Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ibuprofen

Proprietary Product Name: Caldolor

Sponsor: Phebra Pty Ltd

January 2013

TGA Health Safety Regulation

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I. Introduction to product submission

Submission details

Type of Submission	Major Variation (New dose form/New route of administration)
Decision:	Approved
Date of Decision:	28 February 2012
Active ingredient(s):	Ibuprofen
Product Name(s):	Caldolor
Sponsor's Name and Address:	Phebra Pty Ltd Locked Bag 3003, Hunters Hill, NSW 2110
Dose form(s):	Concentrated injection
Strength(s):	400 mg/4 mL and 800 mg/8 mL
Container(s):	Glass vial
Pack size(s):	10 vials per carton
Approved Therapeutic use:	Caldolor injection is indicated in adults for the management of acute mild to moderate post operative pain and moderate to severe post-operative pain with adjunctive reduced morphine dosage, where an IV route of administration is considered clinically necessary. Caldolor is indicated for the reduction of fever in adults where an IV route of administration is considered clinically necessary
Route(s) of administration:	Intravenous (IV)
Dosage:	See Product Information (Attachment 1).
ARTG Number (s)	175191 and 175190

Product background

Ibuprofen is a non-steroidal anti-inflammatory drug and a non-selective inhibitor of cyclo-oxygenase (COX)-1 and -2. It was first marketed in Australia in 1969. It is now registered by a large number of companies in a range of oral dosage forms. This AusPAR describes application by Phebra Pty ltd to register the first injectable form of ibuprofen, Caldolor, for the management of mild to moderate pain, the management of moderate to severe pain as an adjunct to opioid analgesics and for the reduction of fever in adults. At this time, there are no parenteral formulations of ibuprofen approved in Australia for use in fever or pain.

The product is supplied at a concentration of 100 mg/mL, which must be diluted to 4 mg/mL or less before administration. Ibuprofen is currently marketed as 200 mg and 400

mg tablets, 200 mg capsules, 200 mg liquid capsules, 200 mg meltlets, 342 mg tablets, 100 mg/5 mL and 200 mg/5 mL suspension. The ibuprofen oral preparations currently marketed are indicated for rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, primary dysmenorrhoea and pyrexia. Brufen is also indicated for the relief of acute and/or chronic pain states in which there is an inflammatory component.

Although the recommended maximum daily dose for the currently approved oral Ibuprofen preparations ranges from 1600-2400 mg depending on the indication, it is theoretically possible to ingest up to 3200 mg on the first day of treatment. For example, for primary dysmenorrhoea, the initial dose is 400-800 mg at the first sign of pain or menstrual bleeding, then 400 mg 4-6 hourly.

Regulatory status

Ibuprofen injection (Caldolor) 100 mg/mL, 400 mg and 800 mg vials gained marketing approval from the US FDA for use in adult patients in June 2009. The FDA approved indications are the same as those being proposed above in Australia.

Product Information

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

II. Quality findings

Caldolor is a concentrated injection that must be diluted to a concentration of 4 mg/mL or less in 0.9% sodium chloride or 5% glucose prior to IV infusion over a period of 30 minutes. The company also proposed Lactated Ringers Solution as a suitable diluent but the sparse data provided suggest that transient precipitation of ibuprofen may occur in this diluent.

The injection is to be supplied in glass vials in strengths of 400 mg/4 mL and 800 mg/8 mL. Ibuprofen is practically insoluble in water but it is solubilised in the Caldolor injection by *in situ* salt formation with arginine. The injection contains no antimicrobial preservative and has a pH of 7.4.

Figure 1. Chemical structure of ibuprofen and arginine

There are no objections on chemistry, manufacturing and controls grounds to registration of this product. A shelf life of 30 months below 25°C was considered approvable.

This submission was not referred to the Pharmaceutical Subcommittee of the Advisory Committee on Prescription Medicines (ACPM) as ibuprofen is a well established drug, presented in a conventional dosage form.

III. Nonclinical findings

Introduction

General comments

The toxicity profile of ibuprofen has been previously characterised and there is extensive clinical experience with its use. In order to justify the new route of administration, the sponsor submitted bridging studies, which included two 28 day IV toxicity studies (with toxicokinetic data), blood compatibility studies and local irritation studies. The general quality of the submitted studies was good. Pivotal studies examining the repeat-dose toxicity were conducted under Good laboratory Practice (GLP) conditions. Additional submitted studies included dose range-finding IV studies and published repeat dose toxicity studies in rats (oral (PO)), dogs (PO) and monkeys (IV/PO), single dose toxicity studies, genotoxicity studies and reproductive toxicity studies.

The proposed maximum recommended human dose (MRHD) is 3200 mg/day, therefore a 50 kg patient receiving the MRHD would receive 64 mg/kg ibuprofen. The MRHD for ibuprofen administered orally is 2400 mg/day.

Studies in the submitted published literature which were not performed with IV ibuprofen, or with the proposed formulation, were not assessed.

Pharmacology

Mechanism of action

Like that of other NSAIDs, ibuprofen's mechanism of action is not completely understood but may be related to inhibition of cyclooxygenase mediated prostaglandin formation. Ibuprofen possesses anti-inflammatory, analgesic, and antipyretic activity. Ibuprofen inhibits both COX-1 and COX-2 activities and thereby synthesis of prostaglandins and thromboxanes. The inhibition of COX-1 is believed to be responsible for the gastrointestinal (GI) adverse effects related to ibuprofen administration[1].

No pharmacodynamics studies were submitted and this was considered acceptable as there is extensive clinical efficacy data from clinical experience with ibuprofen.

Pharmacokinetics

In the submitted dog studies, oral administration of ibuprofen resulted in lower plasma drug concentration and overall exposure (50-60%) when compared with IV administration at the same dose level. In the two clinical studies in which equal IV and PO doses were compared (Table 1), plasma area under the plasma concentration time curve (AUC) values were similar, indicating 100% PO bioavailability under the conditions of these studies.

In general, all measured parameters were similar between genders and sampling days. AUC and peak plasma concentration (Cmax) values were dose proportional for both males and females on both sampling days and no clear sex differences in systemic exposure were

[1] Insel PA. Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. Chapter 27. In: Hardman J. G. and Limbird L. E. The Pharmacological Basis of Therapeutic. Mc Graw Hill, 1990: 617-658

apparent. Values were only slightly lower on Day 27 than on Day 1, indicating lack of accumulation of ibuprofen with repeated dosing.

Pharmacokinetic drug interactions

No drug interaction studies were provided as part of this submission. It is noted that one of the indications of Caldolor is "*the management of moderate to severe pain as an adjunct to opioid analgesics*". The potential for pharmacokinetic interactions between ibuprofen and opioids was not examined in nonclinical studies.

Toxicology

Acute toxicity

Acute administration of 120 mg/kg ibuprofen (40 mg/kg x 3 doses, 4 h apart) to dogs caused GI and renal toxicity, as would be expected from the known toxicity profile of NSAIDs.

Repeat-dose toxicity

In one 28 day repeat-dose toxicity study, 1, 5 and 15 mg/kg/day ibuprofen was administered IV to beagle dogs. In that study, the no observable effect level (NOEL) was 1 mg/kg/day. The main findings were GI effects (loose faeces) noted at ≥ 5 mg/kg/day IV but not at 15 mg/kg/day PO. Injection site swelling, inflammation and haemorrhage were noted in control and treated animals, with swelling more pronounced at the high IV dose (15 mg/kg/day). Injection site necropsy confirmed the presence of local venular and subcutis inflammation at the high dose (HD). There were no treatment related findings in other tissues, including kidneys and GI tract.

