



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Oxycodone / Naloxone

Proprietary Product Name: Targin

Sponsor: Mundipharma Pty Ltd

June 2017

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The 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 <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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 2017

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>.

Contents

Common abbreviations	5
I. Introduction to product submission	8
Submission details	8
Product background	8
Regulatory status	10
Product Information	10
II. Quality findings	11
Introduction (if applicable)	11
Drug substances (active ingredients)	11
Drug product	12
Biopharmaceutics	13
Quality summary and conclusions	15
III. Nonclinical findings	15
Assessment	15
IV. Clinical findings	16
Introduction	16
Pharmacokinetics	20
Pharmacodynamics	22
Dosage selection for the pivotal studies	23
Efficacy	23
Safety	27
First round benefit-risk assessment	34
First round recommendation regarding authorisation	40
Second round evaluation of clinical data submitted in response to questions	40
Second round benefit-risk assessment	40
Second round recommendation regarding authorisation	40
V. Pharmacovigilance findings	41
Risk management plan	41
VI. Overall conclusion and risk/benefit assessment	49
Quality	50
Nonclinical	50
Clinical	51
Risk management plan	55
Risk-benefit analysis	56
Outcome	70

Attachment 1. Product Information _____ 70
Attachment 2. Extract from the Clinical Evaluation Report _____ 70

Common abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
ASRS	Augmentation Severity Rating Scale
BFI	Bowel Function Index
BMI	Body Mass Index
BPI-SF	Brief Pain Inventory-Short-Form
BSFS	Bristol Stool Form Scale
CI	Confidence Interval
COWS	Clinic Opiate Withdrawal Scale
CSBM	Complete Spontaneous Bowel Movements
CSR	Clinical Study Report
DA	Dopamine Agonist
ECG	Electrocardiogram
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – core 30
EU	European Union
EURLSSG	European Restless Legs Syndrome Study Group
EuroQol EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
EWP	Efficacy Working Party
FA	Full Analysis
FRA	Flexor Reflex Afferents
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
ICH	International Conference on Harmonisation

Abbreviation	Meaning
IRLS	International Restless Legs Syndrome Study Group Rating Scale
IRLSSG	International Restless Legs Syndrome Study Group
IN	Intranasal
IR	Immediate Release
ITT	Intent to Treat
IV	Intravenous
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed Model Repeated Measures
MOS	Medical Outcome Study (Sleep scale)
MPI	(in the context of RLS studies) Max-Planck Institute
MPI	(in the context pain studies) Multidimensional Pain Inventory
NAS	Numeric Analogue Scale
NRS	Numeric Rating Scale
OXN PR	Oxycodone/Naloxone Prolonged Release Combination Tablet
Oxy API	Oxycodone Active Pharmaceutical Ingredient
Oxy IR	Oxycodone Immediate-Release Formulation
OxyPR	Oxycodone Prolonged-Release Formulation
PAC-SYM(b)	Patient Assessment of Constipation
PD	Pharmacodynamic
PI	Product information Sheet
PK	Pharmacokinetics
PLMS	Periodic Limb Movements in Sleep

Abbreviation	Meaning
PP	Per Protocol
PR	Prolonged Release
PSG	Polysomnography
PSUR	Periodic Safety Update Report
PT	Preferred Term
q12h	Every 12 hours
QoL – RLS	Quality of Life Restless Legs Syndrome Questionnaire
QTc QT	Interval Corrected for Heart Rate
R	Randomisation
RCT	Randomised Controlled Trial
RLS	Restless Legs Syndrome
RLS-DI	Restless Legs Syndrome Diagnostic Index
SAE	Serious Adverse Event
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scales
TEAE	Treatment-emergent Adverse Event
V	Visit
VAS	Visual Analogue Scale
Vs	Versus
WASM	World Association of Sleep Medicine
WHO	World Health Organisation
WOMAC	Western Ontario and McMaster Universities Index for Osteoarthritis

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Major variation including Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	14 July 2016
<i>Date of entry onto ARTG</i>	20 July 2016
<i>Active ingredient(s):</i>	Oxycodone/Naloxone
<i>Product name(s):</i>	Targin
<i>Sponsor's name and address:</i>	Mundipharma Pty Ltd GPO Box 5214, Sydney 2001
<i>Dose form(s):</i>	Modified release tablets
<i>Strength(s):</i>	60/30 mg and 80/40 mg
<i>Container(s):</i>	Blister pack
<i>Pack size(s):</i>	20, 28 and 60s
<i>Approved therapeutic use:</i>	<i>Second line symptomatic treatment of patients with severe to very severe idiopathic Restless legs syndrome after failure of dopaminergic therapy.¹</i>
<i>Route(s) of administration:</i>	Oral (PO)
<i>Dosage:</i>	Dependent on symptoms treated see Product Information (Attachment 1).
<i>ARTG number (s):</i>	243252 and 243272

Product background

This AusPAR describes the application by the sponsor to make the following changes to the registration for Targin, Oxycodone/Naloxone, tablets:

1. Extend the indications to include Restless Legs Syndrome (RLS);
2. Register a new maximum daily dose (160 mg/80 mg) and higher strength tablets (60 mg/30 mg and 80 mg/40 mg);

¹ Full indications are now: The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

3. Amend the Product Information (PI) to describe four clinical trials of the abuse-deterrent characteristics of Targin.

The current indications for Targin are:

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

The proposed additional indication as proposed by the sponsor:

Symptomatic treatment of patients with moderate to severe idiopathic RLS insufficiently treated with dopaminergic therapy.

Targin modified release tablet is a registered, fixed dose combination, controlled-release formulation of oxycodone and naloxone in a 2:1 ratio.

Oxycodone is a full opioid receptor agonist with analgesic action.

Naloxone is a competitive opioid antagonist at opiate receptors, and it reduces disorder in bowel function that typically arises during opioid analgesic treatment. The naloxone acts primarily in the gut to reduce the incidence of constipation. Due to its high first pass metabolism little naloxone enters the blood stream. This allows for the centrally acting effects of oxycodone without the antagonist effects of naloxone.

The proposed maximum recommended daily dose of 160 mg oxycodone/80 mg naloxone (in two divided doses of 80/40 mg) is double the current recommended maximum dose.

The Australian PI for modified release oxycodone without naloxone does not specify a maximum dose. The dose is titrated according to response. The highest strength tablet of the various modified release oxycodone products is 160 mg.

1. Extension of indications to include RLS

RLS is a common neurological condition characterised by subjective discomfort in the legs associated with an unpleasant urge to move the legs to relieve the discomfort. It is subdivided into primary RLS, for which the cause is unknown, and secondary RLS, which is usually due to neurogenic discomfort in the legs from peripheral neuropathy or radiculopathy. Primary RLS can be considered as a movement disorder, in part produced by dopaminergic dysfunction in the basal ganglia. RLS may impair quality of life. Subjects may find it intolerable to sit still for prolonged periods, RLS may be painful and symptoms at night may interfere with sleep, leading to subsequent daytime somnolence and mood disorders.

Most treatment guidelines suggest initial treatment with levodopa or dopamine agonists (such as pramipexole), but many patients fail to respond adequately. Some subjects respond initially but eventually experience loss of efficacy with dopaminergic agents, or paradoxical worsening (augmentation) of symptoms with continued treatment. Therapeutic Guidelines Neurology (eTG 46 revised November 2015) recommends temporary use of oxycodone as a second line agent in patients in whom dopamine agonists are contraindicated, or for the management of augmentation. Gabapentin and clonazepam are also recommended as third line treatments.

Products approved for the treatment of RLS are limited to treatment of primary RLS and include various products containing levodopa and the dopamine agonists, pramipexole and ropinirole. While the proposed term 'idiopathic RLS' has been used by the sponsor this condition is referred to as primary RLS in the indications for other products with a RLS indication in Australia.

2. Introduce a new maximum dose and high-strength Targin tablets

The seven strengths tablet strengths currently registered in Australia range from 2.5/1.25 mg to 40/20 mg.

The sponsor seeks approval for two additional strengths of modified release tablet (60/30 mg and 80/40 mg) to coincide with a proposed doubling of the maximum recommended daily dose of Targin from 80/40 mg daily to 160/80 mg daily.

The Targin PI currently states that some patients will not have an adequate analgesic response to the maximum daily dose. For these patients, the current dosage recommendations state that additional oxycodone (without naloxone) can be given up to 80 mg twice daily. Hence, these patients will receive proportionately lower naloxone doses for higher doses of oxycodone. These patients may have higher rates of constipation than if they were treated with concomitant naloxone in the 2:1 ratio used for lower dose treatment regimens. The sponsor seeks to redress this balance by registration of the higher strength Targin tablets.

Modified release oxycodone in monotherapy products such as OxyContin has tablet strengths to 160 mg and no specific maximum daily dose. The sponsor seeks to demonstrate the efficacy and safety of naloxone in the higher strength formulations as a way to amend the dosing recommendations to allow for a maximum daily dose of 160 mg oxycodone/80 mg naloxone daily, that is, a doubling of the naloxone dose, with the maximum daily oxycodone dose, currently taken as Targin and supplementary oxycodone unchanged.

This submission includes a new pivotal efficacy study (OXN3506) in analgesia and other supporting data.

3. Amendments to the PI; Abuse potential of Targin

The sponsor seeks to include detailed descriptions of abuse potential studies in the Product Information. These descriptions include how naloxone, if administered intravenously or intranasally, may antagonise oxycodone, and therefore reduce the abuse potential of Targin if taken via these routes.

Regulatory status

This fixed dose combination product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 12 May 2010.

Targin was approved for the treatment of RLS in May 2014 in Germany as the first country in Europe, subsequently followed by approval in other EU countries.. The indication is more restrictive than proposed in Australia, that is, it is limited to the treatment of severe to very severe idiopathic RLS after failure of dopaminergic therapy.

An increase in the maximum daily dose of Oxycodone/Naloxone (OXN) has been approved in adults in Switzerland (April 2015) and in the EU. Applications to register the higher strengths of OXN (60 mg/30 mg and 80 mg/40 mg) were under evaluation in the EU and Switzerland at the time this application was considered by the TGA.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Introduction

The sponsor currently holds registrations of Targin oxycodone hydrochloride and naloxone hydrochloride 2.5/1.25 mg, 5/2.5 mg, 10/5 mg, 15/7.5 mg, 20/10 mg, 30/15 mg and 40/20 mg modified release tablets in blister pack.

From a pharmaceutical chemistry perspective, the sponsor seeks approval to:

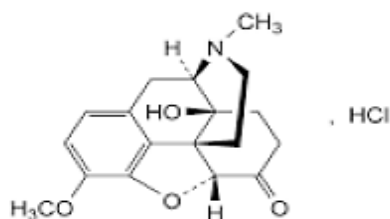
- Register higher strengths of Targin 60/30 mg and 80/40 mg modified release tablet in blister pack, and
- Increase the maximum daily dose from 80/40 mg to 160/80 mg.

The usual starting dose is one 10/5 mg modified release tablet every 12 hours, and titrated every 1-2 days twice daily to achieve pain relief. The maximum daily dose is currently 80/40 mg (12 hourly of Targin 40/20 mg tablet).

Drug substances (active ingredients)

Details of each active ingredient are detailed in the two figures below.

Figure 1: Oxycodone

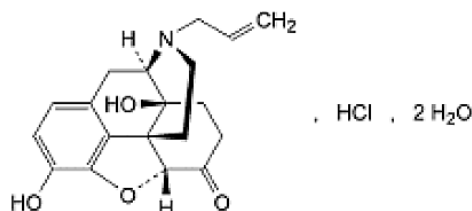


Structure Oxycodone hydrochloride (AAN, BAN). **Chemical name** 4,5 α -Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. **CAS #, MF and MW** 124-90-3 (CAS #), C₁₈H₂₂ClNO₄ 351.82 g/mol.

Chirality There are four chiral centres. Specific optical rotation: -140° to -148° (on anhydrous substance)

Oxycodone Hydrochloride is a hygroscopic, white to almost white crystalline powder. There are four chiral centres. Specific optical rotation: -140° to -148° (on anhydrous substance). It is freely soluble in water and sparingly soluble in anhydrous ethanol.

Figure 2: Naloxone



Structure Naloxone hydrochloride dihydrate. **Chemical name** 4,5 α -epoxy-3,14-dihydroxy-17-(prop-2-enyl)morphinan-6-one hydrochloride dihydrate. **CAS #, MF and MW** 51481-60-8 (CAS #), C₁₉H₂₂ClNO₄·2H₂O 399.9 g/mol.

Naloxone hydrochloride dihydrate is a hygroscopic, white to almost white crystalline powder. There are four chiral centres. It is freely soluble in water and alcohol.

Both drug substances used in the proposed higher strengths [60/30 mg and 80/40 mg] are obtained from *the same manufacturers* approved for the currently registered strengths.

Both drug substances have been adequately controlled by the respective manufacturers in accordance with the Pharmacopeia (Ph Eur) monograph requirements, plus additional tests (acceptable) dependent on the site.

Drug product

The proposed Targin tablet strengths 60/30 mg and 80/40 mg have the following appearances:

- **60/30 mg:** red, film-coated capsule shaped biconvex tablets with OXN marked on one side and “60” on the other side.
- **80/40 mg:** brown, film-coated capsule shaped biconvex tablets with OXN marked on one side and “80” on the other side.

These strengths are to be packaged in PVC/Al blister pack, in pack sizes of 20, 28 and 60 tablets, which are the same as for the currently marketed strengths.

The proposed 60/30 mg and 80/40 mg strengths are manufactured by the same manufacturing process as the registered strengths. Both new strengths have the same qualitative and quantitative composition as the registered 40/20 mg strength.

The dissolution results of both drug substances in the 60/30 mg and 80/40 mg modified release (MR) tablets are comparable to those in the registered strength 40/20 mg.

There is no British Pharmacopeia (BP) or US Pharmacopeia (USP) monograph for the combination product.

Both proposed higher strengths are controlled in accordance with the in-house Specifications, which contain the same parameters controlled for the registered strengths.

The impurities profile for the proposed strengths is essentially the same as the registered strengths, except for the following changes:

- Due to the proposed increase in maximum daily dose of this product, the acceptance limits for all specified impurities were assessed and tightened appropriately, in line with either BP requirements or International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) thresholds.
- Removal of a specified impurity. This was adequately justified, since it is not a degradation product and is controlled in the drug substance Specification in accordance with Ph Eur requirement.
- Inclusion of an additional degradation impurity, degradant of naloxone at release and shelf-life.

The proposed shelf life for the unopened product is 36 months, store below 25°C, when packaged in the proposed blister.

It is noted that ‘Protection from Light’ is not required for the currently registered strengths. The photostability of proposed strengths was confirmed by directly exposing the modified release tablet 60/30 mg and 80/40 mg. The results remain within the specification limits, confirming that the proposed strengths are not sensitive to light.

Biopharmaceutics

Three pharmacokinetic studies were provided in to support registration of the increased strength tablets (Table 1):

Table 1: Open label pharmacokinetic studies in healthy subjects

Study	Description	Type study	Evaluation
OXN1505 (single dose, fed)	Single dose, 3 period cross-over (fed conditions). 80/40 mg MR tablet versus oxycodone hydrochloride liquid 20 mg (20 mL of 5 mg/5 mL solution) and naloxone hydrochloride liquid 10 mg (10 mL of 1 mg/1 mL solution)	Food effect and relative bioavailability studies.	The first two studies were previously submitted and evaluated to support the registration of the 2.5/1/25mg, 15/7.5 mg and 30/15 mg strengths <i>These studies are extended to the proposed strengths will be summarised.</i>
OXN1506 (single dose, fasted)	Single dose, 7 treatments, 5 periods cross over, fasted state. Test: 2.5/1.25 mg, 15/7.5, 30/15 mg, 60/30 mg, 80/40 mg. Ref: 10/5 mg MR tab and 40/20 mg tab.	Demonstrate dose-proportional in the dose range of 2.5/1.25 mg to 80/40 mg.	
OXN1507 (multi dose fasted)	Multi-dose steady state, two treatments, 2 period cross-over, fasted state. Test: 80/40 MR tab vs Ref: 40/20 mg MR tab.	Demonstrate dose adjusted bioequivalence under steady state	<i>This study will be discussed in detail.</i>

OXO-1505 (single dose, fed conditions)

In the 80/40 mg tablets, food intake slightly increased the peak plasma concentration (C_{max}) of both oxycodone and naloxone, but has negligible effect on the area under the concentration versus time curve from time 0 to a defined time t or infinity (AUC_{0-t} and AUC_{0-inf}) of both drug substances.

This behaviour is consistent with those of the registered strengths. The increase in C_{max} was deemed not clinically relevant in the registered strengths.

OXO1506 (single dose, fasted conditions)

The results above indicate that the proposed 60/30 mg and 80/40 mg strengths are bioequivalent to the registered strength 40/20 mg under single dose, fasted conditions, when adjusted to dose (90% CI of AUC_{0-t} , AUC_{0-inf} and C_{max} are within the 80-125% as required to conclude equivalent).

OXO1507 (steady state, fasted conditions)

For AUC to the end of the dosing period (AUC_{tau}) and C_{max} at steady state (C_{maxss}) Oxycodone/Naloxone (OXN) 80/40 mg MR tablet (Test) provided equivalent availability of oxycodone and naloxone compared to OXN 40/20 mg MR tablet (Reference) when adjusted for dose, in terms of the % confidence interval (CI) of least squares (LS) mean ratios of Test/Reference (T/R) falling within the 80-125% range.

With regards to the trough plasma concentration at steady state (C_{minss}) the OXN 80/40 mg MR tablet (test) provided slightly lower availability (not equivalent) of oxycodone compared to OXN 40/20 mg MR tablet (reference) when adjusted for dose. This behaviour was also observed for naloxone-3-glucuronide.

- This will not be an issue for this type of product, given that the results for AUC_{tau} and C_{maxss} are equivalent between two strengths when adjusted for dose.

Fluctuation was slightly higher in the OXN 80/40 mg tablet (Test) compared to OXN 40/20 mg tablet (Reference), but these results are not significant.

- *Oxycodone*: mean fluctuation index ratio values of 95.5% and 79.5% for Test and Reference strength, respectively,
- *Naloxone*: mean fluctuation index ratio values of 116.8% and 109.8% for Test and Reference strength, respectively.

Justification for biowaver

The biostudies OXN1506 (single dose, fasted) were conducted for both 60/30 mg and 80/40 mg strengths.

However, the biostudies OXN1505 (single dose, fed) and OXY1506 (single dose, fasted) OXN1507 (multidose, steady state, fasted) were performed with only with highest proposed strengths 80/40 mg. A justification was provided for not conducting these biostudies for the 60/30 mg strength.

The justification presented the following points:

1. The proposed product Targin is a modified release tablet. All strengths of Targin MR Tablet (including the proposed 80/40 mg and 60/30 mg strength) are manufactured by the same manufacturing process, at the same site.
2. The proposed 80/40 mg strength has the same qualitative and quantitative excipients composition of the tablet core as the 60/30 mg strength,
3. Dose proportional linear pharmacokinetics of oxycodone and naloxone have been demonstrated over the strengths 2.5/1.25 mg, 10/5 mg, 15/7.5 mg, 30/15 mg, 40/20 mg, 60/30 mg and 80/40 mg (from study OXN1506).
4. Both strengths of 60/30 mg and 80/40 mg tablet (biobatch PN3663) have comparable in-vitro dissolution profiles for oxycodone and naloxone across a pH range.
5. Oxycodone has a narrow therapeutic index; however, given that the bioequivalence studies on the highest strength 80/40 mg, this will not be an issue.

In compliance with the requirements stated in Guidance 15 of ARGPM, the justification for biowavers of the 60/30 strength under 'single dose, fed' and 'steady state, fasted' is considered acceptable from pharmaceutical chemistry perspective.

Quality summary and conclusions

Approval for registration of the proposed product is not recommended until the following issues are adequately resolved:

1. The release and shelf-life limit for naloxone related impurities must be tightened in line with the ICH qualification threshold.
2. The revised finished product Specification should be provided for review. The revised finished product Specification should include the Specification codes, version date and signature of responsible personnel.
3. The analytical method for Related Substance should be revised to correct the origin of one impurity from 'oxycodone' to 'naloxone' and the revised Related Substances method should be provided for review.²

III. Nonclinical findings

The nonclinical data were submitted in support of the new indications part only, although the proposed increase in the maximum recommended human dose (MRHD) affects the animal/human exposure margins cited in various nonclinical sections of the PI. Revised wording for the relevant PI statements has been recommended in this nonclinical evaluation report.

