clinical dose on a mg/m<sup>2</sup> basis) was associated with clinical toxicity in pups, including reduced survival and weight gain; the no-effect dose was 40mg/kg/day.

Tramadol is excreted into milk. The use of ZALDIAR during breastfeeding is not recommended.

### ***Effects on ability to drive and use machines***

Tramadol may cause drowsiness or dizziness, which may be enhanced by alcohol or other CNS depressants. If affected, the patient should not drive or operate machinery.

## **INTERACTION WITH OTHER MEDICINES**

*Concomitant use is contraindicated with:*

- Non-selective MAO Inhibitors  
Risk of serotonergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
- Selective-A MAO Inhibitors  
Extrapolation from non-selective MAO inhibitors  
Risk of serotonergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.
- Selective-B MAO Inhibitors

Central excitation symptoms evocative of a serotonergic syndrome: diarrhoea, tachycardia, sweating, trembling, confusion, even coma.

In case of recent treatment with MAO inhibitors, a delay of two weeks should occur before treatment with tramadol

*Concomitant use is not recommended with:*

- Alcohol: Alcohol increases the sedative effect of opioid analgesics. The effect on alertness can make driving of vehicles and the use of machines dangerous. Avoid intake of alcoholic drinks and of medicinal products containing alcohol.
- Carbamazepine and other enzyme inducers: Risk of reduced efficacy and shorter duration due to decreased plasma concentrations of tramadol.
- Opioid agonists-antagonists (buprenorphine, pentazocine): Decrease of the analgesic effect by competitive blocking effect at the receptors, with the risk of occurrence of withdrawal syndrome.

*Concomitant use which needs to be taken into consideration:*

- Serotonergic drugs: Concomitant use of tramadol and serotonergic drugs, such as selective serotonin re-uptake inhibitors (SSRIs) or MAO inhibitors may cause serotonin toxicity. Signs of a serotonin toxicity are spontaneous clonus, inducible clonus, and agitation; or diaphoresis, ocular tonus, and agitation; or diaphoreses, tremor, and hyperreflexia; or hypertonicity, temperature  $>38^{\circ}\text{C}$ , ocular clonus or inducible clonus. Withdrawal of the serotonergic drugs usually leads to rapid improvement. Further treatment depends on the type and severity of the symptoms.
- Other opioid derivatives (including antitussive drugs and substitutive treatments), benzodiazepines and barbiturates: Increased risk of respiratory depression which can be fatal in cases of overdose.
- Other CNS depressants: Other opioid derivatives (including antitussive drugs and substitutive treatments), barbiturates, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, sedative antihistamines, neuroleptics, centrally-acting antihypertensive drugs, thalidomide and baclofen can cause increased central depression. The effect on alertness can make driving of vehicles and the use of machines dangerous.
- Warfarin: Periodic evaluation of prothrombin time should be performed when ZALDIAR and warfarin like compounds are administered concurrently due to reports of increased INR.
- CYP450 interactions: Drugs that inhibit CYP2D6 isozyme may increase concentrations of tramadol and decrease concentrations of active metabolite M1. Drugs that inhibit CYP3A4 isozyme may inhibit the metabolism of tramadol and probably M1. The clinical importance of these potential interactions has not been studied. The CYP-mediated metabolism of tramadol may be inhibited in vivo by amitriptyline, fluoxetine and norfluoxetine.

- Drugs reducing the seizure threshold: Concomitant use of bupropion, serotonin reuptake inhibitor antidepressants, tricyclic antidepressants and neuroleptics with tramadol can increase the risk of convulsions. The speed of absorption of paracetamol may be increased by metoclopramide or domperidone and absorption reduced by cholestyramine.
- Ondansetron: In a limited number of studies the pre- or postoperative application of the antiemetic 5-HT<sub>3</sub> antagonist ondansetron increased the requirement of tramadol in patients with postoperative pain.
- Busulfan: Busulfan is eliminated from the body via conjugation with glutathione. Concomitant use with paracetamol may result in reduced busulfan clearance.
- Diflunisal: concomitant diflunisal increases paracetamol plasma concentrations and this may increase hepatotoxicity.

## ADVERSE EFFECTS

Table 2 shows the most frequent (>1%) treatment emergent adverse events (independent from causal relationship) observed in pooled clinical trials with ZALDIAR versus tramadol alone.