After administration of 15, 30 and 45 mg/kg/day IV ibuprofen to dogs for 28 days in another study, no treatment related mortality was noted. However, liquid faeces and inflammation of the kidney were noted at all doses and various additional faecal changes were observed at the high IV dose (45 mg/kg/day). GI erosions and ulcers were noted at 45 mg/kg/day in 1 animal receiving ibuprofen IV and 1 animal receiving it PO. Dark areas or swelling in the subcutis or surrounding vein were observed in injected veins, accompanied by venous intimal proliferation and thrombosis, both in control and treated animals.

Surprisingly, injection site reactions in the higher dose study were not greater than in the lower dose study. As there were significant injection site effects in the lower dose study, it would have been expected that more severe effects would be present in the higher dose study.

Anaemia was present in animals receiving 15 mg/kg/day PO and IV in the lower dose study but this finding was not confirmed in the higher dose study where there was only one incidental finding of anaemia in an animal receiving 45 mg/kg/day IV.

The HD was associated with GI ulceration in only one dog receiving ibuprofen IV and one receiving it PO, meaning that a dose-dependency could not be confirmed. Injection site irritation (all doses) and mild renal histopathological findings (15-45 mg/kg/day) were observed in the repeat-dose dog studies. Generally, systemic toxicological effects were less pronounced in dogs dosed PO compared with dogs dosed IV at the same dose level, consistent with lower systemic exposure achieved with the PO route (Table 1).

IV administration of 100 and 200 mg/kg/day ibuprofen to monkeys for 14 days caused gastric and duodenal ulcers. However, administration of 300 mg/kg/day PO for 90 days caused no GI tract (GIT) damage.

In conclusion, IV injection of ibuprofen resulted in previously documented systemic NSAID toxicities. The main issue with the current submission was the potential for adverse local tolerance with the proposed IV administration route.

Relative exposure

The proposed MRHD for IV ibuprofen (3200 mg/day) is 33% greater than the MRHD for PO ibuprofen in Australia (2400 mg/day). The clinical exposure data indicate that the plasma AUC was approximately 800 µg.h/mL at the 3200 mg/day IV dose and approximately 600 µg.h/mL at the 2400 mg/day PO dose (Table 1)[2]. Safety margins for toxicities have been assessed using the increased clinical kinetic exposure derived from the IV data compared to the toxicokinetic data from the animal studies.

In the repeat dose dog studies, systemic exposure (plasma AUC) was mostly less than anticipated clinical exposure at the MRHD; exposure was similar to clinical exposure only at the 45 mg/kg/day IV dose. However, given the presence of dose-limiting toxicities at this dose, it is unlikely that further dose escalation in the dog studies would have been feasible. GI effects were observed in repeat-dose toxicity studies at doses ranging from 5 to 45 mg/kg/day in dogs, at relative exposures of between 0.1 and 1.1 times the exposure in humans receiving 3200 mg/day. The low relative exposures at which GI and renal effects were observed in dogs may indicate that administration of 3200 mg/day IV ibuprofen to humans could be associated with the risk of adverse GI and/or renal effects. Although the elicited toxicities were dose-limiting, the effects were consistent with the known adverse effects of clinical ibuprofen administration, and thus potentially clinically relevant. It is noted that the *Precautions* section of the draft Product Information document incorporates extensive warning statements in this regard, and the *Dosage and Administration* section recommends using the lowest effective dose for the shortest duration. The available nonclinical data supports the inclusion of such warning statements.

[2] The IV formulation would be expected to have greater bioavailability than PO formulations, although the submitted clinical studies indicate ca 100% PO bioavailability.

Table 1. Relative exposure in IV and oral repeat-dose toxicity studies. Table continued across 2 pages.

Study details, species, treatment duration	Dose (mg/kg/day), Route	Day	Sex	AUC (µg·h/mL)	AUC (µg·h/mL) extrapolated to 3200 mg dose	Relative exposure
TKCATO-01-4932, beagle dogs, 28 days	15, IV	1	♂ ♀	283.4 332.4	NA NA	0.4 0.4
		27	♂ ♀	270.9 297.4	NA NA	0.3 0.4
	30, IV	1	♂ ♀	562.4 589.6	NA NA	0.7 0.7
		27	♂ ♀	506 521.6	NA NA	0.6 0.7
	45, IV	1	♂ ♀	717.4 848	NA NA	0.9 1.1
		27	♂ ♀	595.9 727.9	NA NA	0.8 0.9
	45, oral gavage	1	♂ ♀	565.5 539.4	NA NA	0.7 0.7
		27	♂ ♀	427.1 413.4	NA NA	0.5 0.5
TKCATO-01-3082, beagle dogs, 28 days	1, IV	1	♂ ♀	21.9 25,5	NA NA	0.03 0.03
		27	♂ ♀	20 20	NA NA	0.03 0.03
	5, IV	1	♂ ♀	111.7 141.1	NA NA	0.1 0.2
		27	♂ ♀	102.2 121.9	NA NA	0.1 0.2
	15, IV	1	♂ ♀	352.3 351.7	NA NA	0.4 0.4
		27	♂ ♀	335.6 335.9	NA NA	0.4 0.4
	15, oral gavage	1	♂ ♀	172.7 167.6	NA NA	0.2 0.2

Study details, species, treatment duration	Dose (mg/kg/day), Route	Day	Sex	AUC (µg·h/mL)	AUC (µg·h/mL) extrapolated to 3200 mg dose	Relative exposure
		27	♂ ♀	163 165	NA NA	0.2 0.2
CPI-CL-001, human healthy volunteers, IV (60 min infusion) or PO n=12/group	200 mg, IV 400 mg, IV 800 mg, IV	1 1 1	NA NA NA	65.5 112.5 198.2	1048 900 **792.8**	NA NA NA
	200 mg, PO 400 mg, PO 800 mg, PO	1 1 1	NA NA NA	69.9 110.9 218.8	838.8^ 665.4^ 656.4^	NA NA NA
CPI-CL-011, human healthy volunteers, IV (5-7 min infusion), or PO n=12/group	800 mg, IV	1	NA	196	**784**	NA
	800 mg, PO	1	NA	196	588^	NA
CPI-CL-004, hospitalized adult febrile patients, IV (30 min infusion) n=30-31/group	100 mg, IV	1	NA	22.3&	713.6	NA
	200 mg, IV	1	NA	32.6&	521.6	NA
	400 mg, IV	1	NA	70.6&	564.8	NA

* = animal AUC compared with human AUC of 788.4 µg·h/mL (mean of studies CPI-CL-001 and CPI-CL-011, bolded; Clinical study data obtained from Clinical Study Reports); ^ = extrapolated to 2400 mg dose (daily MRHD for PO ibuprofen); & = $AUC_{0\text{-}4h}$; The relative exposure would be only slightly higher if animal exposure was compared with exposure in febrile humans.

Toxicity in combination with other drugs

The sponsor did not submit any studies which addressed the potential toxicity of ibuprofen when used in combination with other drugs. The potential for toxicity due to interactions between ibuprofen and opioids was not examined in nonclinical studies.