Assessment

Major Variation

Amendments to nonclinical PI statements were also recommended.

Extension of Indications

The ability of four dopaminergic agents (which may possibly be co-administered with Targin) to inhibit the metabolism of oxycodone and naloxone was investigated in human hepatocytes in vitro. The dopamine agonists ropinirole, (S)-pramipexole and levodopa had little or no effect on either oxycodone or naloxone metabolism. Rotigotine showed inhibition of naloxone reduction (50% inhibitory concentration (IC₅₀) 7.2 µM) and naloxone glucuronidation (IC₅₀ 3.6 µM), but little inhibition of oxycodone N-demethylation (IC₅₀ 210 µM).

Although some inhibition of naloxone metabolism was established under these in vitro conditions, the clinical relevance of this is questionable, given the large concentrations required to observe any effects. The MRHD of rotigotine (Neupro transdermal patch) for the treatment of advanced stage Parkinson's disease is 16 mg/24 h; for the treatment of RLS, the MRHD is 3 mg/24 h. Thus, the concentrations of rotigotine required to inhibit naloxone metabolism are considerably greater than the clinical plasma rotigotine concentrations associated with RLS treatment.

- It is concluded from these data that pharmacokinetic interactions between rotigotine and the active components of Targin are unlikely under clinical usage conditions.

² See *Overall conclusions* and *Outcome* below.

Impurities

There are 3 impurities in the drug product which exceed the relevant the ICH limits. One of these compounds is a human metabolite and is therefore qualified at the proposed specification.

- The other 2 compounds have not been fully toxicologically qualified according to the relevant ICH impurity guidelines, and their specifications in the product should be reduced accordingly.³

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale for existing indications

According to the approved PI, oxycodone

'is a full opioid receptor agonist whose principal therapeutic action is analgesia. It has an affinity for endogenous mu, kappa and delta opiate receptors in the brain, spinal cord and peripheral organs (e.g. intestine). Binding of oxycodone to endogenous opioid receptors in the central nervous system (CNS) results in pain relief. Oxycodone is similar to morphine in its action. Other pharmacological actions of oxycodone are in the CNS (respiratory depression, antitussive, anxiolytic, sedative and miosis), smooth muscle (constipation, reduced gastric, biliary and pancreatic secretions, sphincter of Oddi spasm and transient elevations in serum amylase), and cardiovascular system via histamine release and peripheral vasodilation (pruritus, flushing, red eyes, sweating and orthostatic hypotension).'

When used to treat chronic pain, Targin has two potential advantages over other oral narcotic preparations: the prolonged-release formulation provides a more even pharmacokinetic profile with extended analgesic benefit, compared to immediate-release preparations; and the inclusion of naloxone minimises constipation, one of the major complications of chronic narcotic use.

Clinical rationale for proposed treatment of restless legs syndrome

See also *Product background, Extension of indications to include RLS*, for more details on RLS.

Most treatment guidelines for RLS suggest that initial treatment should be with levodopa or dopamine agonists but many patients fail to respond adequately. Some subjects respond initially but eventually experience loss of efficacy with dopaminergic agents, or paradoxical worsening (augmentation) of symptoms with continued treatment. Many experts^{4,5,6,7} suggest that narcotic analgesics may be useful for refractory cases and there

³ See Outcome below.

⁴ Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord* 2008b; 23: 2267-2302.

⁵ Vignatelli L, Billiard M, Clarenbach P, Garcia-Borreguero D, Kaynak D, Liesiene V, et al. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. *Eur J Neurol* 2006; 13: 1049-1065.

⁶ Walters AS, Wagner ML, Hening WA, Grasing K, Mills R, Chokroverty S, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep* 1993; 16: 327-332.

are widespread anecdotal reports that narcotic analgesics (including paracetamol-codeine combinations) have been adopted by patients to replace or to supplement dopaminergic agents when the response to dopaminergic agents has been unsatisfactory. In part, this treatment was based on the simple logic that opioids may relieve pain and discomfort, and RLS involves an element of leg discomfort. The benefits may involve mechanisms beyond those related to analgesia, however, and it is believed that opioids may have favourable effects on the dopaminergic system in this condition.

The proposed PI states: '*Opioids have their impact on Restless Legs Syndrome (RLS) symptoms by modulating the dopamine system.*' The Clinical Study Report (CSR) for OXN3502 provides a much more extensive rationale for the use of opioids in RLS. Until now, however, there has been no adequate trial data supporting this practice, although it is recommended by many experts. As the sponsor states in the CSR: '*According to expert opinion, oxycodone seems to be the best described opioid in RLS Trenkwalder, 2008b⁸ Vignatelli et al., 2006⁹; Walters et al., 1993¹⁰].*'

The sponsor has performed a single pivotal study for this indication, along with an open-label extension phase, in subjects with inadequate control of RLS following treatment with dopaminergic agents or levodopa.

Clinical rationale for increase in maximum dose

Patients with chronic severe pain may develop tolerance to opioids, requiring dose escalation, or they may have an inadequate response to low doses when these are first used. Usual clinical practice is to cautiously increase the opioid dose as needed. For oxycodone, prolonged-release naloxone-free preparations (OxyContin) have already been approved at doses up to 80 mg twice daily. Targin is currently only approved to doses up to 40/20 mg twice daily and clinical experience suggests that this dose is inadequate for some patients.

The sponsor makes the following observations about the need for higher doses:

'The approved dose range of OXN PR is up to OXN80/40 mg PR per day, which is sufficient to manage a significant segment of the population of patients with severe pain. However, market research conducted in Germany in 2011 (IMS Health Disease analyser; period Sep 2010 to Aug 2011) revealed that 32.2 % of prescriptions were > 80mg oxycodone per day and 11.2 % >160mg oxycodone or equivalent per day for 18051 non-malignant pain patients under the care of 420 General Practitioners [sic] (GPs). This emphasizes that there is a considerable amount of patients requiring doses >80 mg oxycodone per day. Therefore, it is evident that there is a need for OXN PR daily doses higher than 80/40 mg.'

Current recommended practice for patients who are on Targin and require higher oxycodone doses is to combine the maximum approved dose of Targin (40/20 mg twice daily) with top-up doses of OxyContin, up to a total oxycodone dose of 80 mg twice daily, using the two formulations combined. This combination is logistically awkward, requiring multiple prescriptions, and it leads to use of a lower proportion of naloxone, relative to the oxycodone component, than is used at standard Targin doses. (For instance, at the

⁷ Garcia-Borrequero D, Allen RP, Benes H, Earley C, Happe S, Högl B et al. Augmentation as a treatment complication of restless legs syndrome: concept and management. *Mov Disord* 2007b; 22 (Suppl.18): S476-S484.

⁸ Trenkwalder C, Hening WA, Montagna P, Oertel WH, Allen RP, Walters AS, et al. Treatment of restless legs syndrome: an evidence-based review and implications for clinical practice. *Mov Disord* 2008b; 23: 2267-2302.

⁹ Vignatelli L, Billiard M, Clarenbach P, Garcia-Borrequero D, Kaynak D, Liesiene V, et al. EFNS guidelines on management of restless legs syndrome and periodic limb movement disorder in sleep. *Eur J Neurol* 2006; 13: 1049-1065

¹⁰ Walters AS, Wagner ML, Hening WA, Grasing K, Mills R, Chokroverty S, et al. Successful treatment of the idiopathic restless legs syndrome in a randomized double-blind trial of oxycodone versus placebo. *Sleep* 1993; 16: 327-332.

maximum combination dose, subjects would receive oxycodone 80 mg twice daily and naloxone 20 mg twice daily, a 4:1 ratio instead of the standard 2:1 ratio). There is no evidence that a low proportion of naloxone is more appropriate than the standard proportion, and the current awkward situation largely reflects that adequate studies of higher dose Targin had not been performed at the time Targin was registered. If it could be proven that higher doses of Targin were safe and effective, there would be an obvious clinical role for such doses.

Clinical rationale for discussion of abuse potential in PI

Oral narcotics prescribed for treatment of pain can be diverted to recreational use and administered via the intravenous (IV) or intranasal (IN) routes and these routes may be preferred by recreational users because they are associated with a relatively rapid rise in narcotic levels, which produces a likeable effect or 'high'.

When administered orally, naloxone has minimal systemic effects because of extensive first-pass metabolism, but diversion to other routes (IV, IN) could increase the bioavailability of naloxone and this would be expected to antagonise the opioid component of Targin, producing a less satisfying high than other oral agents diverted to the IV or IN routes. Bioavailability of naloxone via the intravenous route is essentially complete, and the sponsor points out that '*The high bioavailability of IN naloxone is supported by studies demonstrating reversal of opioid effects in overdose patients and in animal PK studies^{11,12,13.}*' [Study report for ONU003]. Thus, compared to opioid monotherapy preparations, Targin might be a less attractive agent for opioid abusers to divert.

The sponsor has performed a number of studies broadly confirming these pharmacological principles, and would like to include this data in the new PI. Unfortunately, as will be discussed, the sponsor's proposed description of these studies does not present a balanced summary of the evidence. In particular, the submitted evidence suggests that it is possible for users of Targin to produce a 'high' by chewing the tablet and some of the benefits proposed by the sponsor appear to be seen only in subjects receiving concurrent methadone.

2.3.1.2. Related submissions

Previously submitted study (038-002; with a crossover design with inadequate washout between phases, leading to a significant sequence effect and an unclear efficacy and safety comparison between treatment phases.) is considered supportive of the proposed higher dose and a new study (OXN3506) has been designated as pivotal. The third efficacy study (OXN2001) was felt to be of limited relevance to the proposed increased dose, because results were not reported separately for those receiving a higher dose. A related study report (OXN2001S) has been resubmitted with the current evaluation but it is merely an uncontrolled, open-label extension of the earlier study.

Previously submitted supportive studies (OXN2001 and OXN3006S) have now been re-analysed by the sponsor, along with other studies from the original Targin development program (OXN2001, OXN3001, OXN3006, OXN3401, OXN3001S, OXN3006S, OXN3401S), to characterise the pooled experience of patients exposed to higher doses. Complete study

¹¹ Hussain AA, Kimura R, Huang CH (1984) Nasal absorption of naloxone and buprenorphine in rats. *International Journal of Pharmaceutics* 21:233.

¹² Kerr D, Kelly AM, Dietze P, Jolley D, Barger B (2009) Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. *Addiction* 104:2067-2074

¹³ Robertson TM, Hendey GW, Stroh G, Shalit M (2009) Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp. Emerg. Care* 13: 512-515.

reports for each of the contributing studies were not submitted, but these have been evaluated previously.

2.3.1.3. Guidance

No information relating to guidance from local or international regulatory authorities was contained in the submission.

Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission consisted of three disconnected parts, each with its own clinical overview, efficacy and safety summaries, corresponding to each of the three proposed variations.

In support of the RLS indication, the submission contained the following clinical information:

- One pivotal efficacy and safety study (OXN3502).
- One open-label extension study (OXN3502S).
- Sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety.

In support of the higher dose, the submission contained the following clinical information:

- Three pharmacokinetic studies (OXN1506, OXN1505, and OXN1507).
- One pivotal efficacy and safety study (OXN3506).
- Four supportive efficacy studies (OXN2001S, OXN3503, OXN3505, 038-002).
- Pooled efficacy and safety analysis of data from those studies and supportive studies that have been submitted previously (OXN2001, OXN3001, OXN3006, OXN3401, OXN3001S, OXN3006S, OXN3401S).
- Sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety.

In support of the abuse-potential discussion proposed for inclusion in the PI, the submission contained the following:

- Two bioequivalence studies (ONU1001, ONU1002), comparing UK and US manufacturing.
- A bioavailability study (ONU1009), which assessed the relative bioavailability of oral oxycodone in Targin 20/10 mg compared with a marketed product containing oxycodone (oral OxyContin modified release tablet, 20 mg), and the relative bioavailability of naloxone compared with two marketed products containing naloxone.
- Four safety/pharmacodynamic/pharmacokinetic (Safety/PD/PK) studies (ONU1003, ONU1004, ONU1007, ONU1008), which assessed the abuse potential of Targin versus an active comparator (oxycodone in solution) and placebo.
- Sponsor's Clinical Overview, Summary of Clinical Safety.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The submitted studies included statements of compliance with Good Clinical practice (GCP) and appeared to have been conducted in accordance with the principles of GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

The PK of Targin has already been well characterised but the current submission includes 6 PK studies (two of which have been submitted previously).

Three biopharmaceutical studies (OXN1506, OXN1505, and OXN1507; see Table 2) were submitted in support of the higher-strength tablets and the increased maximum dose.

- The food-effect and relative bioavailability study (OXN1505) had already been submitted to the TGA to register Targin at strengths of 2.5/1.25 mg, 15/7.5 mg and 30/15 mg. This study assessed the effect of a standardised high fat meal on the bioavailability of Targin 80/40 mg and the relative bioavailability of Targin 80/40 mg compared to an oral solution containing oxycodone 20 mg and naloxone 10 mg.
- The dose-proportionality study (OXN1506) had also been previously submitted to the TGA to register Targin at strengths of 2.5/1.25mg, 15/7.5mg and 30/15mg. This study assessed the PK dose-proportionality of Targin in the dose range of 2.5/1.25 mg to 80/40 mg.
- A new multiple-dose study (OXN1507) was submitted. This study assessed the PK of oxycodone and naloxone from Targin 80/40 mg and 40/20 mg tablets at steady state, demonstrating dose-adjusted bioequivalence.

Table 2: PK Studies Submitted for New Dose Strengths

Study ID	Subjects	Objectives
<i>Pharmacokinetics</i>		
OXN1506	Healthy subjects	Dose proportionality
OXN1505	Healthy subjects	Food effect, relative bioavailability
OXN1507	Healthy subjects	Bioequivalence

In reference to the proposed new discussion in the PI of the abuse potential of Targin, the sponsor submitted the following three PK studies:

- Two bioequivalence studies (ONU1001, ONU1002) which compared UK and US manufacturing.
- One bioavailability study (ONU1009) assessed the relative bioavailability of oral oxycodone in Targin 20/10 mg compared with oral OxyContin 20 mg, and the relative bioavailability of naloxone in Targin compared with two marketed naloxone products.

Table 3 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 3: Submitted Pharmacokinetic Studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	OXN1506	*
		OXN1505	

PK topic	Subtopic	Study ID	*
	- Multi-dose	OXN1507	*
	Bioequivalence† - Single dose	OXN1505	
		ONU1001	*
		ONU1002	*
	ONU1009	*	
	- Multi-dose	OXN1507	
	Food effect	OXN1505	*

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The pharmacokinetics of Targin have already been well characterised and the submitted data did not raise any substantive new PK issues. The proposed higher doses can be expected to produce a dose-proportional increase in exposure to oxycodone, as summarised in the table below. The naloxone component undergoes rapid and extensive first-pass metabolism.

Table 4: Summary Statistics for PK of Oxycodone

PK Parameter (unit)		OXN PR 2.5/1.25 mg (N=31)	OXN PR 10/5 mg (N=31)	OXN PR 15/7.5 mg (N=32)	OXN PR 30/15 mg (N=31)	OXN PR 40/20 mg (N=32)	OXN PR 60/30 mg (N=31)	OXN PR 80/40 mg (N=30)
AUCt (ng·h/mL)	n	31	31	32	31	32	31	30
	Geometric Mean	33.4	126.5	197.9	395.7	488.7	721.3	972.9
	log(SD/SE)	0.26/0.05	0.21/0.04	0.27/0.05	0.25/0.04	0.25/0.04	0.28/0.05	0.26/0.05
	Mean	34.45	129.08	205.06	407.87	504.01	749.32	1004.5
	(SD/SE)	(8.99/1.62)	(25.42/4.57)	(55.79/9.86)	(105.87/19.01)	(127.55/22.55)	(213.53/38.35)	(250.94/45.81)
	Median	32.6	130.4	202.3	386.5	501.5	693.1	950.4
Min, Max	22, 57	79, 166	117, 338	275, 735	308, 825	446, 1259	618, 1426	
AUCINF (ng·h/mL)	n	31	31	32	31	32	31	30
	Geometric Mean	34.4	127.4	199.1	397.2	491.0	723.5	977.0
	log(SD/SE)	0.25/0.04	0.21/0.04	0.27/0.05	0.25/0.04	0.25/0.04	0.28/0.05	0.26/0.05
	Mean	35.41	129.98	206.32	409.40	506.29	751.62	1008.5
	(SD/SE)	(8.93/1.60)	(25.58/4.59)	(56.31/9.95)	(106.11/19.06)	(127.54/22.55)	(214.10/38.45)	(251.32/45.89)
	Median	34.0	131.2	203.4	388.7	503.4	697.5	953.9
Min, Max	23, 58	80, 167	117, 339	277, 737	309, 827	446, 1262	619, 1428	
Cmax (ng/mL)	n	31	31	32	31	32	31	30
	Geometric Mean	3.23	11.79	17.74	36.28	39.80	58.32	82.03
	log(SD/SE)	0.222/0.040	0.208/0.037	0.266/0.047	0.228/0.041	0.233/0.041	0.213/0.038	0.221/0.040
	Mean	3.311	12.05	18.35	37.24	40.86	59.60	83.94
	(SD/SE)	(0.746/0.134)	(2.670/0.480)	(4.826/0.853)	(9.042/1.624)	(9.516/1.682)	(12.53/2.252)	(17.83/3.257)
	Median	3.300	11.80	17.75	36.40	40.45	60.60	89.30
Min, Max	2.27, 5.030	8.34, 21.70	11.1, 28.80	25.6, 64.90	24.4, 60.80	36.4, 87.20	57.6, 113.0	
tmax (h)	n	31	31	32	31	32	31	30
	Mean	2.74	2.74	3.03	3.21	3.25	3.34	3.35
	(SD/SE)	(1.33/0.24)	(1.36/0.24)	(1.29/0.23)	(1.38/0.25)	(1.33/0.23)	(1.32/0.24)	(1.61/0.29)
	Median	2.5	3.0	3.0	3.0	3.5	3.5	3.8
	Min, Max	1, 6	1, 6	1, 6	1, 6	1, 6	1, 5	1, 6
	LambdaZ (h ⁻¹)	n	31	31	32	31	32	31
Mean	0.159	0.181	0.177	0.164	0.159	0.159	0.147	
(SD/SE)	(0.0155/0.003)	(0.0253/0.005)	(0.0207/0.004)	(0.0327/0.006)	(0.0341/0.006)	(0.0304/0.005)	(0.0370/0.007)	
Median	0.159	0.178	0.172	0.165	0.160	0.150	0.144	
Min, Max	0.129, 0.189	0.133, 0.237	0.132, 0.227	0.079, 0.228	0.084, 0.218	0.112, 0.228	0.034, 0.219	
t1/2Z (h)	n	31	31	32	31	32	31	30
	Mean	4.39	3.90	3.97	4.43	4.60	4.52	5.30
	(SD/SE)	(0.44/0.08)	(0.54/0.10)	(0.48/0.08)	(1.11/0.20)	(1.18/0.21)	(0.81/0.15)	(2.99/0.55)
	Median	4.4	3.9	4.0	4.2	4.3	4.6	4.8
	Min, Max	4, 5	3, 5	3, 5	3, 9	3, 8	3, 6	3, 20

Cross reference: Table 14.2.2 and Listing 16.2.6.2.

N: Number of subjects in population. n: Number of subjects with data available. SD: Standard deviation. SE: Standard error.

Pharmacodynamics

Studies providing pharmacodynamic data

The sponsor did not perform any reassessment of the primary PD of Targin. The analgesic studies submitted in support of the new maximum dose assessed multiple doses but doses were titrated to individual needs and dose groups were not directly compared, so it is not possible to infer how the analgesic effect varies with dose. Similarly, in the RLS study, doses were titrated according to symptoms, so the efficacy of different doses in treating RLS symptoms cannot be directly compared.

Four PD studies were submitted in support of the proposed changes to the PI regarding the abuse-potential of Targin. These were single-dose PK/PD studies, summarised by the sponsor as follows:

The studies were all single dose. [...] The studies of abuse potential were all randomised, double-blind, crossover studies, two in recreational opioid users (ONU1003, ONU1007), and two in or methadone-treated opioid-dependent subjects (ONU1004, ONU1008). In study ONU1003, the abuse potential of Targin was assessed for three different routes of administration (oral, IN and IV) compared with oxycodone API and placebo. In ONU1004 the abuse potential of chewed Targin (strengths 30/15 mg and 60/30 mg) was compared with oxycodone API and placebo. In ONU1007 the abuse potential of chewed vs intact Targin was compared with oxycodone API. In ONU1008, the abuse potential of chewed vs intact Targin was compared with oxycodone API and placebo.