**Table 2: Incidence of treatment emergent adverse events (>1%) with tramadol/paracetamol versus tramadol alone, stratified by age category**

Adverse Event	All Subjects <sup>a</sup>		Elderly Subjects (≥65 years)	
	Tram/Para (N=1437 <sup>b</sup> )	Tramadol Alone (N=694 <sup>c</sup> )	Tram/Para (N=503)	Tramadol Alone (N=455)
Constipation	11%	41%	15%	49%
Nausea	18%	41%	17%	40%
Headache	11%	31%	9%	30%
Dizziness	15%	29%	15%	30%
Somnolence	12%	21%	12%	23%
Vomiting	6%	18%	7%	19%
Dyspepsia	5%	12%	5%	9%
Diarrhoea	6%	10%	9%	11%
Abdominal pain	3%	10%	4%	11%
Dry mouth	5%	9%	5%	7%
Anorexia	2%	8%	3%	9%
Flatulence	2%	4%	1%	4%
Tremor	1%	5%	1%	6%
Pain	2%	5%	2%	6%
Asthenia	1%	14%	2%	17%
Depression	2%	5%	2%	3%
Anxiety	2%	3%	1%	3%
Confusion	1%	4%	1%	4%
Nervousness	1%	5%	1%	5%



<sup>a</sup>All subjects exposed to tramadol/paracetamol during the double-blind and/or open-label phases.

<sup>b</sup>Includes subjects treated with tramadol/paracetamol combination in TRAMAP-ANAG-006, 008, 009, and 015.

The average daily dose of tramadol delivered as ZALDIAR in these trials ranged from 131 mg to 176 mg.

<sup>c</sup>Includes subjects treated with tramadol alone in TKM, TL2, and TKB.

The average daily dose of tramadol in these trials ranged from 227.5 mg to 258.5 mg.

---

The safety profile of ZALDIAR is characterized by the following adverse reactions. The most commonly adverse reactions were nausea, dizziness and somnolence, observed in more than 10 % of the patients. All adverse reactions identified for ZALDIAR are listed below under the corresponding body organ systems according to the following classification: very common  $\geq 10\%$ ; common  $\geq 1\%$  to  $< 10\%$ ; uncommon  $\geq 0.1\%$  to  $< 1\%$ ; rare  $\geq 0.01\%$  to  $< 0.1\%$ .

*Cardiac disorders:*

- *Uncommon:* arrhythmia, tachycardia, palpitations,.

*Vascular disorders:*

- *Uncommon:* hypertension, hot flush.

*Nervous system disorders:*

- *Very common:* dizziness, somnolence
- *Common:* headache, trembling
- *Uncommon:* involuntary muscular contractions, paraesthesia, tinnitus
- *Rare:* ataxia, convulsions.

*Psychiatric disorders:*

- *Common:* confusion, mood altered, anxiety, nervousness, euphoria, sleep disorders
- *Uncommon:* depression, hallucinations, nightmares, amnesia
- *Rare:* drug dependence.

Post marketing surveillance: *very rare:* abuse.

*Eye disorders:*

- *Rare:* blurred vision

*Respiratory, thoracic and mediastinal system disorders:*

- *Uncommon:* dyspnoea

*Gastrointestinal disorders:*

- *Very common :* nausea
- *Common:* vomiting, constipation, dry mouth, diarrhoea, abdominal pain, dyspepsia, flatulence
- *Uncommon:* dysphagia, melaena

*Skin and subcutaneous tissue disorders:*

- *Common:* sweating, pruritus
- *Uncommon:* dermal reactions (e.g.rash, urticaria)

*Renal and urinary disorders:*

- Uncommon: albuminuria, micturition disorders (dysuria and urinary retention).

*General disorders and administration site conditions:*

- Uncommon: chills, chest pain.

*Investigations:*

- Uncommon: transaminases increased

Although not observed during clinical trials, the occurrence of the following adverse effects known to be related to the administration of tramadol or paracetamol cannot be excluded:

**Tramadol**

- Postural hypotension, bradycardia, collapse (tramadol).
- Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin times.
- Rare cases  $\geq 1/10000$  to  $< 1/1000$ ) : allergic reactions with respiratory symptoms (e.g. dyspnoea, bronchospasm, wheezing, angioneurotic oedema) and anaphylaxis
- Rare cases ( $\geq 1/10000$  to  $< 1/1000$ ) : changes in appetite, motor weakness, and respiratory depression
- Psychic side-effects may occur following administration of tramadol which vary individually in intensity and nature (depending on personality and duration of medication). These include changes in mood, (usually elation occasionally dysphoria), changes in activity (usually suppression occasionally increase) and changes in cognitive and sensorial capacity (e.g. decision behaviour perception disorders).
- Worsening of asthma has been reported though a causal relationship has not been established.
- Symptoms of withdrawal reactions, similar to those occurring during opiate withdrawal may occur as follows: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal symptoms. Other symptoms that have very rarely been seen if tramadol hydrochloride is discontinued abruptly include: panic attacks, severe anxiety, hallucinations, paraesthesia, tinnitus and unusual CNS symptoms.