Genotoxicity

Studies performed in 1986 and 1997 were submitted as part of the application in order to address the genotoxic potential of ibuprofen. Ibuprofen was negative in the Ames test (with and without metabolic activation) and the sister chromatid exchange (SCE) test in bone marrow cells of mice gave a weak positive response. No genotoxicity concerns were found that were specific to the new formulation or the new route of administration.

Carcinogenicity

Ibuprofen was not carcinogenic to mice after administration of 100 mg/kg/day for 80 weeks, or to rats after administration of 60 mg/kg/day for 104 weeks. These (1970) studies were not GLP-compliant and did not incorporate toxicokinetic measurements. No carcinogenic potential was found that was specific to the new formulation or the new route of administration.

Reproductive toxicity

One study from 1969 was submitted, investigating embryofetal development in rats and rabbits (PO dosing) and fertility in rats (dietary dosing). Rabbits treated throughout gestation had interruption of early pregnancy (increased pre-implantation losses). There was no evidence of treatment-related malformations in rabbits or rats following treatment during gestation (including the period of organogenesis) at respective doses up to 60 and 180 mg/kg/day PO, which was sufficient to induce GI lesions and reduce growth. Although this is a very early, non-GLP-compliant study lacking exposure data, it found no evidence of teratogenicity. The rat fertility component of the study was also unremarkable. It is not expected that the new formulation or the new route of administration will change the reproductive toxicity profile of ibuprofen.

Local tolerance

A local tolerance study in rabbit marginal ear veins showed signs of dose/concentration related local irritancy around the vein at single IV doses of 1.6, 4, 20 and 100 mg/kg. The vehicle alone contributed to the local irritation. There were only minimal effects at the lowest dose/concentration (1.6 mg/kg, 1.6 mg/mL), namely increased small vessel congestion, while delayed slight mottling/discolouration was seen with 4 mg/kg (4 mg/mL). Higher doses/concentrations (20-100 mg/kg, 100 mg/mL) elicited more severe reactions (profound discolouration and necrosis). The animal data suggest that 4 mg/mL may be the maximal concentration which could be used without risk of adverse local effects. It is noted that the "*Dosage and Administration Preparation and Administration*" section of the proposed PI recommends dilution of Caldolor to a final concentration of 4 mg/mL or less.

In the single dose local tolerance study, repeated observations of the animals and the injection sites should have been performed during the 48-96 h following the drug administration (according to TGA adopted (with amendment) European Union (EU) Guideline)[3]. Rabbits were sacrificed 1 or 24 h after the single IV dose. The reversibility of the effects was also not studied. Studies assessing the local tolerance of paravenous tissues were not performed with the ibuprofen formulation, which may have been useful to evaluate its local toxicity in sites which might come into contact through accidental exposure. The draft PI does not discuss the potential for adverse infusion site reactions or recommend a maximal duration of treatment and therefore it is difficult to compare the results of this single-dose irritancy study in rabbits with the proposed human use. If repeated/prolonged therapy is envisaged this study may be considered inadequate but appropriate clinical data could overcome this deficiency.

Local swelling and inflammation were observed in dogs from all groups receiving repeated doses of ibuprofen IV (15-45 mg/kg/day in divided doses) or control, indicative of irritancy from ibuprofen and/or the vehicle used. Microscopic changes indicative of inflammation were also found in the injected veins. The local effects were not exacerbated by increasing doses.

[3] Note for guidance on the non-clinical local tolerance testing of medicinal products. CPMP/SWP/2145/00. http://www.tga.gov.au/pdf/euguide/swp214500en.pdf

In clinical practice, the option of varying the infusion site should be considered, in the event of an adverse local reaction and/or prolonged treatment.

Haemocompatibility

Ibuprofen solution up to 100 mg/mL did not induce blood flocculation *in vitro* at a 1:1 ratio between the drug solution and human plasma or serum. A similar study with human whole blood showed haemolysis (97%) of red blood cells at 100 mg/mL ibuprofen but not at 1.6 or 4 mg/mL.

As no blood compatibility effects were detected at a concentration of 4 mg/mL, it is not expected that the diluted ibuprofen solution for infusion (4 mg/mL or less, as directed in the proposed PI) would pose haemolysis risks. It is noted that the "*Precautions Haematological Effects*" section of the proposed PI warns that infusion of Caldolor injection without dilution can cause haemolysis.

The results of the local tolerance testing and the haemocompatibility studies, support the advice in the proposed PI regarding dilution prior to infusion.

Paediatric use

Caldolor is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Other toxicities

The genotoxic, carcinogenic, and reproductive and developmental toxicity potential of ibuprofen have been investigated previously. The sponsor has submitted published literature in support of safety statements proposed in the draft PI document. The studies support the PI safety statements.

Impurities in drug substance and drug product

Impurities A, J, N and F exceed the International Conference on Harmonisation (of technical requirements for registration of pharmaceuticals for human use) (ICH) guidance[4] threshold of 0.05% for a drug substance with a maximum daily dose of >2 g/day. However, the sponsor's specifications for these impurities meet British Pharmacopiea (BP) requirements. All other (unspecified) impurities will be present at no more than (NMT) 0.05%, thereby complying with the ICH guidance document (and BP requirements).

The proposed specifications for impurities in the drug product are within the TGA adopted EU guideline[5] qualification threshold (0.15% for a maximum daily dose of >2 g/day).

Therefore, and given the long history of the oral ibuprofen products containing the drug substance impurities, the presence of the impurities was not considered a safety concern.

[4] Guidance for industry. Q3A Impurities in New Drug Substances. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf

[5] Note for Guidance on Impurities in New Drug Products. CPMP/ICH/2738/99. http://www.tga.gov.au/pdf/euguide/ich273899enrev2.pdf

Nonclinical summary and conclusions

- The maximum recommended human dose (MRHD) is 3200 mg/day in divided doses of 100-800 mg, this is 33% greater than the MRHD for PO ibuprofen (2400 mg/day). The IV formulation may also be expected to have greater bioavailability than PO formulations and therefore safety margins have been reduced. The draft Product Information (PI) document states that "*after observing the response to initial therapy with* Caldolor, *the dose and frequency should be adjusted to suit an individual patient's needs*"; however, the *Dosage and Administration* section of the draft PI does not include a recommended maximum duration of treatment or guidance about switching to PO ibuprofen after a specific period of IV treatment.
- The sponsor has provided a submission of bridging nonclinical studies. Toxicities observed were consistent with known ibuprofen toxicities, such as GI ulceration and renal inflammation. No additional systemic toxicities were observed.
- In 28 day repeat-dose toxicity studies in dogs, ibuprofen caused GI effects (loose/liquid faeces) and mild renal inflammation after IV doses of between 5 and 45 mg/kg/day, associated with exposures (AUC) between 0.1 and 1.1 times the exposure expected in humans receiving the maximum daily dose. Pharmacokinetic studies in dogs indicated increased exposure with the IV route compared to the oral route. No sex differences or accumulation were observed. Local inflammation of the injection site was also observed, as well as thrombosis, oedema and erythema.
- In a single-dose local tolerance study in rabbits, local irritation was observed after IV injection of 4, 20 and 100 mg/kg ibuprofen at respective concentrations of 4, 100 and 100 mg/mL. A dose of 4 mg/kg (4 mg/mL, the concentration proposed for clinical use) produced purple discoloration and the effect was more prominent at doses of 20 and 100 mg/kg, showing histopathological changes. Ibuprofen showed a local irritant effect at injection sites and must be diluted before clinical use.
- In genotoxicity assessment, ibuprofen was negative in bacterial gene mutation (Ames) assays and weakly positive in the sister chromatid exchange (SCE) test in mouse bone marrow cells.
- There was no evidence of carcinogenicity in mice administered ibuprofen 100 mg/kg/day PO for 80 weeks or in rats with 60 mg/kg/day PO for 104 weeks.
- Oral/dietary reproductive toxicity studies in rats and rabbits were unremarkable, with no evidence of teratogenicity or impairment of fertility, apart from increased preimplantation loss in rabbits at a maternotoxic dose.
- Haemolysis was observed when heparinised blood was mixed 1:1 with ibuprofen solution 100 mg/mL (but not 1.6 or 4 mg/mL). Flocculation was not seen at these concentrations.
- The proposed specifications for impurities in the drug substance and the drug product comply with recommended TGA adopted EU guideline levels or with BP requirements.
- Concomitant administration of ibuprofen and opioids may be anticipated but no interaction studies were submitted.