The major conclusions from these studies are summarised below.

Evaluator's conclusions on pharmacodynamics

The primary PD of Targin was not reassessed in this submission but studies of abuse potential clarified the abuse-related properties of Targin relative to other opioids, in the context of potential abuse and diversion to other routes by opioid abusers. The overall impact of these pharmacological properties on the abuse potential of Targin is difficult to estimate, in part because no data was submitted relating to how oral opioids are actually abused or diverted to other routes in the community. Intravenous and intranasal diversion of Targin appears to be an unattractive option for intermittent opioid users seeking to obtain a high, but chewed Targin probably offers the same abuse potential as chewed OxyContin in intermittent users; both agents, once chewed, are rapidly absorbed and appear likely to produce similar effects as immediate-release oxycodone (Endone). In this respect, the benefits of Targin appear modest, although chewing an opioid agent is in many ways more benign than injecting it, particularly in relation to the risks of needle-borne infections.

For regular methadone users, Targin did not produce likeable effects and it appears to offer relatively little abuse potential in this population. It is unknown whether this primarily reflects antagonism of methadone by naloxone, or some other mechanism. It is also unclear whether this result is likely to be replicated in addicts not on regular methadone, because the sponsor did not study addicts not on methadone. If the main reason for the poor likeability of Targin in methadone users was related to methadone antagonism, one would not expect non-methadone-treated addicts to report poor likeability of Targin but this subject group has not been assessed and no conclusions about this important patient group can be drawn.

These conclusions are broadly consistent with the sponsor's proposed addition to the PI, which describes each PD study and then concludes:

The clinical abuse potential studies indicate that Targin modified release tablets have pharmacologic properties that are expected to result in a meaningful reduction in abuse via the intranasal and intravenous routes of administration, although abuse and diversion by these and other routes is still possible.

Clinicians concerned about diversion could find this information useful and the inclusion of such information in the PI could provide clinicians with additional reasons to choose Targin over its competitors. For balance, though, the PI should also mention that the submitted studies showed that chewing Targin produces a likeable high in intermittent recreational opioid users not on methadone. Furthermore, the sponsor should avoid claims that the benefits seen in methadone-treated subjects can be generalised to other opioid addicts. More appropriate wording for the PI summary was proposed to the Delegate but details of this is beyond the scope of this AusPAR.

Dosage selection for the pivotal studies

For the RLS indication, no dose-ranging studies were performed. The sponsor selected a low-to-intermediate dose for the pivotal RLS study (OXN3502), based on previous clinical experience with the analgesia indication and anecdotal reports on the use of oxycodone and other narcotics for RLS. Initial doses were low (OXN 5/2.5 mg twice daily) but up-titration to higher dose levels was permitted if needed (10/5, 20/10, 30/15 or 40/20 mg OXN prolonged release (PR) tablet twice daily). Given that these doses have been well studied for the chronic pain indication, this approach was reasonable. RLS is a chronic condition that is not life-threatening so a slow, cautious dose titration is appropriate.

For studies assessing the chronic pain indication, dose selection was individualised for each patient, and patients were already receiving oxycodone doses in the standard clinical range prior to study entry. The pivotal study (OXN3506) allowed clinicians to titrate the oxycodone dose during a run-in phase and then randomised subjects to blinded naloxone add-on (Targin) or to continued oxycodone monotherapy. The oxycodone dose was therefore determined by clinical analgesic need, and the naloxone dose was determined by the default 2:1 oxycodone: naloxone ratio, which has already been approved for lower doses. No specific rationale was provided for this ratio in the current submission and no other oxycodone: naloxone ratios were assessed. The current PI for Targin already recommends that higher oxycodone requirements (beyond the maximum approved Targin dose) should be met with a mixture of OxyContin and Targin, effectively lowering the naloxone dose in proportion to the oxycodone dose. The proposed new maximum dose of Targin therefore represents an attempt to unify the oxycodone: naloxone ratios across the range of opioid doses used. Although this appears attractive on the basis of simplicity and convenience, no specific evidence was provided to support the assumption that the same ratio is appropriate across the entire dose range.

Efficacy

Studies providing efficacy data

Table 5 provides details of the studies submitted in support of the increased maximum dose in this submission.

Table 5: Efficacy Studies Submitted for Major Variation F (Increased Maximum Dose)

Study ID	Subjects/Indication	Comparator
<i>Pivotal study</i>		
OXN3506	Subjects with cancer and non-cancer pain and opioid-induced constipation	OxyPR
<i>Supportive studies</i>		
OXN3503	Subjects with moderate to severe osteoarthritis and opioid-induced constipation	OxyPR
OXN3505	Subjects with cancer and non-cancer pain and opioid-induced constipation	OxyPR
038-002	Subjects with chronic non-cancer pain and opioid-induced constipation	OxyPR
OXN2001S	Subjects with moderate to severe, chronic cancer pain and opioid-induced constipation in the core phase	none

Evaluator's conclusions on efficacy***Conclusions on efficacy in RLS***

Only one randomised controlled study (OXN3502) was submitted in support of the proposed indication for RLS, so it needs to be judged with a substantial measure of caution. This Phase III pivotal study was only of modest size (completing subjects: OXN n=107; placebo n= 97; total n=204) and duration (12 weeks double-blind treatment) but it achieved strong efficacy results for its primary endpoint ($p<0.001$) and for all major secondary endpoints ($p<0.001$ for nearly all endpoints). The magnitude of the treatment effect, about 7-8 points on the IRLS, from a baseline of ~30 points, exceeded the benefit considered to be clinically significant during power calculations (4 points).

The clinical relevance of the reduction in RLS symptoms is further supported by positive results for the Clinical Global Impression, sleep quality assessed by a couple of different scales, and quality of life using an instrument specific for RLS issues.

One of the main deficiencies of the study was its relatively short duration of treatment (12 weeks). This is offset to some extent by extension of the study into an open-label phase. There are no clear guidelines mandating any particular study duration in the investigation of treatments for RLS. In the European Medicines Agency (EMA) guidelines in relation to insomnia studies (where RLS is listed as a potential cause of insomnia), it is recommended that treatments intended for long-term use should be studied for at least six months:

In principle, a long-term study is needed unless there are compelling safety reasons not to conduct such trials. In this situation, the indication would be 'short-term treatment'. This might be done by a double-blind placebo-controlled extension study or, preferably, by a randomised withdrawal design. In the randomised withdrawal design, responders to the investigational treatment of sufficient duration are randomised to continue the investigational drug or switch to placebo. This is done in two time periods. In the first open and uncontrolled period the stabilised responders continue with the test treatment for 2 to 4 weeks, thereafter they are randomised and followed for at least 6 months depending on the mechanism of action of the studied medicinal product. The alternative, a double-blind placebo-controlled extension study, should equally last for at least 6 months. Those subjects not coming into the maintenance phase should have their medication withdrawn under placebo control to detect any possible dependence.

Overall, considering the strength of the results in the pivotal RLS study, and the lack of apparent loss of efficacy during the open-label extension study for up to 52 weeks in total, the evaluator believes that the evidence for long-term efficacy of Targin in RLS is

adequate. Given that subjects will be in a position to judge their responses to treatment, a gradual decline in efficacy or the development of tolerance would be likely to be noted, and a dose adjustment or withdrawal of therapy could be undertaken.

The other main deficiency in the submitted RLS study program is that there was no study of the efficacy of Targin as add-on therapy, in subjects receiving dopaminergic therapy. The indication being sought is:

Symptomatic treatment of patients with moderate to severe idiopathic Restless Legs Syndrome (RLS) insufficiently treated with dopaminergic therapy.

In many cases, this will lead to use of Targin as an add-on agent but no study has specifically addressed whether Targin has efficacy when used in this manner.

Given that clinicians will be free to phase out dopaminergic agents if they appear not to be contributing to efficacy, leading to Targin monotherapy (which this study suggests is more effective than placebo), the lack of add-on efficacy data is not considered to be a barrier to registration. Also, it should be noted that RLS is a subjective symptom, which patients are in a good position to observe; if Targin lacked efficacy in an individual patient when added to dopaminergic therapy, the patient could note the lack of response and withdraw the ineffective agent.

On balance, despite the fact that only one controlled study was submitted and it did not explore the efficacy of Targin as an add-on agent, the submitted evidence narrowly provides adequate support for the sponsor's claims of efficacy for Targin in RLS.

It should be noted that a similar conclusion has been drawn by the EMA, who have approved Targin for this indication. It could also be argued that a new indication should not be approved without a dose-response study.

Conclusions on efficacy of higher doses in chronic pain

The pivotal analgesia study and the supporting studies provide evidence that Targin, titrated over a range of doses including those already approved, is less constipating than equivalent doses of oxycodone monotherapy but reasonably similar in terms of analgesia. The pivotal study, OXN3506, met both of its primary objectives, demonstrating an improvement in symptoms of constipation (measured by the BFI) and non-inferiority in pain scores (PIS visual analogue scale) in subjects taking OXN PR compared to subjects taking OxyPR. The evidence of non-inferiority was not robust, however, because there appeared to be a significant difference in analgesic efficacy between Targin and OxyContin, in favour of OxyContin, and the study was not powered for specific doses.

The benefit of OXN for bowel symptoms was demonstrated in all major analyses of the pivotal study, including the primary endpoint in the full analysis population (LS mean difference (SE): -16.05 (3.14); $p < 0.001$, CI: -1822.23.19, -7.169.86, $p < 0.001$), as well as bowel-related secondary efficacy analyses. Supportive studies produced similar results.

Broadly similar analgesic efficacy of OXN and OxyPR at intermediate oxycodone doses appears likely. Subjects in both treatment groups of the pivotal study showed reduced pain in the Run-in Phase when they commenced OxyPR, and pain scores remained reasonably constant throughout the Double-blind treatment period. The sponsor's statistical analysis of this result was not particularly convincing. In the primary per protocol (PP) analysis, the sponsor's null hypothesis was that the ratio of 'average pain over the last 24 hours' between OXN PR and OxyPR was $\geq 120\%$. This hypothesis was rejected with $p < 0.001$, but it should be noted that that lesser increases of pain (such as a 19% increase in pain) could be considered clinically significant. Pain scores were quite similar in the two active groups, so it appears very likely that, in clinical practice, any analgesic difference between the two treatments would fall well short of the sponsor's 120% threshold but the provided analyses do not clarify this likelihood. The 95% CIs for the treatment differences in the pivotal study were not reported clearly in the text of the

study report but were included in a subsequent table, and this analysis suggested that pain scores could be almost up to one unit higher with OXN (treatment difference in favour of OxyPR, -0.65; 95%CI -0.99 to -0.3), which is a large difference relative to the mean pain scores of about 3.5 to 4. Also, the 95% CI excluded zero, apparently indicating a significant difference, but the sponsor did not comment on this anywhere in their submission. Given that the maximum-dose subgroup was relatively small, broader 95% CIs would be expected for a dose-specific analysis of this endpoint, and the 95% CIs would be expected to include differences that could be considered clinically significant.

A more substantial issue is that the submitted studies did not specifically assess the efficacy of doses above those already approved, relative to approved doses. Furthermore, exposure to the maximum proposed dose only occurred in a minority of patients in the pivotal study, which was not powered to allow assessment of efficacy at specific doses. Only 31 subjects received the highest proposed dose of Targin (160/80 mg/d) in the pivotal study, only 19 subjects received the maximum dose in the major supportive crossover Study 038-002, and in a pooled analysis of several minor studies, only 47 subjects received Targin at doses above those already approved (>80/40 mg/d). The pooled analysis of minor studies did not specifically assess the maximum proposed dose but it seems very likely that very few patients (and possibly only one patient) received the maximum dose across all of the minor studies.

In particular, the following issues were poorly characterised:

1. The analgesic efficacy of the higher, proposed oxycodone doses (> 40 mg twice a day (BD), up to 80 mg BD) compared to lower, approved oxycodone doses (\leq 40 mg BD) has not been assessed in any study in the current submission. In all studies, oxycodone doses were non-random and titrated to effect; the parallel treatment groups had equivalent oxycodone dosing and only differed in terms of naloxone treatment, so an oxycodone dose comparison across treatment groups is not possible. Subgroup analysis by oxycodone dose was performed to some extent but this is of limited utility given the non-random, unblinded allocation of doses and the small numbers exposed to the highest doses.
2. The efficacy of high-dose naloxone (>20 mg BD, up to 40 mg BD) in preventing constipation due to the proposed higher oxycodone doses has not been directly assessed in an adequately powered study. Although some subjects in the Targin group of the pivotal study received high-dose naloxone and their results can be compared with subjects who received equivalent doses of oxycodone without naloxone, the study was not adequately powered for such a subgroup analysis.
3. Whether or not high-dose naloxone might antagonise oxycodone and compromise the analgesic efficacy of oxycodone has not been directly assessed in an adequately powered study. Pain scores in subjects using higher doses of Targin in the pivotal study were compared with subjects using equivalent doses of oxycodone without naloxone but only descriptive statistics were presented (see table below), and no study was adequately powered for such a comparison. The lack of statistical power in the upper end of the proposed dose range is particularly important given that the sponsor sought to demonstrate non-inferiority of Targin relative to naloxone-free oxycodone.
4. An oxycodone: naloxone ratio of 2:1 has been proposed for the new, higher Targin doses. This ratio is based on consistency with the ratio already used in lower, approved doses but no clinical study directly assessed the suitability of this ratio at high doses in comparison to alternative ratios. In every analgesic study submitted, individual naloxone doses in the Targin group were based directly on the titrated oxycodone dose, at a fixed 2:1 ratio.

5. No study compared the proposed higher doses of Targin with the current recommended practice of combining Targin and OxyContin to reach higher total oxycodone doses.

Table 6: Pain Intensity Scale 'Average Pain Over 24 Hours' Observed Values, Per Protocol Population, Study OXN3506

Timepoint	OXN PR		OxyPR	
	Value	Change from Baseline	Value	Change from Baseline
Dose level 100-120 mg/d				
Baseline	n	60	64	
	Mean (SD)	3.5 (0.79)	3.3 (1.03)	
	Median	4.0	4.0	
	Min, Max	1, 5	1, 6	
Week 5	n	60	62	62
	Mean (SD)	3.6 (1.29)	0.2 (1.32)	3.4 (1.40)
	Median	4.0	0.0	4.0
	Min, Max	0, 6	-4, 4	0, 7
Dose level 140-160 mg/d				
Baseline	n	33	35	
	Mean (SD)	3.7 (0.53)	3.5 (0.78)	
	Median	4.0	4.0	
	Min, Max	2, 4	1, 4	
Week 5	n	33	32	32
	Mean (SD)	3.6 (0.94)	-0.1 (0.70)	3.5 (1.19)
	Median	4.0	0.0	4.0
	Min, Max	1, 6	-1, 2	1, 6

Safety

Studies providing safety data

The sponsor submitted three different Summaries of Clinical Safety (SCS), one for each of the proposed variations (the RLS indication, the higher maximum dose, and the PI revision mentioning new abuse-potential studies). Of these, the most important was the SCS dealing with the proposed increase in the maximum dose. The Targin doses proposed for use in RLS have already been widely used in the treatment of pain and the safety profile of Targin (OXN) in that dose range is well known, so the RLS studies did not add substantially to existing knowledge of the safety profile of Targin. The studies submitted in support of the abuse-potential claims in the proposed PI were all small, single-dose studies, which did little to characterise the safety of Targin outside the narrow context of the pharmacology of abuse.

Patient exposure

For currently approved doses, there has already been extensive exposure to Targin in previously reported studies, as shown in the following table.

Table 7: Duration of Exposure to Oxycodone/Naloxone (all subjects from completed studies)

Indication Duration of Exposure	Number of Subjects (N=4019)	Person time (days)
Total		
Any	4019	484562
> 1 month	1973	461225
> 3 months	1389	422218
> 6 months	1038	381214
> 12 months	702	286629

By contrast, exposure to the proposed high doses (above 80/40 mg/d) has been very limited, as discussed below.

Exposure to high doses in analgesia studies

In the pivotal analgesia study, OXN3506, 123 subjects were exposed to OXN, for a mean duration of 32 days but only 15 subjects were exposed to 140/70 mg/day and only 31 subjects were exposed to the proposed maximum dose of 160/80 mg/day (based on the highest dose to which subjects were exposed for at least 7 days, as shown in the second table below). Considering the highest dose alone, these patient numbers would normally be considered more typical of a Phase I study rather than a Phase III pivotal study. Most of the subjects exposed to the highest dose were already on this dose at the commencement of the Double-blind phase, as shown in the third table below, but some only reached the highest dose during the study. (The tables disagree on the number of subjects exposed to 160/80 mg/day, possibly because subjects with exposure <7 days are not counted in the second table below).

Table 8: Exposure to Study Medication, Study OXN3506

		OXN PR (N=123)	OxyPR (N=120)
Exposure (days)	n	123	120
	Mean (SD)	32.2 (9.94)	33.0 (8.55)
	Median	36.0	36.0
	Min, Max	2, 41	2, 40
Cumulative exposure [n (%)]	Any	123 (100.0)	120 (100.0)
	≥ 1 week	116 (94.3)	115 (95.8)
	≥ 2 weeks	108 (87.8)	111 (92.5)
	≥ 3 weeks	106 (86.2)	109 (90.8)
	≥ 4 weeks	106 (86.2)	106 (88.3)
	≥ 5 weeks	97 (78.9)	93 (77.5)
Daily Dose (mg)	n	123	120
	Mean (SD)	121.4 (23.82)	120.5 (24.02)
	Median	116.7	116.7
	Min, Max	60, 160	57, 160

Reference: CSR Table 38
N: Number of patients in population. n: Number of patients with available data. %: Percentage based on N.
Exposure is defined as the number of days from first dose to last dose where study medication was taken by the patient.

Table 9: Dose Levels in Double-blind Phase, FA Population Study OXN3506

Dose Level (mg/d)	OXN PR (N=121)	OxyPR (N=116)
100	40 (33.1%)	42 (36.2%)
120	26 (21.5%)	30 (25.9%)
140	15 (12.4%)	13 (11.2%)
160	31 (25.6%)	28 (24.1%)

Dose levels are defined as the highest dose taken on more than 7 consecutive days.
*: 12 Patients are excluded due to early dropout and thus violation of the definition above.

Table 10: Shift of Dose from Baseline to End of Study, OXN3506

Dose at Baseline (mg/d)	Dose at End of Study (mg/d)							
	OXN PR (N=121)				OxyPR (N=116)			
	100	120	140	160	100	120	140	160
100	40	6	.	1	43	3	.	.
120	.	25	2	.	1	26	2	1
140	.	.	14	4	.	.	12	1
160	.	.	.	28	.	.	.	27

One patient was two days in study and did not receive full IMP dose and is therefore excluded from this table

The supportive analgesic study, 038-002, was a cross-over study using Targin (designated OXN or OXN PR in the provided tables) at doses of 120/60 or 160/80 mg/d, in two divided doses, and equivalent doses of prolonged-release oxycodone (OxyPR) without naloxone. Patients received OXN for a mean 32.0 ± 8.1 days and OxyPR for a mean of 32.8 ± 7.6 days. Of the 52 patients who received OXN, 33 (63%) received the 120/60 mg/day dose, and 19 received the proposed maximum 160/80 mg/day dose. (Of 54 patients exposed to OxyPR, 36 received 120/60 mg/day and 18 received 160/80 mg/day)

In the open-label period, 34 patients were exposed to OXN for a mean of 124.8 ± 69.9 days. Of those, 16 patients were exposed to 120/60 mg/day and 18 were exposed to 160/80 mg/day.

Exposure in the minor supportive studies is summarised below. The mean daily dose in Studies OXN3503, OXN3505 and OXN2001S was well below the currently approved maximum of 80/40 mg/day. The number of subjects exposed to the maximum proposed dose in these studies was not clearly reported in the sponsor's Summary of Clinical Safety but appears to have been one in total: none from OXN3503, one from OXN3505, and none from OXN2001S.