**Paracetamol**

- Adverse effects of paracetamol are rare but hypersensitivity including skin rash may occur. There have been reports of blood dyscrasias including thrombocytopenia and agranulocytosis, but these were not necessarily causally related to paracetamol.
- There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.
- Patients with chronic or active hepatic disease, especially those with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition (low reserves of hepatic glutathione), and dehydration are more likely to experience hepatic toxicity from the paracetamol component of ZALDIAR. The maximum dose of ZALDIAR must not be exceeded in these patients.

## DOSAGE AND ADMINISTRATION

### ADULTS AND ADOLESCENTS (12 years and older)

The dose should be individually adjusted according to intensity of pain and response of the patient.

An initial dose of two tablets of ZALDIAR (equivalent to 75 mg tramadol hydrochloride and 650 mg paracetamol) is recommended. Additional doses can be taken as needed, not exceeding 8 tablets (film-coated or effervescent) (equivalent to 300 mg tramadol and 2600 mg paracetamol) per day.

The dosing interval should be 4 to 6 hours.

Patients weighing between 50 and 37.5kg should receive a maximum of 6 ZALDIAR tablets daily. Patients weighing less than 37.5kg should not receive ZALDIAR.

ZALDIAR should under no circumstances be administered for longer than is strictly necessary (see *Precautions*). If repeated use or long term treatment with ZALDIAR is required as a result of the nature and severity of the illness, then careful, regular monitoring should take place (with breaks in the treatment, where possible), to assess whether continuation of the treatment is necessary.

### Method of Administration

Oral use

ZALDIAR Film-coated tablets must be swallowed whole, with a sufficient quantity of liquid. They must not be broken or chewed.

ZALDIAR Effervescent tablets should be taken dissolved in a glass of drinking water.

## OVERDOSAGE

ZALDIAR contains a fixed combination of active ingredients. In case of overdose, the symptoms may include the signs and symptoms of toxicity of tramadol or paracetamol or of both these active ingredients.

### *Symptoms of overdose from tramadol:*

In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These include in particular, miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

### *Symptoms of overdose from paracetamol:*

In paracetamol overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects also may occur. Early symptoms following a potentially

ZALDIAR FCT and EFF Tablets: Product information V2.4 (Final) 29 Feb 2012

16 of 18

hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In the treatment of paracetamol overdose, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if paracetamol ingestion is known or suspected to have occurred within a few hours of presentation. Serum paracetamol levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity; paracetamol levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

#### Emergency treatment:

- Transfer immediately to a specialised unit.
- Maintain respiratory and circulatory functions
- Prior to starting treatment, a blood sample should be taken as soon as possible after overdose in order to measure the plasma concentration of paracetamol and tramadol and in order to perform hepatic tests.
- Perform hepatic tests at the start (of overdose) and repeat every 24 hours. An increase in hepatic enzymes (ASAT, ALAT) is usually observed, which normalizes after one or two weeks.
- Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
- Supportive measures such as maintaining the patency of the airway and maintaining cardiovascular function should be instituted; naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
- Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration. Therefore treatment of acute intoxication with ZALDIAR with haemodialysis or haemofiltration alone is not suitable for detoxification.

If you feel you may have been given too much ZALDIAR contact the Poisons Advisory Centre on 131126 for advice on management.

### **PRESENTATION and STORAGE**

ZALDIAR Film-coated tablets are packed in white opaque PVC /aluminium foil or white opaque polypropylene/aluminium foil.

Box of 2, 20, 50, and 100 tablets

Not all packaging sizes may be marketed.

ZALDIAR Effervescent tablets are packed in child-resistant strips of thermo-sealed aluminium foil; outside coated with polyethylene terephthalate, inside coated with polyethylene.

Pack sizes of 2, 20, 50, and 100 effervescent tablets packed in coated aluminium strips

Not all pack sizes may be marketed.

**List of excipients:**

**Film-coated tablet:**

Tablet core: powdered cellulose, pregelatinised maize starch, sodium starch glycollate (type A), maize starch, magnesium stearate.

Film-coating light yellow: hypromellose, lactose, titanium dioxide, Macrogol 6000, iron oxide yellow, propylene glycol, purified talc.

**Effervescent Tablet:**

Sodium dihydrogen citrate, anhydrous citric acid, Povidone, sodium bicarbonate, Macrogol 6000, colloidal anhydrous silica, magnesium stearate, Orange Juice Flavour Permaseal PHS-140561, acesulfame potassium, saccharin sodium, Sunset yellow FCF.

Storage

Store below 25°C.

**POISON SCHEDULES: S4**

**SPONSOR**

Grunenthal Australia Pty Ltd  
Level 8, 616 St Kilda Road  
Melbourne VIC 3004

**AUST R 179677:** ZALDIAR Film-coated Tablets

**AUST R 179678:** ZALDIAR Effervescent Tablets

**Date of first inclusion in Australian Register of Therapeutic Goods (ARTG):-**