Conclusions and recommendation

The two major issues arising from the nonclinical evaluation are the reduced safety margins consequent to the increased MRHD and potential local reactions at the administration site.

Reduced safety margins: Although IV studies with ibuprofen revealed no novel systemic toxicity due to the change in route of administration, the safety margins for GI and renal effects are not large (≤ 1), indicating potential risk of adverse effects on these organ systems with treatment at the maximum daily dose. As such, although there are no nonclinical objections to the proposed new dosage form and administration route, the nominated MRHD of 3200 mg/day may pose a risk of target organ toxicity, and a reduction in the MRHD may be warranted. These concerns may be alleviated by adequate clinical safety data.

Local tolerance: Ibuprofen is a potential local irritant and haemolytic agent, and the proposed mandatory dilution instructions are endorsed.

The safety of Caldolor in patients with renal impairment or history of GI ulceration will need to be assessed from the clinical data.

Amendments to the draft PI document were also recommended.

IV. Clinical findings

Introduction

Initial formulation development efforts were based on an IV formulation that was developed by Upjohn Inc. and used in clinical studies in the 1980's to 1995. That product used sodium hydroxide to solubilise ibuprofen and adjust pH, hydrochloric acid to adjust pH, glycine and sodium chloride. It had several undesirable characteristics, including a pH of approximately 8.5, a considerable amount of sodium and a lengthy processing time. The product was therefore reformulated with arginine, which allowed rapid dissolution of ibuprofen at concentrations higher than 50 mg/mL without the use of sodium and a more neutral pH of 7.2 to 7.8. The proposed products have a pH of 7.4, which is within the normal physiological range (7.2 to 7.6).

The pivotal clinical trials used the arginine-containing formulation that is proposed for registration in Australia. One supporting study (IND 32803) used the earlier Upjohn formulation.

The clinical submission documented an abbreviated clinical development program of pharmacokinetic, efficacy and safety studies.

Clinical data in the submission

The submission contained the following clinical information:

- Three pharmacokinetic (PK) studies. 2 PK studies compared the bioavailability of Caldolor (various doses and infusion durations) and US-marketed oral ibuprofen preparations. The third PK study was a substudy of one of the pivotal efficacy/safety studies in patients with fever, in which ibuprofen pharmacokinetics were determined in the first 94 patients. No comparison of Caldolor with an *Australian* registered oral ibuprofen product was provided, nor was any evidence submitted to show that the US-marketed products used in the PK studies were identical to, or bioequivalent to, an Australian-registered product.
- 5 pivotal efficacy/safety studies (2 Fever, 3 Pain).
- 1 other efficacy/safety study (Fever).
- 1 tolerability study (healthy volunteers).

- *Integrated Summary of Efficacy (Fever), Integrated Summary of Efficacy (Pain), Integrated Summary of Safety*, a summary of the literature comparing the efficacy of ibuprofen and paracetamol for the treatment of pain and fever, and a meta-analysis of the literature comparing the safety of ibuprofen and paracetamol.

Paediatric data

The submission did not include any paediatric studies conducted by the sponsor. Published reports of 3 studies of IV ibuprofen for the treatment of patent ductus arteriosus (PDA) were included in one of the Periodic Safety Update Reports (PSURs). Paediatric studies with Caldolor were underway during the evaluation period of this application The PK study was due to be reported in January 2011 and the other studies are due in early 2012.

If Caldolor is registered for the treatment of fever and pain in adults, off-label paediatric use in these indications and also in the treatment of Patent Ductus Arteriosus (PDA) is possible, but unlikely, due to the very different concentrations of ibuprofen used for the various indications and the presence of approved, specifically targeted therapies on the Australian marketplace e.g. indomethacin. No study of Caldolor for the treatment of PDA is proposed nor has the sponsor stated an intention to pursue that indication.

Good clinical practice

Compliance with Good Clinical Practice (GCP) was documented for 8 of the 9 studies in the submission. GCP compliance was not documented for one supportive efficacy/safety study in patients with fever (IND 32,803). However, that study, which was conducted in the USA and Canada, was performed in accordance with the Declaration of Helsinki and FDA/Canadian clinical trial regulations, with Institutional Ethics Committee or Institutional Review Board approval for all study sites and oversight by Steering, Executive and Data and Safety Monitoring Committees.

Despite the documented compliance with GCP, irregularities were discovered during an FDA inspection of one of the pivotal study sites. This matter is discussed further below.

Pharmacokinetics

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

Study summaries

Assay methods

Caldolor contains racemic ibuprofen, as do the oral dosage forms registered in Australia. The pharmacokinetic studies in the submission used non-stereospecific assays that measured total ibuprofen concentrations. In CPI-CL-001 and CPI-CL-004, ibuprofen concentrations in plasma were determined using a validated high-performance liquid chromatography (HPLC) assay with a lower limit of quantification (LLQ) of 0.2 µg/mL. In CPI-CL-011, ibuprofen concentrations in plasma were measured using a validated liquid chromatography-tandem mass spectrography method with LLQ of 2.0 µg/mL.

Only S(+) ibuprofen is pharmacologically active[6] and it has been shown that after oral administration of the racemate, 60-70% of R(-) ibuprofen is converted to S(+) ibuprofen

[6] Ibuprofen (Drug Evaluation). In: DRUGDEX® System (electronic version). Thomson Reuters (Healthcare) Inc., Greenwood Village, Colorado, USA. http://www.thomsonhc.com (accessed: 23 Dec 2010).

(there is no conversion of S(+) ibuprofen to R(-) ibuprofen)[7]. If the conversion of R(-) to S(+) ibuprofen were occurring presystemically (such as in the intestinal lumen or wall), then total ibuprofen concentrations would not be appropriate for comparing the pharmacokinetics of oral and IV formulations. However, a study using IV ibuprofen enantiomers has shown that the conversion of (R-) to (S+) ibuprofen occurs systemically rather than presystemically[8]. Accordingly, the use of a non-stereospecific assay is acceptable.