Table 11: Exposure to Study Medication for OXN PR across Supportive Clinical Trials

PARAMETER	OXN3503 ¹	OXN3505	OXN2001S
Exposure [days]			
- n	101	111	126
- Mean (SD)	76.0 (23.73)	25.1 (8.46)	122.17 (64.24)
- Median	85.0	28.0	162.0
- Min, Max	2, 92	2, 34	1, 193
Total dose [mg]			
- n	101	110	126
- Mean (SD)	2676.9 (1764.2)	1156 (820)	6675.5 (5086.6)
- Median	1720.0	1015	5290.0
- Min, Max	30, 7880	80, 4960	70, 20160
Average daily dose [mg]			
- n	101	110	126
- Mean (SD)	34.5 (19.79)	48.7 (29.0)	56,24 (28.73)
- Median	26.4	40.0	52.8
- Min, Max	15.0, 96.1	20, 160	10, 120

¹double-blind safety population

Study OXN3503 had a notional maximum dose of 120/60 mg/day, which is below the proposed new maximum, but it seems likely that no subjects were titrated to 120/60 mg/day anyway; only three subjects were exposed to 100/50 mg/day and all other subjects received doses that are already approved.

Study OXN3505 allowed doses up to 160/80 mg/day, but only one patient received this dose, as shown below, and only 12 patients received doses in the range 100/50 to 140/70 mg/day.

Table 12: Initial Dose and Maximum Dose reached, OXN PR, Safety Population, Study OXN3505

Initial dose (mg)	Maximum dose reached (mg)									
	20	30	40	60	80	100	120	140	160	Total
Frequency	25	4	3	1	0	1	0	0	0	34
Percent	22.73	3.64	2.73	0.91	0.00	0.91	0.00	0.00	0.00	30.91
20	0	10	4	2	0	0	0	0	0	16
30	0	0	20	6	2	0	1	0	0	29
40	0	0	0	7	4	1	0	0	0	12
60	0	0	0	0	9	1	2	1	0	13
80	0	0	0	0	0	2	0	1	0	3
100	0	0	0	0	0	0	1	1	0	2
120	0	0	0	0	0	0	0	0	1	1
160	0	0	0	0	0	0	0	0	0	0
Total	25	14	27	16	15	5	4	3	1	110
	22.73	12.73	24.55	14.55	13.64	4.55	3.64	2.73	0.91	100.00

Frequency Missing = 1

Study OXN2001S only allowed dosing up to 120/60 mg/day, below the proposed new maximum, and this study had no control group so it is of limited value.

Exposure in RLS studies

Exposure to Targin in the context of treating RLS was limited to a single pivotal study (OXN3502) and its open-label extension (OXN3502S). In the Double-blind Phase of the pivotal study, the intended duration of treatment was 12 weeks (84 days), and this was generally achieved in the active group, which had a median duration of exposure of 91.0 days. The placebo group had a shorter median exposure (68 days), reflecting the higher discontinuation rate in the placebo group. Overall, 69.3% of the OXN group and 49.4% of the placebo group received study medication for \geq 84 days.

The average daily dose of oxycodone in the OXN group was approximately 22 mg, with a notional average daily dose in the placebo group of approximately 35 mg.

In the Open-label Extension Phase, the median duration of exposure was 281 days (range: 4 to 297 days). The protocol planned duration of treatment was 40 weeks (280 days) and in total 156 (79.2%) subjects received study medication for 271 days or more, in the Extension Phase, resulting in an overall exposure of one year across the two studies.

The mean dose of oxycodone in the Extension Phase was approximately 18 mg daily.

Exposure in PK/PD studies

Exposure in the PK and PD studies was largely restricted to single doses per crossover phase, with the exception of one multi-dose PK study (OXN1507). Three of the studies (OXN1505, OXN1506 and OXN1507) were submitted in support of the proposed increased maximum dose (80/40 mg twice daily) and directly tested individual doses of 80/40 mg.

In Study OXN1506, 40 subjects completed the study and were randomly administered 5 of the 7 doses of study medication over 5 study periods. The test treatments were OXN tablets at 5 different strengths (2.5/1.25 mg, 15/7.5 mg, 30/15 mg, 60/30 mg and 80/40 mg), and the reference treatments were previously well-characterised doses of OXN PR (10/5 mg and 40/20 mg).

In Study OXN1505, 23 subjects completed the study and received all 3 treatments over 3 study periods (OXN80/40 mg in a fed and fasted state and oxycodone/naloxone liquid in a fasted state), 1 subject received two study treatments (oxycodone/naloxone liquid in a fasted state and OXN80/40 mg PR in a fed state), and 4 subjects received one study treatment (1 subject: OXN80/40 mg PR in a fed state, 3 subjects: OXN80/40 mg PR in a fasted state).

In Study OXN1507, 20 randomised subjects received twice-daily doses of 80/40 mg or 40/20 mg over two different crossover sessions of 3.5 days each. All subjects received at least one dose of OXN 80/40 mg, but 2 subjects discontinued from the study without receiving any OXN40/20 mg PR.

In Study ONU1001, 50 subjects were treated on two separate occasions with single doses of oxycodone/naloxone 10/5mg.¹⁴

In Study ONU1002, 55 subjects were treated on two separate occasions with single doses of oxycodone/naloxone 40/20 mg.

In Study ONU1009, 30 subjects were treated with single doses of oxycodone/naloxone 20/10 mg in one of the crossover stages.

In Study ONU1003, 16 subjects were in Group 1 (oral, chewed, 40/20); 27 were in Group 2 (IN, 40/20 mg); and 24 in Group 3 (IV, oxycodone 0.07 mg/kg/naloxone placebo, oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg, or oxycodone placebo/naloxone placebo).

¹⁴ For brevity, discontinuations are not considered and the patient numbers for each minor study refer to those randomised.

In Study ONU1004, 18 subjects completed treatment session 1 (OXN 30/15mg) and 16 subjects completed treatment session 2 (OXN 60/30 mg).

In Study ONU1007, 37 subjects were treated with single doses of OXN 40/20 mg.

In Study ONU1008, 33 subjects were treated with OXN 60/30 mg.

Safety issues with the potential for major regulatory impact

For each of the safety categories below, it should be noted that very few patients have been exposed to the maximum recommended dose of 80/40 mg twice daily, so uncommon reactions to high doses have not been excluded. Also, the pivotal analgesia study only involved five weeks of blinded exposure, so chronic reactions to high-dose naloxone could have been missed by the study program.

8.6.1. Liver toxicity

Targin does not appear to pose a significant risk of causing liver toxicity.

8.6.2. Haematological toxicity

There is no evidence in the submitted data of significant haematological toxicity.

8.6.3. Serious skin reactions

Opioids may cause pruritus, which was reported in the pivotal analgesia and RLS studies and is discussed with other AEs in Attachment 2. More significant skin reactions were not reported.

8.6.4. Cardiovascular safety

Opioids may cause hypotension, and the use of higher doses could increase the risk of this, but Targin should be titrated cautiously like any other opioid. Oxycodone is already registered for use as monotherapy (OxyContin) at doses equivalent to the new proposed maximum dose of Targin, so the proposed maximum Targin dose does not pose substantial new cardiovascular risks on the basis of its oxycodone component. There is no evidence that oral naloxone poses a significant cardiovascular risk but exposure to the proposed new doses has been very limited.

8.6.5. Unwanted immunological events

There is no evidence that Targin is likely to cause unwanted immunological events.

Postmarketing data

Post-marketing exposure to Targin has been extensive but the data only covers currently approved doses. In the Summary of Clinical Safety directed at the registration of higher doses, the sponsor writes:

No postmarketing data are available for daily doses up to OXN160/80 mg PR.

In the Summary of Clinical Safety written in support of the RLS indication, the sponsor estimates that exposure since first launch in 2006 up to March 2013, amounts to 264,006,510 patient days, corresponding to 8,800,217 patient months. The vast majority of this exposure has been in subjects using Targin for analgesia and there is no published post-marketing experience of Targin in the context of RLS treatment. Targin and other opioids have been used off-label for this indication but this usage has not been comprehensively reported.

The sponsor did not provide an in-depth analysis of all of the safety issues arising from the post-marketing experience with Targin, but instead wrote:

Comprehensive safety reviews of OXN PR have been performed in regular PSURs. The results of both the clinical trial and the post-marketing safety data are adequately reflected in the product's SmPC¹⁵.

A review of the Periodic Safety Update Reports (PSURs) is beyond the scope of this report but the risks and side effects of opioids are well known, and in this respect Targin is broadly similar to other opioids. Because the oxycodone in Targin is used in combination with an opioid antagonist, it would be expected that Targin could cause an increase in opioid withdrawal symptoms when given to subjects who are habitual opioid users. Apart from this, no other safety signals of concern have arisen that suggest Targin poses new or unexpected risks compared to other opioids.

Evaluator's conclusions on safety

Safety in relation to RLS syndrome

The safety profile of Targin in subjects treated for RLS was consistent with the known safety profile of this drug when used for analgesia. The doses used in the RLS study were generally low (the average daily dose of oxycodone in the OXN group was approximately 22 mg) and provided no data relevant to the proposed new maximum analgesia dose, so this study added little to what is already known about the safety profile of Targin.

One deficiency in the available safety data is the lack of controlled data exploring the risks of combining Targin with levodopa and dopamine antagonists which are the currently approved agents for RLS. Given that Targin will be used as a second-line agent it will often be combined with first-line agents, so the safety of this combination is of interest. (The proposed additional indication is: '*Symptomatic treatment of patients with moderate to severe idiopathic Restless Legs Syndrome (RLS) insufficiently treated with dopaminergic therapy*'; the PI does not suggest ceasing the dopaminergic therapy on commencement of Targin). Some degree of synergistic central nervous system (CNS) effects in susceptible individuals, particularly elderly subjects, seems likely but there are no data available to quantify this risk. This issue should be explored further during post-marketing surveillance.

Safety in relation to proposed new maximum dose

The submitted safety data only partially characterises the safety profile of high dose Targin. In the pivotal study, the Targin group and the comparator group received similar doses of oxycodone, so the safety of high-dose oxycodone was not assessed in a comparative manner. Furthermore, subjects were titrated to high doses on the basis of need and tolerance, so tolerance and safety in the small proportion reaching the highest dose is not at all representative of the likely safety profile of this dose in a broader population. (This is not necessarily a design flaw, because it was appropriate to individualise doses and to titrate cautiously but it does mean that unselected subjects suddenly exposed to the maximum dose would be expected to have a much worse safety profile than shown in the pivotal study; indeed, this would be very dangerous.)

The design of the pivotal analgesia study therefore means that it only allows inferences to be made on the safety profile of high-dose naloxone, not of high-dose oxycodone. Given that the proposed oxycodone doses are already registered as OxyContin, this is reasonable. Unfortunately, very few subjects were exposed to the new maximum dose (31 in the pivotal study, 19 in the previously submitted crossover study, which had inadequate washout between phases, and very few patients in other studies), so the safety of high-dose naloxone has not been adequately explored.

¹⁵ European Summary of Product Characteristics (SmPC)

With these important caveats in mind, considering the very limited evidence available, the overall safety of Targin when used at higher doses appears broadly similar to what would be expected from experience with lower doses. Compared to OxyContin at equivalent doses, Targin in the submitted analgesia studies did not appear to raise substantial new safety concerns, but some AEs were observed at a higher frequency in the Targin (OXN) group than the OxyContin (OxyPR) group: there was an excess of nausea (9.8% versus 5.0%), hyperhidrosis (6.5% versus 2.5%) and drug withdrawal syndrome (3.3% versus 0.8%) in the OXN group. This is likely to reflect some degree of systemic opioid antagonism. There was also an excess of diarrhoea, despite the requirement that subjects had constipation at study entry. (This is likely to reflect the resolution of constipation and a subsequent adjustment phase in diet and bowel physiology, and could be less of a problem in subjects titrated directly onto Targin but there is no direct evidence to clarify this).

A review of deaths and serious adverse events did not raise any new concerns about the safety of high-dose Targin relative to high-dose oxycodone monotherapy but no firm conclusions can be drawn given that exposure to the maximum proposed dose was very limited.

Safety in relation to substance-abuse and PK studies

The substance abuse studies did not produce reliable safety data, because low numbers of patients were exposed to single doses, and systemic naltrexone was given in most PK studies to limit opioid side effects. The few AEs observed were consistent with the known safety profile of opioids.

The PK/PD results confirmed that chewed tablets lead to a more rapid absorption of oxycodone, which could lead to substantial toxicity if patients deliberately or accidentally chewed the tablets, circumventing the slow-release properties of the tablet. The PI already contains appropriate warnings about this potential risk. The studies also showed that, in subjects accustomed to opioids, in particular those receiving regular methadone, the systemic absorption of naloxone may lead to withdrawal symptoms. On balance, this is a favourable pharmacological feature of Targin, making the drug less desirable for recreational opioid abusers but this effect could lead to adverse effects (withdrawal symptoms) in subjects misusing the product. The PI contains an appropriate discussion of these issues.

First round benefit-risk assessment

First round benefit-risk assessment in RLS

First round assessment of benefits in RLS

The benefits of Targin in the treatment of RLS are:

- A clinically meaningful reduction in the severity of RLS symptoms in subjects who have failed to respond adequately to dopaminergic therapy.
- Improved sleep.

9.1.2. First round assessment of risks in RLS

The risks of Targin in RLS are:

- An increased incidence of constipation.
- An increased incidence of CNS side effects.
- Opioid dependence.

- Exacerbation of sleep apnoea.

The risks of constipation, sedation and other opioid side effects are already familiar to clinicians, and patients will usually be in a good position to decide whether these side effects are present and whether they represent an acceptable price to pay for improved control of RLS. The doses required to produce benefit are generally in the lower range of Targin doses and the evidence from the analgesia studies provides good grounds to expect that constipation will be reduced in this context by the co-administration of naloxone, compared to other opioids. The risk of CNS side effects when used in combination with dopaminergic agents is not well defined but this is likely to be a manageable risk with appropriately cautious titration.

The risk of producing opioid dependence in the context of RLS treatment is poorly characterised but it did not emerge as an apparent problem during the pivotal RLS study and its open-label extension. Subjects resorting to second-line treatment of refractory RLS are likely to be motivated to continue any successful treatment and the condition is usually chronic, so the question of whether they also have opioid dependence as an additional motivation to continue treatment would be difficult to gauge. On balance, given the impact of RLS on quality of life, this is a risk that many clinicians and patients will find acceptable.

Exacerbation of sleep apnoea can occur with any sedative medication including opioids, and sleep apnoea is more common in patients with RLS. The proposed PI includes an appropriate warning about this risk.

Sleep apnoea is more common in patients with restless legs syndrome and caution is advised in treating such patients with Targin tablets due to the additive risk of respiratory depression.

First round assessment of benefit-risk balance in LS

The benefit-risk balance of Targin for RLS, given the proposed usage, is favourable.

First round benefit-risk assessment of higher maximum dose in chronic pain

First round assessment of benefits of higher doses

The benefits of Targin over naloxone-free oxycodone and other opioid treatments for chronic pain have already been well established. The benefits include:

- a significantly reduced incidence of constipation
- broadly similar analgesic efficacy as naloxone-free oxycodone
- a sustained analgesic effect due to the prolonged-release formulation (a benefit also present in other prolonged-release formulations, such as OxyContin).

Given that Targin is already registered for use in chronic pain, the important question is what benefits could be expected from increasing the maximum dose from the currently approved maximum of 40/20 mg twice daily to 80/40 mg twice daily.

The sponsor claims the following benefits:

For patients in need of higher oxycodone doses, the increase of the daily maximum dose of OXN PR up to 160/80 mg would have the following advantages:

- Maintaining analgesia whilst improving opioid induced constipation (OIC) with a naloxone component in doses up to 160/80 mg/d.

- Simplification of therapy and facilitation of the prescription process by administering only fixed combination tablets (OXN PR) instead of combining OXN PR with oxycodone (OxyPR).

The first of these proposed benefits has only been partially demonstrated in the submitted studies, as discussed below; the second proposed benefit is accepted.

On the basis of experience with other opioids and with naloxone-free oxycodone in the form of OxyContin, it seems very likely that higher doses of Targin could provide analgesic benefit in some subjects who have failed to respond to lower doses, but this assumption was not directly tested in any submitted study. No dose-response studies were submitted. The parallel treatments in the pivotal study only differed in terms of the naloxone component and the oxycodone doses in each group were equivalent. A perceived requirement for higher doses was a prerequisite for entry into the pivotal study, so the need for higher doses was built in as an assumption in the study design and therefore could not be confirmed or refuted by any subsequent results. Even within the dose range explored (50/25 mg twice daily to 80/40 mg twice daily), dose titration largely occurred before randomisation and it is unclear if the higher doses used actually increased analgesic efficacy relative to what patients would have experienced at currently approved doses.

The lack of any dose-response study directly justifying an increase in dose would normally be considered a major deficiency in a study program aimed at increasing the approved dose of an analgesic agent but the oxycodone doses tested in the pivotal study have already been approved in the form of OxyContin, so at least the assumption that higher oxycodone doses are needed in some patients has been confirmed in a different context. Unfortunately, even if one accepts that higher oxycodone doses are needed in some patients (up to 80 mg twice daily), this does not necessarily mean that the same benefit can be obtained during co-administration with naloxone, which is known to produce at least some systemic opioid antagonism.

Also, it should be noted that increasing the maximum approved Targin dose would not actually change the maximum approved oxycodone dose available to clinicians. For patients where the maximum Targin dose is not thought to be adequate, current recommended practice is to combine maximum-dose Targin (40/20 mg twice daily) with top-up OxyContin (to a total of 80 mg twice daily oxycodone), so all the assumed analgesic benefits of higher Targin doses are already available with current practice. Unfortunately, the submitted studies have not compared this practice with the proposed alternative strategy of using higher Targin doses without OxyContin. Current practice with combination therapy was not actually assessed in any study instead high-dose Targin was compared to naloxone-free oxycodone.

The sponsor's first claimed benefit for an increased Targin dose was '*Maintaining analgesia whilst improving opioid induced constipation (OIC) with a naloxone component in doses up to 160/80 mg/d*'. This has two components: analgesia equivalence and improved constipation, relative to OxyContin.

No study was adequately powered to assess whether maximum-dose naloxone compromises the analgesic efficacy of maximum-dose oxycodone. The number of subjects exposed to the proposed new maximum dose was low (31 subjects in the pivotal study, 19 subjects in a crossover study that had inadequate washout, and probably one other patient in minor supportive studies). Power calculations in the pivotal study were based on pooled results across multiple doses, and the comparison between treatments at specific doses was not adequately powered for the demonstration of non-inferiority. The results actually suggested that Targin was significantly inferior to OxyContin, based on 95% CIs for the treatment difference, a point not discussed or acknowledged by the sponsor. (Of additional concern, the sponsor's definition of non-inferiority was overly inclusive, with

the 120% equivalence threshold suggesting that moderate increases in pain were not considered significant.)

Also, while it is possible that a high-dose combination of Targin and OxyContin (current recommended practice) does not contain enough naloxone to produce the same constipation benefits seen at lower Targin doses and that a higher maximum dose of Targin would therefore be beneficial, this hypothesis has not been directly assessed in any study.

Relative to current practice, then, the only clear benefits of increasing the maximum Targin dose would be:

- simplifying dosing decisions;
- reducing the number of scripts and different medications that patients require to achieve the necessary daily oxycodone dose (potentially improving compliance and minimising dosing errors).

These are not trivial benefits, because dosing errors are likely to be reduced with simpler regimens and the current recommended practice of combining two different slow-release oxycodone preparations is complex and counter-intuitive but they are not benefits that justify any substantive risks.

First round assessment of risks of higher doses

The risks of using higher doses of Targin (up to 80/40 mg twice daily) for chronic severe pain include those already inherent in the use of high-dose oxycodone:

- respiratory depression, which can be fatal;
- hypotension;
- severe CNS depression;
- opioid dependence;
- constipation (but this is less with Targin than naloxone-free oxycodone);
- other well-defined opioid side effects (such as hyperhidrosis).

The risks of severe opioid side effects, including death, would be increased if high-dose Targin tablets were inappropriately chewed, or if subjects were commenced on high doses without a cautious titration phase.

These risks are already inherent in naloxone-free preparations, such as OxyContin, and the proposed new maximum dose of Targin (80/40 mg twice daily) does not increase these risks compared to OxyContin which is already approved at equivalent doses (up to 80 mg twice daily).

Compared to current recommended practice (combination therapy with Targin and OxyContin), or naloxone-free oxycodone preparations (OxyContin monotherapy), the proposed new maximum dose of Targin poses the following new risks:

- an increased incidence of opioid withdrawal symptoms when switching to Targin from naloxone-free preparations, due to systemic opioid antagonism by naloxone;
- an increased incidence of diarrhoea;
- a (probably small but poorly defined) potential for reduced analgesic efficacy and a subsequent increase in pain when switching from equivalent doses of naloxone-free oxycodone;
- an unknown potential for new, unexpected side effects related to use of high-dose naloxone, with which there is currently minimal published experience.