CPI-CL-001

CPI-CL-001 examined the pharmacokinetics and tolerability of single doses of ibuprofen 200, 400 and 800 mg administered IV (Caldolor) or orally (US- marketed ibuprofen capsules). The study enrolled 3 groups of 12 healthy adults aged 18 to 50 years, with 8 males and 4 females in each group; one group for each dose level. Subjects received the IV and oral formulations in a randomised, crossover fashion after an overnight fast, with a washout period of 7 days between doses. All doses of Caldolor were administered IV over 1 h. Initially, the undiluted 100 mg/mL solution was injected using a syringe pump and all subjects in the 200 mg dose group received Caldolor in this fashion. However, the first 3 subjects in both the 400 and 800 mg dose groups experienced administration site adverse events (AEs) such as irritation, pain and bruising. Because of this, subsequent doses of Caldolor were diluted in 500 mL (400 mg dose) or 600 mL (800 mg dose) of normal saline prior to administration. Total ibuprofen concentrations in plasma were measured in blood samples collected before and 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after the start of the IV infusion, and before and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 h after the oral dose.

All 36 subjects were included in the pharmacokinetic analysis, the results of which are summarised in Table 2, below. Table 3 shows the results of the IV versus oral bioavailability comparison.

Table 2. CPI-CL-001: Summary pharmacokinetic results (mean, CV%).

Dose (mg)	Route	AUC_{last} (µg.h/mL)	AUC_{inf} (µg.h/mL)	C_{max} µg/mL	t_{max} (h)	$t_{1/2}$ (h)
200	IV	63.6 (20.7)	65.5 (21.5)	19.3 (16.0)	1.13 (20.3)	2.34 (12.4)
	Oral	68.0 (24.8)	69.9 (25.7)	24.7 (17.1)	0.65 (25.9)	2.33 (9.6)
400	IV	109.3 (26.4)	112.5 (29.2)	39.2 (15.5)	1.05 (15.8)	2.22 (20.1)
	Oral	108.3 (22.0)	110.9 (24.2)	42.9 (11.4)	0.55 (25.6)	2.23 (19.5)
800	IV	192.8 (18.5)	198.2 (20.0)	72.6 (13.2)	1.00 (0.0)	2.44 (12.9)
	Oral	212.1 (22.5)	218.8 (25.1)	81.0 (23.2)	0.85 (60.4)	2.48 (15.6)

[7] Cheng H, Rogers JD, Demetriades JL, et al: Pharmacokinetics and bioinversion of ibuprofen enantiomers in humans. Pharmaceutical Res 1994; 11:824-830.

[8] National Heart Lung and Blood Institute. How is patent ductus arteriosus treated? http://www.nhlbi.nih.gov/health/dci/Diseases/pda/pda_treatments.html (accessed 26 April 2011).

Table 3. CPI-CL-001: Bioavailability comparison of IV and oral ibuprofen (% ratio of LS-means of log-transformed values [IV/Oral], 90%CI).

Dose (mg)	AUC_{last}	AUC_{inf}	C_{max}
200	94.3 (84.2 - 105.6)	94.5 (84.3 - 105.9)	78.2 (70.0 - 87.4)
400	100.3 (92.7 - 108.5)	100.6 (93.0 - 108.8)	90.9 (83.8 - 98.7)
800	91.3 (86.9 - 96.1)	91.2 (86.5 - 96.2)	91.1 (83.1 - 99.7)

The C_{max}, AUC_{last} and AUC_{inf} of ibuprofen increased linearly with dose after IV and oral administration. All three parameters were also proportional to the dose after oral administration but after IV administration this was true only for C_{max}. For AUC_{last} and AUC_{inf} after IV administration, the best-fit regression model was linear but included a constant in addition to the term for dose.

Systemic exposure to ibuprofen was equivalent after IV and oral administration, with the 90% confidence intervals (CIs) for AUC_{last} and AUC_{inf} falling within the standard 80-125% bioequivalence limits at each dose level. The 1 h infusion produced C_{max} values that were bioequivalent to oral administration for the 400 and 800 mg doses but lower for the 200 mg dose. The 1 h infusion period also led to a delayed the time to peak plasma concentration (t_{max}) compared to oral administration, which would presumably be accompanied by a delay in the onset of analgesia.

The 1 h infusion duration does not match the 30 minute duration used in the efficacy/safety trials or the durations of 30 or 7 minutes that are proposed in the draft PI. These shorter durations would lead to higher C_{max} values with a shorter t_{max}.

The bioavailability comparisons were with a US-marketed oral capsule rather than an Australian-registered oral preparation.

CPI-CL-004

CPI-CL-004 was a multicentre, randomised, double-blind, placebo controlled trial to evaluate the efficacy, safety and pharmacokinetics of ibuprofen injection in adult febrile patients. In brief, the study enrolled hospitalised patients with new-onset fever ≥ 101°F (38.3°C) who were randomised to receive Caldolor 100 mg, 200 mg, 400 mg or placebo (normal saline), administered IV over 30 minutes, every 4 h for 24 hs. Caldolor solution was diluted in 100 mL normal saline prior to infusion. Randomisation was stratified according to illness severity (critically or non-critically ill). Critically ill patients were defined as receiving vasopressor support for systemic hypotension and/or mechanical ventilation. Further details of the study design and population are covered later in this report.

Blood was collected from the first 98 patients enrolled in the study at 0, 0.5, 1, 2, 3 and 4 h after the first dose and 0, 0.5, 1.5, 2, 4 and 6 h after the last (sixth) dose, for the determination of total ibuprofen concentrations in plasma. Ibuprofen C_{max}, t_{max}, trough plasma concentration (C_{min}), $AUC_{0\text{-}4h}$ and the half-life ($t_{1/2}$) were determined after the first dose.

Examination of plasma concentration at 0 h (C_{0h}) and at 4 h (C_{4h}) for the last dose when compared with C_{4h} after the first dose allowed an assessment of whether steady state had been reached and the extent of drug accumulation. However, C_{max} and $AUC_{0\text{-}4h}$ were not determined after the last dose, so steady-state values for these parameters were not available. C_{min} and t_{min} were determined after the last dose but the values were irrelevant as they merely reflected the timing of the final sample 6 h after the dose (which did not correspond to the dosing interval in this study).

Summary pharmacokinetic results from CPI-CL-004, stratified according to illness severity, are shown in the following tables.

Table 4. CPI-CL-004: Summary pharmacokinetic results (mean).

Dosage (mg q4h), Illness stratum		Dose 1							
		n	AUC_{0-4h} (µg.h/mL)	AUC_{0-4h} /Dose	C_{max} (µg/mL)	t_{max} (h)	C_{min} (µg/mL)	t_{min} (h)	$t_{1/2}$ (h)
100	A: Critical	9 ‡	16.1	161	8.2	0.6	2.2	4.0	2.42
	B: Non-Critical	14 †	26.3	263	14.5	0.5	2.9	4.0	2.49
	Ratio *	-	0.61	0.61	0.57	-	0.76	-	-
200	A: Critical	9	19.6	98	11.5	0.5	2.3	3.8	2.56
	B: Non-Critical	17 §	39.5	198	22.9	0.5	4.7	3.9	1.86
	Ratio *	-	0.50	0.49	0.50	-	0.49	-	-
400	A: Critical	10 #	45.9	115	25.7	0.5	4.7	3.9	2.32
	B: Non-Critical	15 $	87.1	217	49.1	0.5	10.7	3.8	2.22
	Ratio *	-	0.53	0.53	0.52	-	0.44	-	-

*Critical/Non-critical, calculated by evaluator. ‡n=6 for $t_{1/2}$. †n=15 for C_{max} and t_{max}. ‡n=16 for $t_{1/2}$. #n=9 for $t_{1/2}$. $n=14 for $t_{1/2}$

Table 5. CPI-CL-004: Trough ibuprofen concentrations (mean).

Dosage (mg q4h), Illness stratum		n	Dose 1	Dose 6		Ratio *	
			C_{4h} (µg/mL)	C_{0h} (µg/mL)	C_{4h} (µg/mL)	$C_{0h(Dose\ 6)}$ / $C_{4h(Dose\ 1)}$	$C_{4h(Dose\ 6)}$ / $C_{4h(Dose\ 1)}$
100	Critical	9	2.2	3.8	2.6	1.7	1.2
	Non-Critical	15	2.9	4.6	4.4	1.6	1.5
200	Critical	9	3.1	4.0	2.7	1.3	0.9
	Non-Critical	17	4.8	6.4	5.2	1.3	1.1
400	Critical	10	6.8	8.1	8.2	1.2	1.2
	Non-Critical	15	11.8	14.3	11.3	1.2	1.0

*Calculated by evaluator.

Peak and trough ibuprofen concentrations and systemic exposure were markedly lower in critically ill patients than in non-critically ill patients, although the pharmacokinetics remained first order in both patient groups. The reason for the difference is not known. Importantly, the elimination half-life of ibuprofen did not differ between critically ill and

non-critically ill patients, so no adjustment to the dosing interval should be necessary. This is supported by a similar extent of drug accumulation in the two patient groups during 4 hly dosing (last two columns in Table 5).

The sponsor's *Clinical Overview* argues that the reduced systemic concentrations in the critically ill support the proposed availability of higher doses for this population (800 mg per dose with a maximum of 3200 mg daily), especially if the response to lower doses is unsatisfactory. However, subgroup analyses in the *Integrated Summary of Efficacy - Fever* (presented in greater detail below) showed that in the critically ill subgroup of CPI-CL-004 the response to Caldolor 400 mg four hly (q4h) was similar to the response to doses below 400 mg q4h; that is, there was no evidence of a dose-response or concentration-response relationship, although both dose levels were superior to placebo. This suggests that a further dose increase to above 400 mg q4h may not actually improve efficacy. In addition, there are potential safety concerns associated with the use of higher doses in patients who already have an increased risk of renal compromise due to their underlying illness, given the potential for NSAIDs to adversely affect renal function.

The mean half-lives ranging from 1.9 to 2.6 h in this study imply that steady-state should be achieved within 10 to 13 h during repeated dosing. This is supported by the concentrations measured before and 4 h after Dose 6, which were consistent with steady-state having been reached before that dose (20 h after the start of treatment).

CPI-CL-011

CPI-CL-011 examined the pharmacokinetics and tolerability of a single dose of ibuprofen 800 mg administered IV (Caldolor) or orally (US-marketed ibuprofen tablets). The study enrolled 12 healthy adults aged 18 to 50 years (9 males and 3 females). Subjects received the IV and oral formulations in a randomised, crossover fashion after an overnight fast, with a washout period of 7 days between doses. Caldolor was diluted in 192 mL normal saline (to make a total infusion volume of 200 mL) and infused over 5 to 7 minutes, as intended, in 11 subjects. The Caldolor infusion lasted 8 minutes in 1 subject due to a minor protocol violation. Blood was collected pre-dose, immediately following completion of the IV infusion, 15, 30, 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 h post-dose for the measurement of total ibuprofen concentrations in plasma. All 12 subjects were included in the pharmacokinetic analysis.

Summary pharmacokinetic results and the bioavailability comparison are shown in Table 6.

Table 6. CPI-CL-011: Summary pharmacokinetic results (mean ± SD) and bioavailability comparison.

Treatment	C_{max} (µg/mL)	t_{max} * (h)	AUC_{last} (µg.h/mL)	AUC_{inf} (µg.h/mL)	$t_{1/2}$ (h)
IV Caldolor 800 mg	120 ± 13	0.11	188 ± 37	196 ±37	2.0 ± 0.5
Oral ibuprofen tablet 800 mg	63 ± 12	1.50	189 ± 36	196 ± 36	1.9 ± 0.3
Geometric ratio of LS-means	1.94	-	1.00	1.00	-
90% CI of ratio	1.72 - 2.19	-	0.90 - 1.12	0.90 - 1.11	-

* Median

Infusion site pain was reported by 4 (33%) subjects during rapid infusion of Caldolor, although it was mild in all cases. A more comprehensive assessment of infusion pain, for example, using a visual analogue score (VAS), was not conducted and would not have been meaningful in the absence of placebo control.

Systemic exposure to ibuprofen after an 800 mg dose of Caldolor, when infused over 5-7 minutes, was equivalent to exposure after a single US-marketed 800 mg tablet, administered orally. The t_{max} of ibuprofen was much shorter after rapid IV administration than after oral dosing or IV administration over 30 minutes (in CPI-CL-004) or 1 h (in CPI-CL-001). This reduced t_{max} would probably translate into a faster onset of analgesia after the first dose, and after subsequent doses if they are not given until pain recurs. This would be clinically useful in a postoperative or other acute pain setting.

However, the C_{max} of ibuprofen after rapid IV infusion was approximately doubled compared to oral administration of the same dose. As noted in the sponsor's *Clinical Overview*, the clinical implication of these higher peak concentrations is not known. Although there was no evidence of systemic toxicity in this small study, the potential for an adverse effect of high peak concentrations in a patient population cannot be excluded. The main clinical studies used a 30 minute infusion which provided reasonably rapid onset of analgesia with lower peak ibuprofen concentrations (similar to those seen with to oral dosing - see Table 7, below). In view of this consideration and the paucity of tolerability data for the proposed rapid infusion, approval of the rapid infusion is not recommended.

Table 7. Mean ibuprofen C_{max} (µg/mL) after a single dose of IV Caldolor or US-marketed oral ibuprofen preparations, according to infusion duration and study population.

Dose (mg)	IV infusion (Caldolor)				Oral	
	Healthy, 60 min	Critically ill, 30 min	Non-critically ill, 30 min	Healthy, 5-7 min	Healthy	Healthy
	CPI-CL -001	CPI-CL -004	CPI-CL -004	CPI-CL -011	CPI-CL -001	CPI-CL -011
100	-	8.2	14.5	-	-	-
200	19.3	11.5	22.9	-	24.7	-
400	39.2	25.7	49.1	-	42.9	-
800	72.6	-	-	120	81.0	63

Summary of pharmacokinetics

Systemic exposure to ibuprofen after IV administration of Caldolor was equivalent to systemic exposure after oral administration of a matching dose of US-marketed ibuprofen capsules and tablets. However, no comparison to an Australian-registered ibuprofen product was submitted.

Ibuprofen C_{max} and AUC were less than proportional to the dose after administration of IV and oral ibuprofen.

When Caldolor was infused over a period of 30 to 60 minutes, peak ibuprofen concentrations were roughly comparable to those seen when the same dose was given orally, although this is based on cross-study comparisons to US-marketed oral products.

With the 60 minute infusion, t_{max} was delayed compared to oral dosing. Rapid infusion of Caldolor over 5 to 7 minutes led to a shorter t_{max} compared to a US-marketed oral tablet but a doubling of peak ibuprofen concentrations with potential adverse safety implications. Rapid infusion was also associated with a high incidence of infusion site pain, as was infusion of undiluted Caldolor.