The incidence of withdrawal symptoms appears to be low and manageable but it is poorly defined at the proposed doses because of limited exposure. Diarrhoea is an acceptable risk for someone in severe pain and could possibly be reduced with cautious, gradual switching. Reduced analgesic efficacy and increased pain was probably shown in the submitted studies, but appears to be minor in magnitude. No analgesic study was adequately powered to address this issue at the upper end of the dose range of interest.

Major new side effects from naloxone are likely to be limited by its extensive first-pass metabolism and low bioavailability (about 3%), but the current safety database is very limited in the dose range of interest. In the pivotal analgesic study, approximately one third of patients (40 OXN recipients) received 50/25 mg twice daily which is only slightly above the current maximum dose, another third (41 OXN recipients) received intermediate doses and only a quarter of patients (31 OXN recipients) received the maximum proposed dose. Furthermore, very few subjects were exposed to the maximum dose in supportive studies (19 subjects in a crossover study with inadequate washout between phases, and probably only one subject in the pooled double-blind phase of the submitted minor studies).

Table 13: Number of Patients Receiving \geq 100 mg/day by Treatment Group, Study OXN3506

Dose Level (mg/d)	OXN PR (N=121)	OxyPR (N=116)
100	40 (33.1%)	42 (36.2%)
120	26 (21.5%)	30 (25.9%)
140	15 (12.4%)	13 (11.2%)
160	31 (25.6%)	28 (24.1%)

* 12 patients were excluded due to early dropout

There are no formal TGA guidelines on the minimum exposure needed to establish safety of a new proposed dose. The following online document, titled '*Population Exposure: The Extent of Population Exposure to Assess Clinical Safety*', was produced by the European Medicines Agency (EMA), and it discusses the general need for adequate exposure in clinical trials.

Although the document does not anticipate the specific situation of increasing the approved dose of a currently registered agent, two sections give broad indicators of the exposure needed '*at dosage levels intended for clinical use*':

*Available information suggests that most [Adverse Drug Events] ADEs first occur, and are most frequent, within the first few months of drug treatment. **The number of patients treated for 6 months at dosage levels intended for clinical use, should be adequate to characterise the pattern of ADEs over time.** To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5%-5%). **Usually 300-600 patients** should be adequate.*

There is concern that, although they are likely to be uncommon, some ADEs may increase in frequency or severity with time or that some serious ADEs may occur only after drug treatment for more than 6 months. Therefore, some patients should be treated with the drug for 12 months. In the absence of more information about the relationship of ADEs to treatment duration, selection of a specific number of patients to be followed for 1 year is to a large extent a judgement based on the probability of

*detecting a given ADE frequency level and practical considerations. **100 patients exposed for a minimum of one-year is considered to be acceptable to include as part of the safety data base. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use. When no serious ADE is observed in a one-year exposure period this number of patients can provide reasonable assurance that the true cumulative one year incidence is no greater than 3% [emphasis added by evaluator].***

Exposure to the maximum proposed dose in the submitted studies clearly falls well short of these targets. In addition to low patient numbers at the highest proposed dose, the pivotal study was also very short, with only 5 weeks of double-blind treatment. The supportive crossover Study 038-002, included a long-term extension phase, but only 18 of 34 long-term subjects received the highest proposed dose in that study, and the crossover design interferes with safety assessments. Although some minor supportive analgesic studies also included longer follow-up, much of this was open-label and uncontrolled and the maximum proposed dose was either disallowed by the study protocols or usually not taken up as a titration option such that only one patient appears to have received the maximum proposed dose in the minor supportive analgesia studies.

The extensive experience with currently approved doses makes it unlikely that major new toxicities will emerge at the lower end of the proposed new doses (50/25 mg twice daily, which is only slightly above the approved maximum of 40/20 mg twice daily) but the previous experience does not provide adequate reassurance about the upper end of the proposed new dose range (such as 80/40 mg twice daily), which is double the dose for which there is adequate exposure.

The risk of high-dose Targin is therefore inadequately defined.

First round assessment of benefit-risk balance of higher doses

The benefit-risk balance of the proposed new maximum dose of Targin has not been adequately defined.

The main issues are:

- The study program relies heavily on the assumption that higher oxycodone doses are necessary and effective in some patients, as previously demonstrated for OxyContin but this assumption was not directly tested for Targin. The fact that naloxone produces some systemic opioid antagonism means that the dose-response experience with OxyContin cannot be taken as directly representative of the dose-response properties of Targin.
- The submitted studies were underpowered for dose-specific analysis, particularly at the maximum dose where only 31 subjects were exposed in the pivotal study.
- Too few patients have been studied at the proposed maximum dose to assess the analgesic efficacy of high-dose Targin, compared to naloxone-free oxycodone or the current practice of combining Targin and OxyContin.
- The only clear benefit of the proposed higher doses, compared to the current recommended practice of combining Targin with OxyContin is convenience so it is particularly important to establish the safety of the proposed doses.
- Too few patients have been exposed to high-dose naloxone to characterise the safety profile of naloxone at the proposed doses.
- The pivotal analgesic study was too brief to allow the assessment of safety in an agent intended for chronic use.

First round recommendation regarding authorisation

Recommendation regarding RLS

The sponsor's application to register Targin for the treatment of RLS that has not responded adequately to dopaminergic therapy should be approved.

Recommendation regarding higher maximum dose

The sponsor's application to register Targin at the proposed maximum dose of 80/40 mg twice daily should be rejected (for the reasons listed above).

Recommendation regarding proposed discussion of abuse potential in PI

The sponsor's application to modify the PI to include discussion of abuse potential should be approved, but the PI should be further modified.

Second round evaluation of clinical data submitted in response to questions

For details of the Clinical Questions and the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

The extra material provided by the sponsor in their response does not materially alter any of the conclusions listed in the First Round CER.

The evaluator concedes that the reduced abuse potential of Targin via the intravenous and intranasal routes is of value but remains of the opinion that this benefit must be balanced against the residual risk of abuse via the oral chewed route in subjects not on methadone.

The evaluator remains concerned that exposure to the highest proposed dose of Targin has been very limited, falling well short of the recommended exposure required for adequate demonstration of efficacy and safety.

Second round recommendation regarding authorisation

Recommendation regarding RLS

The sponsor's application to register Targin for the treatment of RLS that has not responded adequately to dopaminergic therapy should be approved.

Recommendation regarding higher maximum dose

The sponsor's application to register Targin at the proposed maximum dose of 80/40 mg twice daily should be rejected (for the reasons listed above).

Recommendation regarding proposed discussion of abuse potential in PI

The sponsor's application to modify the PI to include discussion of abuse potential should be approved, but the PI should be further modified.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 5.0 (dated 12 September 2013, Data Lock Point (DLP) 12 April 2013) and Australian Specific Annex Version 5.0 (dated June 2015); EU-RMP Version 6.0 (dated 23 September 2015, DLP 31 July 2015) with Australian Specific Annex Version 6.0 (dated January 2016)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14.

Table 14: Summary of ongoing safety concerns

Summary Ongoing Safety Concerns	
Important identified risks	Constipation
	Diarrhoea
	Physical dependence and drug withdrawal syndrome
	Respiratory depression
Important potential risk	Accidental overdose
	Drug abuse (including intentional misuse and drug diversion)
	Psychological dependence
	Serious hepatic events
Important missing information	Paediatric use
	Use in pregnant and breast feeding women
	Long-term treatment (>12 months) in RLS
	Off-label use in RLS

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities for all safety concerns and missing information. Additional pharmacovigilance is proposed in the form of the EU drug utilisation study (DUS) OXN9514.

Risk minimisation activities

The sponsor initially proposed routine and additional minimisation (educational materials) activities but the latter were removed in an updated version of the EU-RMP and ASA.

Reconciliation of issues outlined in the RMP report

Table 15 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the TGA's evaluation of the sponsor's responses.

Table 15: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>The sponsor has addressed the specific safety concerns under the respective questions. The sponsor does not consider any of these safety concerns significant new safety information and therefore no updates are required to the Targin RMP.</i></p>	<p>The sponsor's response is noted.</p> <p>However, it is further noted that the Safety Specification in the EU RMP has been updated with notable changes between Version 5.0, which was evaluated in the Round 1 RMP evaluation, and Version 6.0, which was submitted in the sponsor's response.</p> <p>In effect, updates to the Targin RMP were required following the First Round RMP evaluation.</p>
<p>2. The sponsor should provide further clarity on why educational materials relating to physical/psychological dependence, drug withdrawal syndrome, and drug abuse are still considered additional risk minimisation activities in the EU but no longer for Australia. The</p>	<p><i>The sponsor wishes to clarify that there are ongoing activities relating to educational materials in the EU, that is an updated version of the EU RMP has been prepared (version 6.0) and is currently under assessment in the EU.</i></p> <p><i>The market authorisation holder (MAH) in EU proposed the removal of the educational materials that had been in use in some EU countries from version 6.0 of the RMP, because based on the experience with oxycodone hydrochloride and naloxone hydrochloride (OXN) products those materials were no longer deemed appropriate or necessary.</i></p>	<p>The sponsor has advised of the removal of educational materials as additional risk minimisation in the EU.</p> <p>The sponsor's justification for removing the proposed educational materials from the EU RMP includes that these are well-established risks of opioids that are addressed in the Product Information and familiar</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>sponsor should also advise of the measure of effectiveness of the educational materials, which could be in the form of the overseas evaluation of effectiveness (if available).</p>	<p><i>Regardless of the proposed removal, routine pharmacovigilance monitoring will be continued for all risks in the RMP.</i></p> <p><i>In this context the sponsor would like to provide some background regarding the initial implementation of educational material in EU. Targin was approved in Germany in 2006. With the introduction of the Decentralised Procedure (DE/H/1612/001-004/DC) in 2009, BfArM entailed a post approval commitment as part of the Final Assessment Report regarding the provision of educational material for healthcare professionals (HCPs) in accordance with local regulations and customs. As Targin was a new drug combination, a few member states requested the provision of educational material as risk minimization activity during the procedure. Therefore, Mundipharma committed to submit educational material for HCPs on the potential risks of abuse, misuse, diversion, dependence, withdrawal on cessation of treatment and acute withdrawal in the case of inadvertent or by drug users of Targin in accordance with individual country local requirements and custom if required prior to launch of Targin. Of 20 EU countries, only a few requested submission of such educational material. Even though only applicable to a few EU countries, Mundipharma decided to include provision of educational material in the EU RMP as additional risk minimisation activity.</i></p> <p><i>Following nine years of post-marketing experience and the accumulation of additional data from interventional studies, Mundipharma is of the opinion that these materials are no longer deemed appropriate or necessary as justified below.</i></p> <p><i>All above listed risks of interest are appropriately addressed in the safety sections of the approved Summary of Product Characteristics (SmPC) of the OXN products in Europe and also in the Australian proposed product information. This includes clear explanatory texts and instructions to the HCPs about abuse, dependence and also the need to taper</i></p>	<p>to healthcare professionals.</p> <p>The evaluator notes that while this is the case, health professionals are likely to be less familiar with recommended practise in the use of opioids in RLS than in pain.</p> <p>The Delegate's attention is drawn to Advisory Committee on Safety of Medicines' (ACSOM's) support for educational materials for health professionals and concern that the instructions in the Product Information to conduct 3 monthly clinical evaluations and annual consideration of a discharge regimen may not be practical and effective measures to minimise opioid exposure and address the risks of physical dependence and drug withdrawal, drug abuse, and psychological dependence in RLS.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>the OXN dose down when treatment is meant to be stopped. Also the Targin PI provides adequate advice to the prescriber regarding the risk of dependence, abuse and withdrawal, and the type of patient who may not be suitable for opioid therapy. These risks are discussed under Precautions in the Targin PI under the sub-headings Use in chronic, non-malignant pain and Dependence. Further, as stated in the Targin RMP, a targeted follow-up questionnaire is sent to HCPs reporting abuse, misuse, diversion and dependence. The data collected from these reports are reported into Mundipharma Research Limited central drug safety database and reviewed.</i></p> <p><i>The risks of abuse, intentional misuse, diversion, dependence, and drug withdrawal on cessation of treatment are all well-established risks of all opioid drug products. They represent textbook knowledge, and accordingly HCPs can be expected to be aware of these topics. In addition various regulations such as narcotic scheduling are already in place for opioid products such as OXN.</i></p> <p><i>The only aspect that may be unique to the OXN products compared to other opioid products without a naloxone component is the possibility of acute withdrawal in the case of parenteral administration of Targin (drug abuse in drug addicts) which is well covered by a respective warning in the PI. HCPs are well aware that naloxone is used parenterally as antagonist in opioid overdose and hence the information from the educational materials with regards to this particular abuse by addicts does not provide any new or relevant information to them and might even promote such abuse.</i></p> <p><i>Sixteen (16) PSURs have been written for OXN products up to December 2015. Significant post marketing experience has become available over time in connection with more than 20 million patient months exposure. Those PSURs have not indicated any particular issue upon review of cumulative case listings with regards to the topics in question.</i></p>	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>The current version 6.0 of the OXN RMP covers all above risks as important risks. An ongoing assessment of these risks occurs in the drug safety and Pharmacovigilance group via ongoing monitoring. The benefit-risk profile of the OXN products is likewise continuously monitored. The processes relevant to signal detection include amongst others individual medical case review for index cases, weekly reviews of scientific literature for cases or other relevant safety information and aggregate review for trending (monthly interval case listings, six-monthly case listings and annual cumulative case listings). No new signals with regards to the topics covered by the educational materials have arisen from this process indicating that there does not seem to be a risk in excess of what is to be expected from therapy with any opioid product.</i></p> <p><i>With the most recent version 6.0 of the Targin RMP which is currently subject to assessment by EU authorities, Mundipharma has removed the provision of educational material as risk minimisation measure. Of note, the preliminary assessment report by the reference member state Germany (BfArM) endorses this change. Upon approval of RMP version 6.0 which is expected to happen in the first quarter of 2016 in the EU, both the Australian and EU territory will be aligned.</i></p>	
<p>3. Regarding the educational materials for RLS proposed for Australia, they are identified only as 'planned' in the submission and thus have not been provided for review. The sponsor should provide the draft educational materials to the TGA if available.</p>	<p><i>The sponsor wish to clarify the status of educational material for the RLS indication.</i></p> <p><i>Mundipharma submitted an indication variation for RLS in the EU in 2013 (DE/H/XXXX/WS/044). During the variation procedure one Member State requested conduct of a drug utilisation study (DUS) to assess potential off-label use of Targin in the RLS indication. As an alternative educational material was discussed but was not accepted by the competent authorities.</i></p> <p><i>As no consensus was achieved during the regular variation procedure a final decision was reached in 2015 at the</i></p>	<p>The sponsor's response is noted; the sponsor has explained the intentions in initially nominating educational materials relating to off-label use in the RLS indication.</p> <p>It is further noted that the updated EU RMP (Version 6) no longer identifies 'off-label use in RLS' as a safety concern, but 'off-label use' in general.</p> <p>Regarding the provision of educational materials,</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>European Commission (EC) level. The scientific discussion at the CHMP (EMA/H/A-13/1402) which requested conduct of a DUS was endorsed by the European Commission (http://ec.europa.eu/health/documents/community-register/html/ho25423.htm).</i></p> <p><i>Mundipharma has subsequently finalised a protocol and initiated DUS OXN9514. The EC decision did not request the provision of educational material for RLS and therefore, Mundipharma has never generated such educational material. However, during the variation procedure the Targin RMP had to be updated and due to the ongoing discussions at the time educational material for RLS was proactively included as risk minimisation activity.</i></p> <p><i>The SmPC and Australian proposed PI provides further guidance and clarity on the appropriate use of Targin for treatment of RLS such as detailing of second line treatment; specification of dopaminergic failure, supervision of treatment by adequately experienced physicians and regular re-evaluation of patients to determine the continuation of treatment with Targin. In addition, Mundipharma has prepared two PSURs since granting of the RLS indication which do not point to specific safety issues related to the RLS indication.</i></p> <p><i>DUS OXN9514 undertaken by the EU is a cross-sectional study to investigate the characteristics of patients with RLS who have been prescribed Targin. In addition, treatment, and health service use patterns will be observed amongst a cohort of patients who have been diagnosed with RLS, in order to describe the incidence of development of tolerance, dependence, drug abuse and misuse in patients treated with OXN products for RLS.</i></p> <p><i>The patient populations are considered the same in Europe and Australia hence the safety data generated from these studies are relevant to the use of Targin in Australia. Therefore the sponsor considers this study to be representative for the RLS target population in Australia</i></p>	<p>please see the evaluator comment for Recommendation 2 above.</p> <p>Regarding DUS OXN9514, ACSOM made comment on the relevance of the DUS as a proposed pharmacovigilance activity for Australia. ACSOM advised that they do not view the EU DUS as relevant to Australia given different socio-cultural factors and local medical practices relating to opioid use. In addition, ACSOM has noted that the indications approved in Europe are narrower, which further reduces the applicability of the DUS in Australia.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<i>as well. Thus the generation of Australian specific RLS educational material is not deemed necessary. Consequently no specific additional risk minimisation activities are considered necessary for Australia.</i>	

Summary of recommendations

It is considered that the sponsor's response to the TGA has not adequately addressed all of the issues identified. There are outstanding issues (see below)

There are additional recommendations for consideration by the Delegate.

Outstanding issues

Issues in relation to the RMP

In EU-RMP Version 5.0, the sponsor proposed no additional pharmacovigilance activity for Australia but referenced additional risk minimisation in the form of healthcare professional education. Upon request for clarification, the sponsor submitted changes in EU-RMP Version 6.0; updated to include *no* proposed additional risk minimisation and instead additional pharmacovigilance in the form of EU drug utilisation study (DUS) OXN9514.

The evaluator recommends implementation of a drug utilisation study in Australia to assess off-label use, dependence, abuse and misuse. This position is supported by ACSOM advice which notes that the indications approved in Europe are narrower than those proposed for Australia and socio-cultural factors and local medical practices related to opioid use in Australia are likely to differ from those in Europe so that the results of the EU drug utilisation study are unlikely to reflect the Australian experience.

The sponsor's justification for removing the proposed educational materials relating to dependence, abuse, withdrawal and misuse from the EU RMP includes that these are well-established risks of opioids that are addressed in the PI and familiar to healthcare professionals. The evaluator notes that while this is the case, health professionals are likely to be less familiar with recommended practise in the use of opioids in RLS than in pain. The Delegate's attention is drawn to ACSOM's support for educational materials for health professionals and concern that the instructions in the PI to conduct 3 monthly clinical evaluations and annual consideration of a discharge regimen may not be practical and effective measures to minimise opioid exposure and address the risks of physical dependence and drug withdrawal, drug abuse and psychological dependence in RLS.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM has advised of several issues, including:

- The committee advised that the precaution in the PI relating to sleep apnoea should be revised to more clearly show that patients with sleep apnoea are the at-risk population, not patients with RLS.
- The committee commented that the availability of higher strength combinations of oxycodone/naloxone facilitates dose escalation and creates a higher potential for dependence.

- There is a theoretical possibility of naloxone accumulation from the high naloxone content tablets in older patients taking the higher strength tablets long-term for RLS.
- The European DUS is designed to look at RLS patients for the development of tolerance, dependence, drug abuse and misuse. These outcomes should be assessed in Australia which has socio-cultural factors and local medical practices related to opioid use that are likely to differ from those in Europe. Further, the indications approved in Europe are narrower which reduces the applicability of the European DUS in Australia.
- The committee noted that there was very limited evidence of efficacy for the proposed indication [RLS], and therefore, given the potential for toxicity, tolerance, dependence, drug abuse and misuse, it was uncertain whether the overall benefit-harm ratio was favourable.
- The committee advised that the risks associated with the use of oxycodone/naloxone could be further minimised by restricting the indications to use in patients with 'severe to very severe' disease rather than 'moderate to severe' disease.
- The Dosage and Administration section of the PI proposes that a three monthly clinical evaluation be undertaken, and additionally that there be annual consideration of a discharge regimen of gradually reducing the dose of oxycodone/naloxone tablets over a period of approximately one week. It was unclear that these suggestions will be practical measures, in a chronic condition, to minimise opioid exposure once prescribing has commenced.
- The committee queried whether withdrawal over one week was too fast or would be effective after 12 months use of oxycodone/naloxone. Information should be provided in the PI on the management of withdrawal symptoms.
- The committee noted that Version 6 of the European RMP reports on a pharmacovigilance study conducted to address the risks of cardiovascular events in connection with drug withdrawal syndrome. The committee advised that the focus on cardiovascular events was too narrow to address the risks of withdrawal after long-term opioid use.