During repeated administration of Caldolor q4h, systemic exposure to ibuprofen and peak ibuprofen concentrations were reduced in critically ill patients compared to non-critically ill patients but $t_{1/2}$ was unchanged.

Evaluator's overall conclusions on pharmacokinetics

An IV administered product such as Caldolor is 100% bioavailable, so it cannot be *less* bioavailable than Australian-registered oral ibuprofen products. Caldolor was also shown to be bioequivalent in terms of AUC to two different US-registered products. These US-registered oral products and Caldolor could potentially be *more* bioavailable than Australian-registered oral ibuprofen products but a clinically important AUC difference is unlikely given the following considerations:

The Australian PI for Brufen (ibuprofen, Abbott) states that it is "well absorbed after oral administration".

Ibuprofen is a weak acid with poor solubility at low pH (in the stomach) and high solubility at neutral pH (in the small intestine). These physicochemical properties of ibuprofen lead to an expectation that an immediate-release oral preparation would be fully absorbed in the small intestine. Since there is no significant first pass metabolism (as evidenced by the full bioavailability of the US-registered oral products), full absorption would in turn lead to full bioavailability. Consistent with this, there is anecdotal regulatory experience that different immediate release oral ibuprofen preparations proposed for registration do not differ in relation to AUC[9].

The situation is more complicated in regard to C_{max}. Experience has shown that proposed immediate-release oral formulations of ibuprofen often differ in their rate of absorption, leading to differences in C_{max} [10]. This means that the C_{max} similarities between a 30 minute infusion of Caldolor and the same dose of a US-registered oral ibuprofen product (which are in any case based on cross-study comparisons) do not permit a conclusion that Caldolor and Australian-registered ibuprofen would also be similar with respect to C_{max}. On the other hand, the physicochemical properties of ibuprofen mean that when ibuprofen is given orally, it cannot be absorbed until it passes into the small intestine. Consistent with this, the Australian PI for Brufen (ibuprofen, Abbot) reports a t_{max} of 45 minutes when given to fasted subjects (1.5 to 3 h when given after food). Since the AUC of Caldolor cannot be lower than that of Brufen and its t_{max} when given as a 30 minute infusion is *shorter* than that of Brufen, it is reasonable to conclude that the ibuprofen C_{max} when Caldolor is given as a 30 minute infusion as proposed in the PI should not be lower than that of the same dose of oral Brufen (although it could be higher).

It would have been preferable if the sponsor had performed a direct bioavailability comparison of Caldolor with an Australian-registered ibuprofen product. Nevertheless, the pharmacokinetic reasoning above indicates that the efficacy of Caldolor in the indications for which oral ibuprofen is approved in Australia (which includes the treatment of fever

[9] Langguth P, Bolger M, Tubic M. Biowaiver for BCS Class II compounds? Application of Simulation for BCS Classification. http://www.aapspharmaceutica.com/meetings/files/90/29Langguth.pdf. Accessed 19 April 2011.

[10] Langguth P, Bolger M, Tubic M. Biowaiver for BCS Class II compounds? Application of Simulationfor BCS Classification. http://www.aapspharmaceutica.com/meetings/files/90/29Langguth.pdf. Accessed19 April 2011.

and various forms of pain) should be at least as good as the efficacy of the oral preparations.

Extrapolation of the safety of Caldolor on PK grounds is more problematic. Firstly, the proposed maximum daily dose of Caldolor is higher than the dose that is approved in Australia for oral ibuprofen. Secondly, the PK data still leave open the possibility that the C_{max} of Caldolor might be *higher* than that of Australian-registered oral ibuprofen products, and the risk of some adverse effects could theoretically be related to peak ibuprofen concentrations and not just AUC. These considerations mean that one cannot infer the full safety profile of Caldolor on the basis of experience with Australian-registered oral ibuprofen products. One might, of course, infer a safety profile on the basis of experience with US-registered oral ibuprofen products (as reflected in the FDA-approved PIs for those products). This, however, is not usually regarded as an acceptable approach because the TGA does not have access to the original data and it is tantamount to accepting a product for registration in Australia purely because it has been approved in the USA.

The FDA noted that there is little experience with the use of oral ibuprofen in critically ill patients - a clinical situation in which an IV preparation such as Caldolor is likely to be used. Also, oral ibuprofen preparations are not specifically approved in Australia or the USA for perioperative pain management, another use for which Caldolor is likely to be promoted, given the studies that were conducted by the sponsor. The FDA was unwilling to rely solely on bioequivalence data and insisted on clinical studies of Caldolor in these situations, even though the issues mentioned above regarding the comparator in the bioequivalence studies and the proposed maximum dose were not relevant to the FDA. Those clinical studies have also been provided to the TGA.

While insufficient to infer that Caldor is safe for the proposed indications, the PK data, in association with the tolerability study CPI-CL-006 (see *Dosage Selection in Pivotal Studies* below) are sufficient to justify the choice of doses and the use of a 30 minute infusion in the pivotal studies. They also showed that Caldolor injection needs to be diluted prior to infusion to avoid an unacceptable incidence of infusion site pain.

The PK data indicate that the proposed alternative of rapid infusion of Caldolor over 5 to 7 minutes is not acceptable, due to the resultant doubling of C_{max} with untested safety consequences. Rapid infusion was also associated with a high incidence of infusion tie pain, albeit mild.

The PK findings in CPI-CL-004 indicate that no change to the Caldolor dose *interval* is required in critically ill patients. Although the PK data also show that ibuprofen concentrations are approximately halved in critically ill patients for a given dose of Caldolor, the lack of a positive dose response in critically ill patients and potential safety concerns (most notably about adverse renal effects in patients with underlying fluid balance abnormalities and compromised renal perfusion) argue against routinely increasing the dose of Caldolor in patients who are critically ill.

Pharmacodynamics

The current submission did not include any clinical studies of the pharmacological effects of ibuprofen but these are well known from studies of oral preparations and need not be reiterated here.

Dose- or concentration-response relationship

In the current submission, plasma ibuprofen concentrations were measured in a large majority of patients in the fever study CPI-CL-004 but no formal analysis of the relationship between ibuprofen plasma concentration and temperature reduction was

performed. In the CPI-CL-004 study report, efficacy was analysed separately for the three dosage levels (100, 200 and 400 mg q4h), which would normally be sufficient data to describe a dose-response relationship for temperature reduction. However, the same study showed that for a given Caldolor dose, plasma concentrations were halved in critically ill patients compared to non-critically ill patients. The analysis of efficacy according to dose in the main study report combined data from both patient groups at each dose level. In view of the pharmacokinetic differences, such combined data are not suitable for assessing a dose-response relationship. Furthermore, secondary analyses in the *Integrated Summary of Efficacy - Fever* showed that not only was the placebo response markedly lower in critically ill compared to non-critically ill patients but also that while there was evidence of a positive dose-response relationship in non-critically ill patients, the response in critically ill patients did not change with dose. These data will be covered in more detail under the discussion of efficacy in section 0 of this evaluation.

A positive dose-response relationship was seen when Caldolor 400 mg or 800 mg every 6 h (q6h) was given to non-critically ill patients as an adjunct to morphine for post-operative analgesia. This is covered in detail in the efficacy evaluation (see below).