The committee advised that the graph on page 10 of the PI should be more clearly presented, explain the information accurately and show 95% Confidence Intervals.

Key changes to the updated RMP

EU-RMP Version 5.0 (dated 12 September 2013, DLP 12 April 2013) and Australian Specific Annex Version 5.0 (dated June 2015) has been superseded by:

EU-RMP Version 6.0 (dated 23 September 2015, DLP 31 July 2015) and Australian Specific Annex Version 6.0 (dated January 2016).

Key changes from the version evaluated at first round are summarised below in Table 16.

Table 16: Key changes between EU-RMP versions 5.0 and 6.0

Summary of key changes between EU RMP Version 5.0 and EU RMP Version 6.0	
Safety specification	<p>'Overdose' and 'Medication Error' have been added as Important Identified Risks</p> <p>'Physical dependence and drug withdrawal syndrome' has been changed to 'Drug dependence and drug withdrawal syndrome' as an Important Identified Risk</p> <p>'Accidental overdose' has been removed as an Important Potential Risk</p> <p>'Psychological dependence' has been removed as an Important Potential Risk</p> <p>'Serious hepatic events' has been changed to 'Hepatic Disorders' as an Important Potential Risk</p> <p>'Panic attack/reaction' has been added as an Important Potential Risk</p> <p>'Aphasia' has been added as an Important Potential Risk</p> <p>'Paediatric Use' as Missing Information has been changed to 'Use in paediatric patients < 18 years'</p> <p>'Use in patients with hepatic impairment' and 'Use in patients with renal impairment' have been added as Missing Information</p> <p>'Off-label use in RLS' has been changed to 'Off-label use' as Missing Information</p>
Pharmacovigilance activities	Epidemiological study OXN9514 has been added as additional Pharmacovigilance for the safety concerns of 'Drug dependence and drug withdrawal syndrome' and 'Drug abuse, misuse and diversion'
Risk minimisation activities	Only routine risk minimisation is now proposed for all safety concerns (reference to educational materials has been removed in EU RMP Version 6.0).
ASA	The ASA has <i>not</i> been updated to reflect the Safety Specification in Version 6.0 of the EU RMP; it reflects the safety concerns of EU RMP Version 5.0, but with removal of the educational materials as additional risk minimisation.

The ASA (as Version 6.0) should be updated to reflect the safety concerns identified in Version 6.0 of the EU RMP.

Suggested wording for conditions of registration

RMP

The RMP wording for conditions of registration cannot be provided at this time. Suggested wording cannot be provided until the outstanding RMP issues detailed in this report are satisfactorily addressed.

VI. Overall conclusion and risk/benefit assessment

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

Quality

Quality data were submitted to support the proposed additional tablet strengths. There are unresolved chemistry issues however the sponsor and the quality evaluator have now agreed on revised impurity/degradation product limits for the higher strength tablets and there are no objections to approval on quality grounds.

Nonclinical

There are no nonclinical objections to approval of the higher strength tablets or of the RLS indication.

Nonclinical data were submitted to support the proposed extension of indications to include treatment of RLS. Nonclinical comment was provided on 3 identified impurities and amendments to nonclinical sections of the PI have been proposed. The nonclinical evaluator noted that there is no valid animal model for RLS.

An in vitro study (OXN-P-064) conducted in pooled, cryopreserved human hepatocytes examined the potential for metabolic drug interactions between a combination of oxycodone and naloxone and various dopaminergic agents likely to be used concomitantly in RLS (rotigotine, ropinirole, (S)-pramipexole, levodopa). Ropinirole, (S)-pramipexole and levodopa had little or no effect on either oxycodone or naloxone metabolism. Rotigotine showed inhibition of naloxone reduction (concentration at 50% inhibition (IC_{50}) 7.2 μ M) and naloxone glucuronidation (IC_{50} 3.6 μ M) but little inhibition of oxycodone N-demethylation (IC_{50} 210 μ M). The lowest tested rotigotine concentration (0.1 μ M), which elicited only 17% inhibition of the naloxone reactions, was still 40x the plasma C_{max} at the maximum recommended human dose (MRHD) for RLS treatment. Thus, the concentrations of rotigotine required to inhibit naloxone metabolism are considerably greater than the clinical plasma rotigotine concentrations associated with RLS treatment.

There are 3 impurities in the drug product which exceed the relevant ICH limits. One of these compounds is a human metabolite and is therefore qualified at the proposed specification. The other 2 compounds have not been fully toxicologically qualified according to the relevant ICH impurity guidelines and their specifications in the product were reduced after consultation with the sponsor.

Clinical

Pharmacology

Restless legs syndrome

No pharmacology data were submitted.

High-strength Targin (160/80 mg)

Dose proportionality of the proposed 80/40 mg tablets with the current highest strength 40/20 mg tablets was demonstrated.

Abuse potential of Targin

Four FDA approved single dose single centre pharmacodynamic/pharmacokinetic studies were submitted to support the abuse-related properties of oxycodone/naloxone relative to other opioids, in the context of potential abuse and diversion to other routes (chewed, intranasal and intravenous) by opioid abusers.

As noted by the clinical evaluator, the PD results suggested oxycodone/naloxone combinations had significantly reduced abuse potential, compared with oxycodone monotherapy, *when taken by the intranasal or intravenous routes*. The oxycodone was more rapidly absorbed by these routes but the presence of naloxone appeared to antagonise its effects, leading to low scores on the 'likeability' scale. In keeping with the poor oral bioavailability of naloxone, however, the presence of naloxone in a chewed Targin tablet did *not* substantially modify the likeability of the medication, compared to oral oxycodone solution. Furthermore, the PK part of this study suggested that, when chewed, the prolonged-release properties of Targin were largely circumvented, with a median time to C_{max} (T_{max}) for oxycodone concentration of 0.60 hours, which was similar to oxycodone solution (0.57 h).

This study (ONX1003) therefore suggests opioid abusers will be able to get a likeable high from Targin if they chew it, circumventing its slow-release properties and subjecting the naloxone to first-pass metabolism but not if they try to administer it intranasally or intravenously. In contrast, chronic methadone users had an overall negative experience even with chewed OXN. This suggests there is an enhanced systemic exposure of naloxone in this population, with concomitant increase in opioid antagonism (of oxycodone and methadone) and subsequently low likeability of OXN.

Efficacy

Restless legs syndrome

To support this indication the sponsor submitted a 12 to 13 week pivotal Phase III study, OXN3502, and a 40 week open-label extension phase described in the CER Attachment 2.

Study OXN3502 was a randomised, double-blind, placebo-controlled, parallel-group, multicentre trial to assess the efficacy of Targin (OXN) up to 40/20 mg twice daily in subjects with moderate to severe RLS with daytime symptoms, who reported an inadequate response to dopaminergic treatment.

A total of 304 subjects were randomised to treatment with 150 given OXN and 154 given placebo. OXN was titrated beginning with 5/2.5 mg BD and increased if required at weekly intervals to a maximum dose of 40/20 mg BD over 6 weeks followed by a stable maintenance dose for a further 6 weeks. Standard treatments for RLS such as dopamine agonists were not allowed during the study. At the end of the maintenance phase there was a one week down-titration phase and then a 40 week open-label Extension Phase, in

which all subjects received active treatment irrespective of their previous randomised treatment assignment. This is described as a separate study (OXN3502S).

The diagnosis of RLS was to be made according to the 'Restless Legs Syndrome Diagnostic Index' (RLS-DI). In addition, to ensure a diagnosis of primary RLS, subjects had to have at least one of the following criteria:

- positive family history of RLS
- positive response to dopaminergic treatment or
- objective findings of periodic limb movements in PSG or actigraphy or they had to
- have a normal neurological examination.

Subjects were also required to have onset of RLS symptoms during the day (before 18:00) on at least 4 days per week, to have had symptoms for at least 6 months and to have an International Restless Legs Syndrome Study Group Rating Scale (IRLS) score of at least 15 at the screening visit.

The IRLS scale is a ten-question rating scale for RLS that assesses: diagnostic features; associated sleep problems; intensity and frequency of the disorder; and impact of symptoms on the subjects' mood and daily functioning. The scale ranges from 0 to 40, with higher scores indicating more severe symptoms (0 to 10 = mild; 11 to 20 = moderate; 21 to 30 = severe; 31 to 40 = very severe).

The primary efficacy endpoint was the improvement of symptom severity of RLS. Data from pre-randomisation visits (1 to 3) were excluded from the analysis model. To express the difference between active treatment and placebo, 95% confidence intervals (CIs) for changes in IRLS (OXN PR - placebo) from baseline to Visits 5, 6, 7, 8 and 9 were calculated. No missing-value imputation was used. In order to find the earliest time point in which a significant treatment effect emerged, the hypothesis tests were carried out separately for each of the Maintenance Period assessments beyond Visit 4 in descending order from Visit 10, as long as the null hypothesis was rejected for all subsequent Maintenance Period assessments. This was performed as an intersection-union test across the various visit outcomes, so that the overall analysis kept a multiple 5% significance level.

The demographic characteristics of both treatment groups were similar, except there were approximately 10% more subjects aged ≥ 65 years in the OXN group compared with the placebo group. Baseline disease characteristics were similar between the two treatment groups (RLS- Diagnostic Index scores were OXN 16.54 ± 1.85 ; Placebo 16.47 ± 1.99). The mean duration of RLS prior to study entry was > 10 years with 5% of the patients with RLS symptoms for < 1 year.

The average daily dose of oxycodone during the titration + maintenance phase (Visits 3 through to 9) in the OXN PR group was approximately 22 mg. The distribution of OXN doses is shown in *Clinical efficacy, Pivotal study in RLS (OXN3502)* section of the CER Attachment 2. The overall study completion rate was 67.1% (OXN 71.3% and placebo 63.0%), with the highest discontinuation rates from lack of efficacy in the placebo group (19.5%) and adverse events in the active group (13.3%).

The primary efficacy analysis for superiority of OXN compared with placebo in the treatment of RLS was performed on the Full-Analysis Population (FAS). At randomisation (Visit 3), immediately after the wash-out period (to remove all previous RLS treatments), the mean IRLS score of the FAS was 31.70 in the OXN group and 31.55 in the placebo group, representing a severe to very severe study population. Change from baseline by week is also detailed in the CER Attachment 2. Improvement in symptoms was seen in both groups increasing over time however the improvement was larger in the group given OXN compared with placebo with the difference apparent from Week 5 (one week after commencement of titration) with each visit from Visit 5 showing a statistically significant

difference in IRLS scores favouring OXN over placebo. A statistically significant differences between Targin and placebo in change from baseline IRLS by visit ($p < 0.001$ from Visit 5 onwards) was shown.

At the end of the maintenance period (Visit 9) mean IRLS scores were 15.11 in the OXN group and 22.09 in the placebo group. Mean (SD) changes from baseline were 16.52 (11.32) in the OXN group and 9.44 (10.91) in the placebo group, a between group difference of 7.08 on the 40 point IRLS scale.

A significant treatment effect ($p < 0.001$), was confirmed by several secondary efficacy endpoints that included IRLS responder rates (proportion of subjects with at least 50% improvement in the IRLS sum score from baseline to Visit 9 [47.0% versus 22.9%]), remitter rates (IRLS scale 0 or a final IRLS score ≤ 10 ; 74.2% versus 26.4%), Clinical Global Impression, RLS Pain and a range of Quality-of-Life and sleep measures. The withdrawal or discontinuation drop-out rate was also significantly lower in the active group (22.7% versus 34.0%, $p = 0.004$), which provided an indirect measure of overall efficacy and tolerability.

Study OXN3502S was a 40-week extension of Study OXN3502. This study examined the longer-term efficacy and safety of OXN, and the incidence of RLS augmentation. A total of 197 subjects started on OXN 5/2.5 mg twice daily with daily dose titration (upwards or downwards) permitted to OXN 40/20 mg twice daily.

Of 197 subjects who entered the study, 101 were previously randomised to double-blind OXN. Forty ($n = 40$; 20.3%) subjects discontinued study treatment: 21 due to adverse events and 6 from lack of therapeutic effect. Most subjects were taking oxycodone in the range 5 to 20 mg twice daily.

The primary efficacy variable was the IRLS sum scale score. The mean score for the total population decreased to 9.72 by Week 40, consistent with mild RLS. Overall, the results were consistent with the results of the pivotal study, OXN3502, and provide supportive evidence of longer term efficacy of Targin in RLS.

High-strength Targin

The clinical evaluator has recommended that the increase in maximum daily dose, which is supported by the higher strength tablets be rejected. The basis for rejection is listed in the CER Attachment 2.

The sponsor submitted one pivotal efficacy study in analgesia and four supportive efficacy studies in subjects with chronic pain. Overall the aim of the studies was to demonstrate superiority of Targin relative to oxycodone monotherapy in terms of constipation prevention, while showing non-inferiority in terms of analgesic efficacy. No study specifically assessed the maximum proposed Targin dose of 80/40 mg twice daily.

Study OXN3506 was a multicentre, multiple-dose, randomised, double-blind, double-dummy, active-controlled, parallel-group study in adult subjects with non-malignant or malignant pain requiring opioids, who exhibited constipation. The primary objective was to assess analgesic efficacy and symptoms of constipation secondary to opioid treatment with OXN 50/25 to 80/40 mg twice daily ($n = 123$) in comparison to OxyContin (prolonged release oxycodone tablets; OxyPR) 50 to 80 mg twice daily ($n = 120$).

Eligible subjects had on-going requirements for analgesia and were already taking opioid analgesics but were dissatisfied with them because of poor efficacy or side effects. Subjects with poorly controlled pain or significant confounding conditions were excluded.

Subjects were randomised to OXN or OxyPR (OxyContin) for up to 5 weeks, after an initial titration phase using OxyPR. If needed, further dose titration up to 80 mg twice daily (total 160 mg oxycodone per day) was allowed during the double-blind phase. Given both treatment arms used oxycodone, with similar pharmacokinetic profiles, the study could be

regarded as a placebo-controlled naloxone add-on study in which subjects received continued prolonged-release oxycodone with or without the addition of naloxone.

The primary efficacy measures were

- the Bowel Function Index (BFI) for constipation and
- the subject's 'Average Pain over the last 24 Hours' assessed at each Double-blind Phase visit with an 11 point (0 – 10) Pain Intensity Scale.

The primary population for the bowel-symptoms *superiority* (BFI) analysis was the FAS, an intent-to-treat equivalent population but excluded subjects without meaningful efficacy data. The primary population for the analgesic *non-inferiority* (Pain Intensity) analysis was the PP set. The non-inferiority margin was 20% on the pain intensity scale.

Baseline demographics were similar across treatment groups. Mean age was 57.7 years with 25.5% aged > 65 years. The distribution of doses of OXN and OxyPR is shown in *Efficacy studies in chronic pain (submitted in support of increased maximum dose)* section of the CER Attachment 2. 31 subjects received the 160/80 mg proposed new maximum dose of OXN with 112 subjects receiving a daily dose of at least 20% above the current maximum recommended dose. The distribution of oxycodone received was similar across the two groups. A total of 209 subjects (86.0%) completed the study with similar completion rates in the treatment groups (OXN 86.7% and OxyPR 85.4%).

The OXN group demonstrated statistically significantly superior BFI scores compared with the OxyPR group (LS mean difference [SE]: -16.05 [3.14]; $p < 0.001$, 95% CI: -22.23, -9.86). The OXN group improved by approximately 30 points by Week 5 compared with an improvement of approximately 10 points in the OxyPR group. Sensitivity and sub-group analyses (by gender and age group) of the primary efficacy variable and secondary bowel function efficacy analyses (rescue laxative and spontaneous and complete bowel motions) supported the primary efficacy results. Pain intensity scores did not change substantially during double-blind treatment in either group, consistent with the titration of doses that occurred prior to randomisation and the exclusion of subjects with poorly controlled pain.

Non-inferiority of OXN PR to OxyPR with regard to pain intensity scores was confirmed within the limits of the study; the null hypothesis that the ratio of 'average pain over the last 24 hours' between OXN PR and OxyPR was $\geq 120\%$ was rejected with $p < 0.001$ in the primary PP population.

Sensitivity analyses using the FAS set and with last observation carried forward (LOCF) imputation also rejected the null hypothesis with $p < 0.001$. Comparisons between the groups overall and post hoc subgroup analyses for the 100/120 mg oxycodone daily and 140-160 mg oxycodone daily doses are shown in the CER Attachment 2. 95% CIs larger than 20% are apparent in the primary Mixed effect Model Repeat Measurement (MMRM) analysis by visit suggesting that there may be some reduction in the analgesic effect of oxycodone with the addition of higher doses of oral naloxone.

Safety

Restless legs syndrome

In the pivotal study, the OXN group had a higher discontinuation rate than the placebo group (14.7% versus 6.5%, respectively). Adverse events that commonly lead to OXN treatment discontinuation were: nausea (2.7%), vomiting (2.0%), fatigue (2.0%), vertigo (2.0%), blood creatinine increased (2.0%), ALT increased (1.3%) and GGT increased (1.3%).

Exacerbation of sleep apnoea can occur with any sedative medication, including opioids, and sleep apnoea is more common in patients with RLS, although no case of sleep apnoea syndrome was identified in the pivotal and extension studies with OXN treatment.

Augmentation, which can complicate dopaminergic therapy in the treatment of RLS, was initially assessed using the Screening Tool for Augmentation, and then further assessed using the Max-Planck Institute criteria checklist if potential augmentation was suspected. Final verification was made by Local Augmentation Experts and an Independent Augmentation Expert. No case of augmentation was identified in the pivotal and extension studies.

The safety profile of Targin in subjects treated for RLS is consistent with the known safety profile of this drug when used for analgesia. Dose titration up to 40/20 mg BD was allowed during the extension phase and some patients reached a higher dose than in the original double-blind phase, but most subjects continued to use oxycodone doses in the range of 5 to 20 mg twice daily (10 to 40 mg daily). The changes in dose do not suggest that tolerance was a major problem during long term treatment but it remains possible that some up-titration occurred in response to (and potentially masked) a gradual waning of efficacy.

High-strength Targin

The submission did not include an analysis of adverse events in elderly subjects (≥ 65 years). No falls were recorded for double-blind OXN treatment in the pivotal analgesia study and the incidences of insomnia and somnolence were low (2.4% and 1.6%, respectively).

The pivotal analgesia study did not have a long-term extension so assessment of the effects of long-term exposure, including development of tolerance is limited. However, these oxycodone doses are currently permitted for other products containing oxycodone.

There were no appreciable differences in safety profiles between equivalent doses of OxyContin and Targin except for an excess of adverse events in the OXN group compared with the OxyContin group for nausea (9.8% versus 5.0%), hyperhidrosis (6.5% versus 2.5%) and drug withdrawal syndrome (3.3% versus 0.8%). The between-group difference in total Clinic Opiate Withdrawal Scale scores (to assess drug withdrawal) were small (< 2) and below 5, which is regarded as the lowest value determined as mild withdrawal symptoms.

In Study OXN3506, the proportion of AEs at the highest dose level, oxycodone 160 mg per day, was not specifically reported. No new safety concerns were identified.

Only 31 subjects were exposed to the proposed maximum dose of Targin in the pivotal analgesia study (OXN3506) with a further 19 in the supportive study (038-002) and 1 subject from the pooled analysis of supportive studies. While naloxone undergoes extensive first-pass metabolism and therefore toxicity would be expected to be low, a toxicity assessment of high-dose naloxone was limited due to the small subject numbers across trials.

The major area of concern is a possible reduction in efficacy of oxycodone due to CNS effects of naloxone with the higher doses of naloxone given with the higher doses of Targin.

A review of deaths and serious adverse events did not raise new concerns about the safety of high-dose Targin relative to high-dose oxycodone monotherapy but no firm conclusions can be drawn given that exposure to the maximum proposed dose was very limited.

Risk management plan

There were unresolved issues concerning the RMP. The Australian Specific Annex (ASA) of the RMP has not been updated to reflect the Safety Specification in Version 6.0 of the EU RMP. It reflects the safety concerns of EU RMP Version 5.0 but with removal of the educational materials as additional risk minimisation.

No additional pharmacovigilance active was planned for Australia. No education material to support a higher dose of Targin was proposed however a drug utilisation study (DUS) is planned to be conducted in the EU. The RMP evaluator recommended a DUS be conducted in Australia to assess off-label use, dependence, abuse and misuse. This recommendation was supported by ACSOM. That committee noted that the indications approved in Europe are narrower than those proposed for Australia and socio-cultural factors and local medical practices related to opioid use in Australia are likely to differ from those in Europe so that the results of the EU drug utilisation study are unlikely to reflect the Australian experience.

ACSOM supported the provision of educational materials for health professionals and was concerned that the instructions in the draft PI to conduct 3 monthly clinical evaluations and annual consideration of a discharge regimen may not be practical and effective measures to minimise opioid exposure and address the risks of physical dependence and drug withdrawal, drug abuse, and psychological dependence in RLS.

The RMP evaluator has recommended that the ASA (as Version 6.0) be updated to reflect the safety concerns identified in Version 6.0 of the EU RMP. Pending further negotiations with the sponsor no condition of registration pertaining to the RMP has been recommended.

Risk-benefit analysis

Delegate's considerations

Restless legs syndrome

Targin has shown efficacy as monotherapy in patients with primary RLS whose symptoms were not adequately controlled with standard RLS therapy in a short term study. The extent of difference between Targin and placebo was statistically and clinically significant from the first week after titration of Targin commenced. Secondary efficacy analyses and sensitivity analyses in the pivotal study supported the primary efficacy results. The mean daily dose of Targin was relatively modest and there was no evidence of a reduction in RLS symptom control during the fixed dose maintenance period of the pivotal trial. The doses given in the extension study also suggest that dose escalation over time was modest. Long term efficacy of Targin in the treatment of RLS has not been fully assessed, certainly not to the same extent as efficacy of the dopamine antagonists. It is unclear whether dependence, dose escalation and tolerance would be significant issues with longer term use.

Targin doses were titrated rather than randomised so no dose-response efficacy analysis could be undertaken. This is acceptable given the nature of RLS. The mean daily dose of oxycodone was approximately 22 mg. Under these circumstances lack of dose-response data is not a barrier to approval of Targin for the short term treatment of primary RLS. Treatment should be reassessed every 3 months.

There were no data on efficacy or safety of Targin as add-on therapy in RLS, though this use is implied by the proposed indication. Some degree of additive adverse CNS effects in susceptible individuals, particularly elderly subjects, seems likely. Of particular concern are effects such as nausea and vomiting, somnolence, dizziness, impaired alertness and confusion. There are no data available to quantify the extent of these risks. The advice of the committee is requested on whether dual therapy with dopamine agonists should be specifically excluded in the indications, as is the case in the EU. The sponsor so date has not proposed specifically excluding combination therapy of dopaminergic agents and Targin, though the risk of synergistic/ additive CNS side effects has been acknowledged.

High-strength Targin

To allow for an increase in the daily dose of Targin ideally the submission would have demonstrated that maintaining the 2:1 oxycodone/ naloxone ratio for daily doses above 80/40 mg did not reduce the analgesic effect of oxycodone and that the reduction in opioid-induced constipation effect for which naloxone has been added to oxycodone in Targin was unaffected. Instead the submission included a study which demonstrated a clinically significant effect in the reduction of opioid induced constipation compared with high dose oxycodone alone. The effect of the increased oral naloxone on pain reduction is less clear. There may be some reduction in the analgesic effect of high doses of oxycodone when given with high doses of oral naloxone, relative to the same dose of oxycodone alone. No study assessed this specifically.

It may be that a degree of loss of efficiency of first pass metabolism of naloxone occurs with increasing oral intake of naloxone. The generous non-inferiority margin for assessment of pain intensity difference in the pivotal study to support the higher daily dose (Study 3506) allowed a conclusion of non-inferiority of analgesic effect between OXN and OxyPR. The clinical evaluator has provided a detailed discussion on the size of the non-inferiority margin for pain intensity in Study 3506 in response Clinical question 2 in Attachment 2. Additional subgroup analyses suggest a small reduction in analgesic effect of oxycodone with naloxone compared to oxycodone alone at the higher doses.

While it has not been convincingly demonstrated that the analgesic effect of oxycodone in Targin compared with oxycodone alone is the same for Targin doses above 80/40 mg daily it is clear that higher doses of Targin (to 160/80 mg daily) have a clinically significant analgesic effect that is similar, though possibly reduced compared with equal doses of oxycodone alone. The higher doses also have an opioid induced constipation antagonist effect.

There was no evidence of a dose-response relationship for efficacy with regard to reduction in opioid-induced constipation so it is difficult to determine whether the effect of naloxone, in the prevention of opioid induced constipation, is the same at higher doses compared with the current regimen.

The submitted safety data only partially characterised the safety profile of high-dose naloxone. Compared with OxyContin at equivalent doses, Targin did not appear to raise substantial new safety concerns.

Abuse potential of Targin

The abuse potential of Targin is difficult to estimate given lack of data on the extent of abuse in the community and by which routes Targin is, or is likely to be, abused.

Intravenous and intranasal diversion of Targin seems unattractive for opioid addicts. However, chewed Targin appears to offer similar abuse potential as available formulations of prolonged release oxycodone in intermittent users. Both agents, once chewed, are rapidly absorbed and appear likely to produce effects similar to immediate-release oxycodone. This more rapid absorption of oxycodone, could lead to substantial toxicity if patients deliberately or accidentally chewed the tablets, thereby circumventing the slow-release properties of the tablet. Furthermore, systemic absorption of naloxone administered by the intravenous or intranasal routes may lead to withdrawal symptoms in subjects misusing the product by these routes. The proposed PI contains a discussion of these issues, although it does not state Targin produces a likeable high when chewed.

Targin did not produce likeable effects in regular methadone users so it appears to offer minor abuse potential in this population. An association with naloxone dose and withdrawal symptoms is already included in the current PI (Pharmacology section), particularly at higher naloxone doses (70 mg daily). This is indicative of enhanced systemic exposure at higher doses (with potential reduction in loss of efficacy).

On balance, the relatively minor abuse potential is a favourable pharmacological feature of Targin. However, given lack of supporting data for Targin abuse in the community, the relatively low doses of oxycodone and naloxone used in the abuse potential studies, and lack of well-controlled long-term clinical data, the usefulness of inclusion of such detailed information in the PI is questionable. However, inclusion of an abridged or summary of the key findings in the four abuse potential studies may be acceptable and helpful for clinicians.

Summary of issues

- Whether Targin could be adjunctive to dopaminergic therapy in RLS or only as a replacement where dopaminergic therapy is not tolerated or provides inadequate relief.
- Whether the duration of use of Targin in RLS should be limited to the duration of use in the randomised double-blind clinical trials or whether long term use should be permitted.
- Whether the use of Targin in RLS should be limited to those with at least severe RLS symptoms.
- Whether the maximum daily dose for any indication should be increased from 80/40 to 160/ 80 mg.
- The extent of inclusion of information about the abuse potential studies to be included in the PI.

Proposed action

6. The Delegate had no reason to say, at this time, that the application to extend the indications for Targin to include RLS should not be approved, subject to successful negotiation of the PI.
7. The Delegate is not in a position to say, at this time, that the application to increase the maximum recommended dose to 160/80 mg daily should be approved.
8. The extent of information on the abuse deterrence of Targin to be included in the PI requires ongoing negotiation.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. The pivotal trial in RLS did not allow for adjunctive dopaminergic treatment. Given the lack of assessment of efficacy of combination treatment and the overlapping side effects of opioids and dopaminergic agents does the committee consider there are any circumstances in which a combination of the two treatments could be recommended?
2. The sponsor has proposed registration of Targin in RLS which is a chronic condition. The committee is requested to provide advice on whether one pivotal trial of 12-13 weeks' duration with a 40 week open, uncontrolled extension phase is sufficient to register Targin for RLS. While there was no clear evidence of tolerance or dose escalation from that extension study these are known effects with prolonged use of opioids.
3. The three dopamine agonists approved for primary idiopathic RLS in Australia (pramipexole, ropinirole and rotigotine) all had either randomised double-blind placebo-controlled studies to 6 months or double-blind studies and a randomised withdrawal studies in support of their initial registration for this indication.

4. The sponsor has proposed the RLS indication apply to patients with moderate to severe RLS symptoms. While subjects who entered the pivotal study had at least moderate symptoms at baseline, no subject had less than severe symptoms at randomisation to active treatment (IRLS range 21 to 39). Would limiting the RLS indication to patients with severe symptoms be appropriate? Additionally, given only patients with primary RLS were enrolled should the indication be restricted to those patients?
5. The sponsor has proposed increasing the recommended maximum daily dose of Targin to 160/80 mg that is double the currently recommended maximum dose. While this would not be an increase on the recommended maximum dose of oxycodone, it is an increase in the maximum daily dose of oral naloxone. This may cause alterations to the efficacy of the opioid antagonist action in the gut and may increase opioid antagonist action in the CNS compared to the current oral naloxone doses. The studies presented do not allow exploration of this concern.
6. The proposed increase in dose primarily relates to efficacy and safety of high-dose oral naloxone rather than the high-dose oxycodone however the proposed maximum doses (of oral naloxone) are not well represented in the pivotal study to support increasing the dose. The committee is requested to provide advice on whether the lack of high-dose specific clinical trial data and lack of a demonstrable efficacy dose-response relationship at the highest naloxone dose is acceptable.
7. The sponsor has proposed inclusion of detailed descriptions of four abuse potential studies in the PI. These studies emphasise intranasal and intravenous routes of administration. The committee is requested to provide advice on the extent of information on these studies that is appropriate for inclusion in the Product Information.
8. The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor notes that the Delegate is incline to recommend approval for Targin in the treatment of Restless Legs Syndrome (RLS) and the sponsor propose for the indication to be:

Symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy

In addition the sponsor acknowledges that the abuse deterrence claim in the PI needs further discussion and the sponsor will work with the Delegate on the most suitable wording. However, the sponsor notes that the Delegate is not inclined to approve the increase in the maximum daily dose of Targin to 160 mg/80 mg (two divided doses of 80 mg/40 mg) based on the increased exposure to naloxone, the potential for naloxone to impact the analgesic effect at high doses and the small patient numbers exposed to the highest dose in the clinical trials. The sponsor disagrees with the Delegate's proposed recommendation and believes that the discussion below addresses the concerns regarding the proposed maximum daily dose of Targin as follows:

- The oral bioavailability of naloxone¹⁶ demonstrated a consistent < 3% bioavailability level up to a single dose of 120 mg naloxone. This supports the expectation that the

¹⁶ Smith K, Hopp M, Mundin G, Bond S, Bailey P, Woodward J, Bell D Low absolute bioavailability of oral naloxone in healthy subjects. International Journal of Clinical Pharmacology and Therapeutics, Vol. 50 - No. 5/2012 (360-367)

ratio of oxycodone and naloxone can be maintained in doses above the approved dose range of 80/40 mg daily dose.

- Alterations to the analgesic efficacy are not expected. Due to the low oral bioavailability of naloxone, there is no increase in opioid antagonist action in the CNS. A daily dose of 160/80 mg oxycodone/naloxone (OXN) would represent a single naloxone intake of 40 mg twice daily, which is far below the tested naloxone doses.
- Study OXN3506, the 6 months open-label Extension Phase OXN3506S, the post-hoc statistical analysis as well as the results of the supporting Study 038-002, provide evidence that the administration of doses up to OXN160/80 mg provides effective analgesia for the treatment of severe pain. OXN has an analgesic efficacy comparable to controlled release (CR) oxycodone, which represents a well-established strong opioid. Therefore, doses up to 90 mg naloxone per day do not antagonise the analgesic efficacy of oxycodone.
- The observed safety profile for patients receiving the maximum proposed OXN dose; the overall number of patients with AEs in the ≥ 160 mg dose group is comparable to the number in the OXN treatment group. The risk profile in this dose group of OXN 160/80 mg per day is not different to the approved (20 to 80 mg) OXN adverse event profile.
- To further address the Delegate's concerns, the sponsor will amend the proposed PI to restrict the proposed strengths OXN60/30 and OXN80/40 mg to patients who are already receiving opioids.

Increase of maximum daily dose up to 160 mg/80 mg

The currently approved dose range of OXN prolonged-release (PR) is up to OXN 80/40 mg PR per day. There is a clinical need for OXN daily doses higher than 80/40 mg. The Targin PI allows for this situation for patients requiring higher doses of OXN PR that the administration of supplemental oxycodone at the same time interval should be considered taking into account the maximum daily dose of oxycodone PR. The Delegate has acknowledged in the overview that the maximum dose of oxycodone with Targin is already permitted. However, with the supplemental oxycodone dosing the beneficial effect of naloxone on the bowel function may be impaired. Consequently, patients in need of higher doses would clearly benefit from the maintenance of the 2:1 ratio in doses beyond OXN 80/40 mg PR per day. During the initial development programme of OXN PR, a sub-group of subjects received daily doses higher than OXN 80/40 mg PR per day. This supportive data demonstrated the efficacy and safety of daily doses of greater or equal to OXN 100/50 mg PR.

The clinical rationale for use of doses above 80/40 mg is a consistently low oral bioavailability of naloxone. This was assessed in a bioavailability study of oral naloxone up to 120 mg (OXN1019¹⁷).

The mode of action of OXN is based on the low bioavailability (< 3%) of oral naloxone. To establish that the low oral bioavailability is maintained throughout the entire dose range up to OXN160/80 mg per day, the sponsor performed a Phase I study (OXN1019, published by Smith et al., 2012¹⁷). Study OXN1019 was an open-label, single dose, 7-treatment, 5-period, randomised incomplete crossover study to compare the pharmacokinetics of different doses of orally administered prolonged release naloxone tablets 5 mg, 20 mg (2 x 10 mg), 40 mg, 80 mg (2 x 40 mg), 120 mg (3 x 40 mg); and rectally administered prolonged release naloxone tablet 40 mg; with intravenous naloxone

¹⁷ Smith K, Hopp M, Mundin G, Bond S, Bailey P, Woodward J, Bell D Low absolute bioavailability of oral naloxone in healthy subjects. *International Journal of Clinical Pharmacology and Therapeutics*, Vol. 50 - No. 5/2012 (360-367)

1 mg. It was shown that, even for a single dose of 120 mg oral naloxone, the bioavailability remained stable and constantly low (< 3%).¹⁷ Therefore it is expected that the ratio of oxycodone and naloxone can be maintained in doses above the approved dose range of 80/40 mg daily dose.

Exposure to the higher doses in preliminary studies

Across various Phase III studies (OXN3401, OXN3001, OXN3006) a total of 99 patients received OXN PR doses higher than OXN80/40mg PR per day. Of those, 27 patients received OXN PR in the Double-blind Phase and 72 patients received daily doses beyond OXN 80/40 mg PR in the open label Extension Phases. The results of this subgroup were similar compared to the entire population, demonstrating superiority of OXN PR over OxyContin prolonged-release (OxyPR) based on primary analysis of the BFI. Furthermore as expected, both treatment groups, OxyPR as well as OXN PR, had the same analgesic efficacy.

Results of OXN3506, OXN3506S

The confirmatory Phase III study, OXN3506, was intended to establish the efficacy and safety of OXN in daily doses up to OXN160/80 mg. The primary and secondary analyses confirmed the results previously seen in other Phase III studies (such as OXN3001 and OXN3006) that treatment with doses > OXN80/40 mg significantly improves the bowel function of patients who have to take high doses of opioids, while still providing comparable analgesic efficacy.

During the *Double-blind Phase* of Study OXN3506, in total 68 patients of the per protocol population received a daily dose of 140 to 160 mg oxycodone PR, of those 33 patients received OXN PR and 35 patients received oxycodone PR. Subgroup analyses by dose level showed that subjects receiving 100 to 120 mg oxycodone per day started with a mean pain score of 4.4 in the OXN PR group and 4.6 in the OxyPR group in the Run-in Phase), which was almost 1 score lower than in subjects receiving 140-160 mg/day, who had mean pain scores of 5.4 in the OXN PR group and 5.1 in the OxyPR group. However, pain scores at the beginning of the Double-blind Phase (baseline) and at Week 5 were comparable in the subgroups, which points to a greater level of pain relief in the higher dose subgroup. There was also no notable difference in the change to baseline, which was 0.0 median in all dose groups and treatment groups, and between 0.2 and -0.1 in the means.

Those results are further supported by the data established in the *open-label Extension Phase* designed to assess the long-term efficacy and safety of OXN in doses up to 180/90 mg daily.

This study provides evidence that treatment with OXN in daily doses up to 180/90 mg is safe and efficacious over a period of 24 weeks. The patients received stable doses of OXN PR between 100/50 mg and 180/90 mg per day. One hundred and sixty seven (167) of 195 patients (85.6%) completed the study. The pain scores in these patients remained stable and low throughout the Extension Phase, with mean values between 3.6 and 4.0, and a median of 4.0 throughout. The bowel function in these patients, as measured by the BFI, remained stable after the first week (on a low BFI score of below 35). Especially in the group of patients who had received OxyPR in the Double-blind Phase, the BFI decreased by -30.4 (26.15) in the mean throughout the Extension Phase. A subgroup analyses was performed for dose levels as well as dosing groups: 100 mg, 120 mg, 140 mg, 160 mg, 180 mg, 100 to 120 mg, 140 to 160 mg and >160 mg, respectively. Overall 68 subjects did receive 140/70 to 160/80 mg OXN PR per day, of which a total of 46 subjects were treated with 160/80 mg OXN PR per day. In addition 24 subjects were treated for at least 7 consecutive days with OXN180/90 mg PR during the open-label Extension Phase. No clinically relevant difference between the dosing subgroups could be observed with respect to mean (SD) pain scores. All the subgroups showed the same pattern. No clinically relevant differences were observed between the subgroups, showing comparable

analgesic efficacy in every dose level from 100/50 mg OXN PR to 180/90 mg OXN PR. The pain was stable with minimal changes to baseline.

The results of Studies OXN3506/OXN3506S showed that, in the dose range up to OXN180/90 mg, the naloxone component does not antagonise the analgesic efficacy of oxycodone, improves bowel function and does not lead to any safety concern.

In reference to the Delegate's concern about the generous non-inferiority margin chosen in the pivotal study the sponsor offers the following: In Study OXN3506 the non-inferiority bound was defined as a 20% difference between both treatments groups, which was based on the following definitions:

- Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials (IMMPACT) recommendations state that changes of approximately 2.0 points or 30% to 36% represent 'much better,' 'much improved,' or 'meaningful' decreases in chronic pain and in consequence can be regarded as a margin to define a clinically relevant difference.¹⁸
- A clinically important difference can be defined as a reduction of approximately two points (Numeric Rating Scale (NRS) pain 0 – 10) or a reduction of approximately 30% in the Pain Intensity (PI) NRS represented.¹⁹
- A change of 2 units on a pain scale (NR 0 – 10) was defined as a clinically relevant change (minimal important change (MIC)). When the baseline score is taken into account, a 30% improvement was considered a useful threshold for identifying clinically meaningful improvement on each of these measures.²⁰
- FDA approach: To establish a non-inferiority margin the FDA recommends to determine in the first instance the margin for the treatment effect of the active comparator compared to placebo (M1) and then calculating the margin for the test intervention (M2) by taking a percentage (for example, 50 percent of M1)²¹. During the clinical development program of OXN PR and based on available literature^{22,23} an improvement in pain scores of 3.0 units (NRS 0 - 10) due to oxycodone was established. A treatment effect of 2.0 difference (NRS pain 0 –10) due to oxycodone was demonstrated in a randomised, placebo-controlled trial to assess the efficacy and safety in the treatment of post-herpetic neuralgia.²⁴ Taking into account those difference of oxycodone compared to placebo a difference of 1.0 up to 1.5 (NRS 0 – 10) units representing M2 (M1/2) in pain score can be regarded as non- inferior margin to establish efficacy and safety of an analgesic.

In conclusion, the half standard deviation (SD) approach, the FDA approach, as well as taking the superiority approach into account to define a lower threshold for non-inferiority, consistently support the appropriateness of 20% as a valid non-inferiority bound for pain assessment.

¹⁸ Dworkin RH et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *The Journal of Pain*, Vol 9, No 2 (February), 2008: pp 105-121

¹⁹ Farrara, JT et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 94 (2001) 149–158

²⁰ Ostelo RW et al. Interpreting Change Scores for Pain and Functional Status in Low Back Pain. *Towards International Consensus Regarding Minimal Important Change*. *SPINE* Volume 33, Number 1, pp 90–94

²¹ Guidance for Industry, Non-Inferiority Clinical Trials

²² Sunshine A et al. Analgesic Efficacy of Controlled-Release Oxycodone in Postoperative Pain. *J Clin Pharmacol* 1996;36:595-603

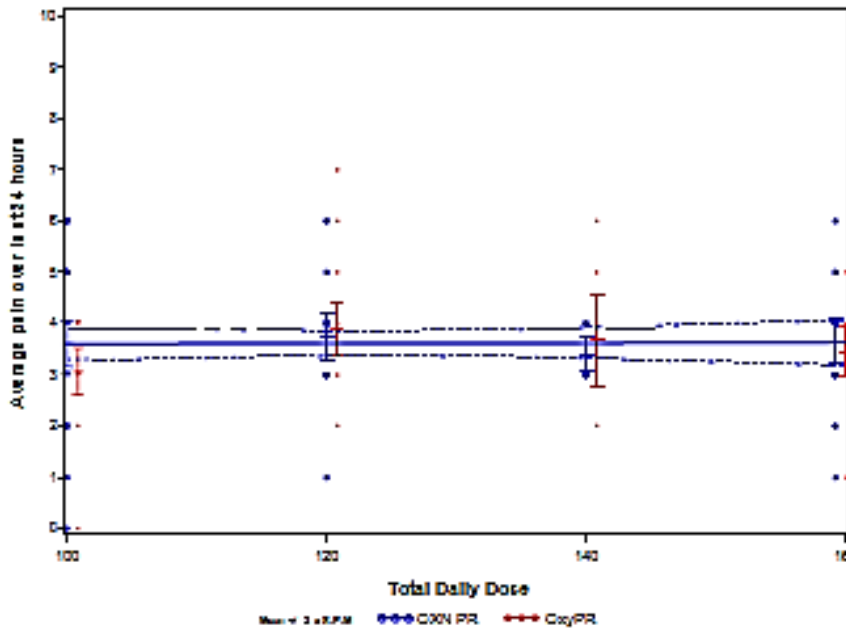
²³ Watson CPN et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 105 (2003) 71-78

²⁴ Watson CPN and Babul N. Efficacy of oxycodone in neuropathic pain. A randomized trial in postherpetic neuralgia. *Neurology* 1998; 50: 1837-1841

Dose specific post-hoc regression analysis of Average pain over last 24 hours assessed in OXN3506

In order to support the results of the subgroup analysis by dose level, the following figure displays the average pain over last 24 hours in Week 5, by treatment and dose groups. The error bars, representing the standard error of the mean (SEM), support the initial assumption of constant variance across all displayed dose groups and a descriptive linear regression with 95% confidence intervals does not indicate any clinically meaningful differences in pain across all dose groups.

Figure 3: Average pain over last 24 hours in week 5 (mean +/- 2 SEM) and linear regression with 95% CI (Per-Protocol population, no baseline adjustment, no missing imputation)



This observation is further supported by an exploratory, post hoc Analysis of Covariance (ANCOVA) comparing the lowest (100 mg) with the highest dose (160 mg).

Table 17: Results from an Analysis of Covariance (ANCOVA*) model for 24 hours average pain at week 5, comparing 100 mg with 160 mg dose group.

Comparison	Estimate (LS means difference)	SE	Lower Confidence limit	Upper confidence limit
100 mg versus 160 mg	0.0556	0.3598	-0.6549	0.7661

*(ANCOVA with fixed regression term for the baseline (Visit 3) and fixed treatment by dose group effect).

The results in Table 17 show a very small difference in average pain of 0.05 between the two dose groups and the confidence limits are within the pre-defined non-inferiority margin of ± 0.8 , confirming a comparable effect in both dose groups. Therefore, the increase in dose of Targin does not correspond with a decrease in efficacy due to the effect of naloxone.

Pooled safety analysis

A pooled safety analysis was performed for all subjects receiving at least one dose of \pm OXN160/80 mg per day during the double-blind phase ('core') or open-label extension phase.

The analysis on the Double-blind Phase was based on studies OXN3503 (parallel-group, double-blind, 12 weeks, OA pain, OXN: 101 subjects, OxyPR: 108 subjects), OXN3505 (parallel group, double-blind, 4 weeks, non-malignant and malignant pain, OXN: 111 subjects, OxyPR: 114 subjects) as well as OXN3506 (parallel-group, double-blind, 5 weeks, non-malignant and malignant pain, OXN: 123 subjects, OxyPR: 120 subjects). The respective analysis for the Extension Phase was based on Studies OXN3506S (open-label, 6 months, non-malignant and malignant pain, OXN: 195 subjects) and 038- 002S (open-label, 6 months, non-cancer pain, OXN: 34 subjects).

The pooled data from the Double-blind Phases is summarised as follows:

- Forty five (45) versus 44 patients received study medication for a mean period of 38.2 versus 34.1 days, respectively OXN versus oxycodone single active substance). The mean dose amounted to an average of approximately 161/162 mg per day and was comparable in both groups.
- Twenty one (21) subjects in the OXN group versus 14 patients in the oxycodone PR group experienced at least one AE (46.7% versus 31.8 %, respectively). In comparison, the number of patients with at least one AE across core pain studies amounted to 70.6 % of 832 OXN patients (versus 65.9 % of 993 comparator patients).

The data from the extension studies are summarised as follows:

- One hundred nine (109) patients received OXN study medication for a mean period of 127.5 days. The mean dose amounted to an average of 163.6 mg per day.
- Sixty nine (69) patients experienced at least one AE (63.3%). In comparison, the number of patients with at least one AE across extension pain studies amounted to 76.3 % of 903 OXN patients.

The higher number of patients experiencing adverse events under OXN versus oxycodone (21 versus 14 patients) does not raise a safety concern in view of the pattern of adverse events observed.

Furthermore, the relative number of patients with at least one AE under OXN treatment was lower in the ≥ 160 mg oxycodone dose group than in the general OXN pain population across the approved dose range (20 to 80 mg), this holds for both core and extension,

respectively. Upon medical review, there was no particular cluster of any AE in the ≥ 160 mg dose group, neither in core nor extension that might raise a safety concern.

OXN in the treatment of restless legs syndrome (RLS)

Clinical study OXN3502 and the respective open-label phase was conducted to establish the efficacy and safety of OXN in the treatment of moderate to severe idiopathic RLS with daytime symptoms compared to subjects taking placebo (PLA). Subjects had to terminate their pre-study RLS treatment at the start of the wash-out period (Visit 2). No other RLS medication (such as dopaminergic) other than the study medication (OXN, placebo) was permitted during the Double-blind Phase. According to the study protocol, patients with an IRLS sum score of ≥ 15 representing at least moderate RLS could be included in the study and 28 patients with moderate RLS were enrolled. The majority of patients (89.9%) entering the study suffered from severe to very severe RLS. Despite the relatively small sample size in the moderate severity subgroup, the results of this descriptive subgroup analysis showed a consistent clinical improvement for the patients treated with OXN PR. This is illustrated by a profound decrease of the mean IRLS sum score from study entry and from randomisation in all subgroups as well as by the meaningful differences to the respective placebo group at the end of the double-blind phase. The Delegate has acknowledged that Targin has shown efficacy as monotherapy in patients with primary RLS whose symptoms were not adequately controlled with standard RLS therapy in this study.

Even though moderate RLS patients were included and a clinical improvement for the subgroup was shown, the sponsor has revised the proposed indication to:

Symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy

This modification would exclude the treatment of patients with moderate idiopathic RLS. This indication is aligned with the approved indication in the EU. The sponsor does not believe that it is necessary to add 'Second line' to the indication as suggested by the Delegate as it is evident the treatment is for patients who were insufficiently treated with dopaminergic agent (that is, that have failed a prior therapy).

The Delegate raised concerns whether the duration of use of Targin in RLS should be limited to the duration of use in the randomised double-blind clinical trials. The sponsor disagrees and wishes to explain that the open-label Extension Phase study OXN3502 was performed in order to establish the long-term efficacy and safety of OXN in this indication. The Extension Phase provided strong evidence for the effectiveness of OXN PR in treating patients with RLS, reflected by further improvements in the IRLS scale at the end of the Extension Phase compared with the end of the Double-blind phase. The subjects mean condition had changed from moderate to mild or even a not detectable RLS, on a stable dosage regimen. Overall, there were no new or unexpected safety observations in this population of subjects with RLS. The safety results observed in the RLS population are in line with the well-established safety profile of OXN PR in the pain population, which is built on 8 years of market experience and approximately 8.8 million patient months of exposure. The results from Study OXN3502 Extension Phase indicate that OXN PR is safe and efficacious for the long-term (up to 52 weeks) treatment of RLS patients.

As RLS represents a chronic disease, treatment with OXN should be guided by a clinical expert in RLS therapy and based on an ongoing benefit: risk basis. Furthermore in order to ensure that patients are not unnecessary exposed to OXN it should be assessed regularly if the patient still requires an opioid treatment. Therefore the following statement is included in the proposed PI under Dosage and Administration:

At least every three months during therapy patients should be clinically evaluated and treatment should only be continued if Targin tablets are considered effective and

the benefit is considered to outweigh adverse effects and potential harms in individual patients.

Prior to continuation of RLS treatment beyond 1 year a discharge regimen by gradually reducing the dose over a period of approximately one week should be considered to establish if continued treatment with Targin tablets is indicated.

When opioid treatment is no longer needed, the dose should be gradually reduced over a period of approximately one week, as recommended to minimise symptoms of withdrawal (see Precautions section).

The Delegate raised concerns related to CNS adverse effects associated with dopamine agonists and oxycodone and other concerns on the concurrent use of Targin with dopaminergic agents in RLS patients. As per the Delegate's request, the applicant has amended the PI sections 'Precautions, and Interactions with Other Medicines', to include information related to synergistic/additive CNS side effects. However supported by the detailed discussion below, the sponsor disagrees with the Delegate's comments to add specific statements in the PI that concurrent use of Targin with dopaminergic agents in RLS patients is not recommended. It is the sponsor's view that such decision is up to the treating specialist's discretion, to determine the appropriate therapy for patients with RLS, based on assessment of patient's condition. The sponsor proposes alternative wording to inform the treating specialist that there is no clinical experience of concomitant dopaminergic agents with Targin in the treatment of RLS and that the combination was not tested in the clinical trial OXN3502 in RLS patients. This alternative paragraph is supported and consistent with the pivotal RLS study data that concurrent use of dopaminergic agents and Targin was not assessed.

During Study OXN3502, OXN was not given in addition to dopaminergic RLS therapy due to the nature of the study design and objective of the study. Therefore even without any dopaminergic treatment OXN provides a clinically relevant improvement in RLS therapy. The sponsor has conducted a placebo-controlled clinical Phase II study (OXN2504, published by Trenkwalder et al., 2015⁸) to establish the efficacy and safety of OXN for the treatment of Parkinson Disease (PD) related pain, in which the OXN was given as an adjunctive to dopaminergic therapy. Study OXN2504 was a multicentre, double-blind, randomised, placebo controlled study to determine the efficacy and tolerability of OXN PR for the treatment of severe Parkinson's disease associated pain. In this study OXN PR or matching placebo was given as add-on therapy to current PD therapy. The primary analysis of the mean averaged 24 hour pain score at Week 16 showed a strong indication for a clinically favourable analgesic effect of OXN PR compared to placebo although it narrowly failed to meet statistical significance ($p=0.058$). The safety analyses (AEs, clinical laboratory, vital signs and electrocardiogram (ECG)) did not raise any safety concerns for the use of OXN PR in the treatment of severe Parkinson's disease associated pain.⁸ Therefore it can be concluded that the concomitant use of OXN and dopaminergic therapy does not put any patient at risk and can be regarded as safe treatment option for PD related pain.

Although no data are established for the concomitant use of OXN and dopaminergic for the treatment of idiopathic RLS it is not expected that this combination of treatments would put patients at risk. Additionally, based on discussions with European experts in RLS, specialists in the area of RLS would prefer the therapeutic option to add or keep low doses (even at sub-therapeutic level) of dopaminergics during treatment with OXN as they may expect a synergistic clinically beneficial effect, while also minimising the risk of augmentation through the higher dopaminergic doses regularly used.

RMP

The Delegate has noted outstanding issues concerning RMP evaluation. The sponsor does not concur with the Delegate's comments and wishes to note that these comments did not

take into account the sponsor's response to the Second round RMP evaluation report, dated 14 April 2016. The applicant has responded as summarised below and addressed each one of these issues and we believe the outstanding issues have been resolved.

- The sponsor narrowed the indication for the use of Targin in RLS in patients with 'severe to very severe' disease, in-line with the indications approved in Europe, hence the need for a DUS be conducted in Australia is not deemed necessary.
- The sponsor has updated the ASA (as Version 6.0) to reflect the safety concerns identified in Version 6.0 of the EU RMP.
- The sponsor believes that the need of specific RLS educational material is not deemed necessary and has provided justification in the RMP response dated 14 April 2016.

Abuse potential studies

The Delegate has requested an abbreviation of this section and recommended specific text is included in the PI. The sponsor as requested has extensively abbreviated this section, adopted the delegate's recommended text together with suggestions of alternative text as outlined below:

Under the heading 'Studies in non-dependent opioid abusers'

- The sponsor wishes to present information to show the 95% Confidence Intervals. This would ensure consistency with the information presented under heading 'Study in Opioid-Dependent Subjects'.
- The sponsor has also included data related to Study ONU1007 where Targin was administered chewed or intact tablets. This would represent a balanced summary of the overall submitted results of the abuse potential clinical studies.

Advisory Committee considerations

The ACPM resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Targin modified release tablets containing oxycodone hydrochloride / naloxone hydrochloride 2.5/1.25 mg, 5/2.5 mg, 10/5 mg, 15/7.5 mg, 20/10 mg, 30/15 mg, 40/20 mg to have an overall positive benefit-risk profile for the delegate's amended indication;

Second line symptomatic treatment of patients with severe to very severe primary restless legs syndrome (RLS) after failure of dopaminergic therapy.

In making this recommendation the ACPM

- was of the view that Targin should be used as second line therapy after failure of dopaminergic therapy to reflect the data presented in the clinical trials.
- was of the view that the indication should be for severe to very severe primary restless legs syndrome consistent with the efficacy data in the clinical trial.
- advised that the duration of treatment should be at the discretion of the physician as it is a chronic condition and that treatment would be discontinued if the patient is not responding.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that Targin modified release tablets containing oxycodone hydrochloride 60 mg/ naloxone hydrochloride 30 mg and oxycodone hydrochloride 80 mg/ naloxone hydrochloride 40 mg has an overall negative benefit-risk profile for all indications approved for Targin.

In making this recommendation the ACPM:

- Was of the view that higher dose of oxycodone/naloxone and the higher strength tablets were not needed in current clinical practice and that access to higher strengths may be outweighed by the potential for harm.
- Expressed concern that the risk of increased doses of naloxone was still unknown based on the data presented.
- Noted that there were insufficient patients in Study OXN3506 and that the duration of treatment was too brief (5 weeks) to assess non-inferiority of Targin or the safety of the higher dose.
- Noted that the above study was not designed to answer whether the increase in the dose of naloxone could lead to alterations in the efficacy of the opioid antagonist action in the gut or increase opioid antagonist action in the CNS.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- advised that the PI needed to be more balanced with respect to advice given about the potential for abuse and supported the amendments to the PI proposed by the Delegate as well as the Risk Management Plan.
- was of the view that under *Interactions with Other Medicines* there was reference to cimetidine, which is rarely used in clinical practice and that this should be updated with more appropriate H2 antagonist and proton pump inhibitor (PPI) medications.
- under *Use in Renal and Hepatic Impairment*, specific dosing instructions should be stated for use in patients with chronic kidney disease, particularly in patients undergoing dialysis, rather than a general direction to reduce the dose for patients with mild hepatic or renal impairment by half to 1/3.
- highlight that Targin was used as monotherapy after failure of dopaminergic agents in study OXN 3502.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *The pivotal trial in RLS did not allow for adjunctive dopaminergic treatment. Given the lack of assessment of efficacy of combination treatment and the overlapping side effects of opioids and dopaminergic agents does the committee consider there are any circumstances in which a combination of the two treatments could be recommended?*

The ACPM was of the view that Targin could potentially augment CNS adverse events, such as confusion, if used as combination therapy and that this may potentially change the benefit - risk profile. The ACPM noted that there were insufficient data to support combination therapy as patients were not allowed to use dopaminergic agonists in Study OXN3502. The ACPM therefore advised Targin should be used as monotherapy in second-line treatment to reflect use in Study OXN3502.

2. *The sponsor has proposed registration of Targin in RLS, a chronic condition. The committee is requested to provide advice on whether one pivotal trial of 12-13 weeks'*

duration with a 40-week open, uncontrolled extension phase is sufficient to register Targin for RLS. While there was no clear evidence of tolerance or dose escalation from that extension study these are known effects with prolonged use of opioids.

The three dopamine agonists approved for primary idiopathic RLS in Australia (pramipexole, ropinirole and rotigotine) all had either randomised double-blind placebo-controlled studies to 6 months or double-blind studies and a randomised withdrawal studies in support of their initial registration for this indication.

The ACPM was of the view that the length of time of the study presented was short compared with the studies for the dopamine agonists for RLS. However, the ACPM advised that as there was a demonstrated statistically significant improvement in both primary and secondary outcomes for Targin versus placebo, this was sufficient to support registration.

- 3. The sponsor has proposed the RLS indication apply to patients with moderate to severe RLS symptoms. While subjects who entered the pivotal study had at least moderate symptoms at baseline, no subject had less than severe symptoms at randomisation to active treatment (IRLS range 21 to 39). Would limiting the RLS indication to patients with severe symptoms be appropriate? Additionally, given only patients with primary RLS were enrolled should the indication be restricted to those patients?*

The ACPM noted that the sponsor had agreed to restrict the indication to severe to very severe idiopathic restless legs syndrome, which was considered appropriate. The ACPM was of the view that the indication should also be restricted to primary restless legs syndrome to reflect the population in the clinical trials.

- 4. The sponsor has proposed increasing the recommended maximum daily dose of Targin to 160/80 mg i.e. double the currently recommended maximum dose. While this would not be an increase on the recommended maximum dose of oxycodone, it is an increase in the maximum daily dose of oral naloxone. This may cause alterations to the efficacy of the opioid antagonist action in the gut and may increase opioid antagonist action in the CNS compared to the current oral naloxone doses. The studies presented do not allow exploration of this concern.*

The proposed increase in dose primarily relates to efficacy and safety of high-dose oral naloxone rather than high-dose oxycodone however the proposed maximum doses (of oral naloxone) are not well represented in the pivotal study to support increasing the dose. The committee is requested to provide advice on whether the lack of high-dose specific clinical trial data and lack of a demonstrable efficacy dose-response relationship at the highest naloxone dose is acceptable.

The ACPM advised that there were insufficient numbers of patients and too brief duration of treatment (5 weeks) in Study OXN3506 to support the use of the requested higher dose. In addition, the question about whether the efficacy of oxycodone was affected by the higher naloxone dose was not answered. The ACPM was of the view that access to higher strengths may be outweighed by the potential for harm and therefore did not support the registration of the proposed higher dose.

- 5. The sponsor has proposed inclusion of detailed descriptions of four abuse potential studies in the PI. These studies emphasise intranasal and intravenous routes of administration. The committee is requested to provide advice on the extent of information on these studies that is appropriate for inclusion in the Product Information.*

The ACPM supported the Delegate's proposed amendments to the PI regarding abuse potential as well as the proposed Risk Management Plan.

The ACPM advised that 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of

1. Two new strengths:
 - Targin oxycodone hydrochloride/naloxone hydrochloride anhydrous 60/30 mg modified release tablets blister pack.
 - Targin oxycodone hydrochloride/ naloxone hydrochloride anhydrous 80/40 mg modified release tablets blister pack.
2. A new maximum daily dose of Targin to 160 mg/80 mg.
3. PI changes and the following new Indication:

Second line symptomatic treatment of patients with severe to very severe idiopathic Restless legs syndrome after failure of dopaminergic therapy

The full indications are now:

The management of moderate to severe chronic pain unresponsive to non-narcotic analgesia. The naloxone component in a fixed combination with oxycodone is indicated for the therapy and/or prophylaxis of opioid-induced constipation.

Second line symptomatic treatment of patients with severe to very severe idiopathic Restless legs syndrome after failure of dopaminergic therapy. Specific conditions of registration applying to these goods

The implementation of the Targin (oxycodone hydrochloride and naloxone hydrochloride) EU-RMP Version 6.0 (dated 23 September 2015, DLP 31 July 2015) with Australian Specific Annex Version 6.0 (dated April 2016) included with submission PM- 2015-01090-1-1, and any future updates as a condition of registration as agreed with the TGA.

Attachment 1. Product Information

The PI for Targin approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au>