Dosage selection for the pivotal studies

Dosage selection in the pivotal studies was based on the pharmacokinetic finding that systemic exposure to ibuprofen was the same for a given Caldolor dose as a matching oral ibuprofen dose. Accordingly, the pivotal studies used the range of doses that have previously been shown to be effective when oral ibuprofen is used for the treatment of fever and pain.

As previously described, Caldolor was originally administered over 1 h in undiluted form but this was soon found to cause an unacceptable incidence of injection site AEs. Dilution in relatively large volumes of normal saline (400 mL for the 400 mg dose and 500 mL for the 800 mg dose) reduced the injection site AEs. However, infusion over 1 h led to C_{max} values that were a little lower than desired. Accordingly, the infusion duration was reduced to 30 minutes.

To avoid the infusion of unnecessarily large fluid volumes over this shorter period, the tolerability of dilution in 100 mL normal saline was assessed in a small study, CPI-CL-003, described below.

CPI-CL-003

CPI-CL-003 was a randomised, placebo-controlled cross-over study that enrolled 14 healthy subjects, of whom 12 (11 males; 1 female; age 18-39 years) received study treatment. Each subject received 3 doses of Caldolor 400 mg, diluted in 100 mL normal saline and infused over 30 minutes at 4 h intervals. In the other treatment period, subjects received 3 doses of 100 mL normal saline infused over 30 minutes at 4 h intervals. Subjects self-assessed infusion site pain during and after each infusion using a 100 mm visual analogue scale (VAS). Infusion site bruising, swelling and erythema were also assessed by investigators. The principle findings were as follows:

Pain was reported during 33% of the Caldolor infusions and 14% of the placebo infusions. The mean pain score during the infusion was a little higher with Caldolor than placebo but very low in both groups (3.7 versus 1.1 mm) and the difference was not statistically significant. One patient reported moderate “pressure” (VAS 50 mm) during the third dose of Caldolor, leading to discontinuation of the infusion.

The mean score for infusion site pain from assessments performed at the beginning and end of each infusion and 1 and 12 h after the last infusion was a little lower with Caldolor than placebo and again very low in both groups (0.4 versus 0.8 mm). The difference was

not statistically significant. The maximum VAS for site pain in these assessments was 15 mm for Caldolor and 10 mm for placebo.

No injection site swelling or bruising were seen in any subject.

Injection site erythema was seen in 1 subject after Caldolor infusion and 1 subject after placebo infusion. In both cases the erythema was limited in area, arose on the day after infusion and was considered to be related to IV catheterisation.

On the basis of these findings, it was concluded that Caldolor doses up to 400 mg could be safely diluted in 100 mL normal saline and infused over 30 minutes and this infusion protocol was used in the pivotal fever studies. The pivotal analgesia studies used doses of 400 or 800 mg Caldolor, diluted in 200 to 250 mL of normal saline (depending on the volume of the standard normal saline bags at each investigation site) and infused over 30 minutes. The pivotal studies did not systematically examine the severity of injection site pain associated with such Caldolor infusions and some infusions were given via central rather than peripheral catheters. However, the percentage of Caldolor recipients who reported injection site pain as an adverse event was quite low (about 3%) and similar to the percentage for placebo groups (2% - see below).

As previously described, a later study (CPI-CL-007) assessed the pharmacokinetics and tolerability of rapid infusion of a single dose of Caldolor 800 mg diluted in 200 mL normal saline over 5 to 7 minutes. The percentage of Caldolor infusions accompanied by infusion site pain was the same as in CPI-CL-003 but the assessment of tolerability was limited and insufficient to support approval of the rapid infusion. In addition, the rapid infusion led to a doubling of ibuprofen C_{max} with untested safety consequences.

Efficacy

Reduction of fever in adults

Pivotal efficacy studies - fever

The submission included 2 pivotal studies for the proposed indication of reduction of fever in adults. These were CPI-CL-004 and CPI-CL-006. Both were randomised, double-blind placebo-controlled studies in hospitalised febrile patients but differed in design to an extent that requires them to be reported separately rather than grouped together.

CPI-CL-004

Study design, objectives, locations and dates

CPI-CL-004 was a multi-centre, randomised, double-blind, parallel group, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of Caldolor injection in hospitalised adult febrile patients. The study was conducted in the USA, Australia and Thailand between June 2002 and August 2005.

Inclusion and exclusion criteria

The study enrolled hospitalised adults with acute fever, defined as temperature ≥101.0°F or 38.3°C that had begun within the 7 days prior to screening. Randomised patients were to be febrile within 15 minutes prior to the first dose of study medication. An overall study requirement was that at least 33% of the enrolled patients were to be critically ill (requiring mechanical ventilation for respiratory failure, pressor support for hypotension, or both), and at least 33% were to be non-critically ill.

Prospective patients were excluded if they had received an antipyretic drug within the last 4 hs, had a contraindication or major precaution to NSAID use (such as known NSAID allergy, platelet abnormalities, bleeding risk, renal impairment), or whose fever was due to

certain causes for which NSAID treatment is not expected to be useful (neurogenic fever, blood or drug reaction).

The entry criteria were sufficiently broad to potentially provide a representative study population. In practice, this was offset (from an Australian clinical practice perspective) by a high proportion of patients with malaria (31%), all of whom were enrolled at the Thai centre. This large contingent of patients with malaria caused difficulties in the interpretation of the safety data, as discussed later in this report. However, although malaria is uncommon in Australia, it is one of the standard models for testing the efficacy of antipyretic treatments and the efficacy results are generalised to the treatment of fever due to most other causes (notable exceptions would be neurogenic fever and malignant hyperthermia because of their particular pathogenesis).

The main exclusion criteria were appropriately based on the standard precautions and contraindications for ibuprofen and other NSAIDs.

The requirement for a mix of critically ill and non-critically ill patients enabled the investigation of pharmacokinetic and efficacy differences between these two populations, although the small number of critically ill patients limited the investigation of safety issues in that subgroup.

Study treatments

Study participants were randomised to receive one of four study treatments IV every 4 h for 6 doses:

- Caldolor 100 mg in 100 mL normal saline;
- Caldolor 200 mg in 100 mL normal saline;
- Caldolor 400 mg in 100 mL normal saline;
- Placebo (100 mL normal saline).

All study treatments were to be infused over 30 minutes.

Because the study employed a placebo arm, rescue treatment was available to patients who met treatment failure criteria. Rescue treatment included paracetamol, any other antipyretic medication excluding aspirin or NSAIDs (which were disallowed) and physical measures such as cold packs, cooling blankets. A treatment failure was defined as a patient who had a temperature of 103.0°F (39.4°C) or greater during the Treatment Period, a minimum of 2 h after a dose of study medication.

The 200 mg and 400 mg doses of Caldolor were based on the US-recommended oral dose of ibuprofen for the treatment of fever (200 to 400 mg every 4 to 6 hs) and previously-discussed PK data. The lower (100 mg) Caldolor dose was included to expand the dose range studied in an attempt to define a minimum effective dose. A placebo control was used because, at the time of the study, no IV agent had been approved for the treatment of fever. This remains the case in the USA, where CPI-CL-0004 was designed. IV paracetamol (Perfalgan) has been registered in Australia since 2004 for the treatment of pain and fever.

Efficacy variables and outcomes

The only efficacy variable was body temperature. The preferred method of temperature measurement was tympanic. Oral temperature was to be used if a tympanic temperature could not be obtained. The method of temperature measurement used immediately before randomisation was to be used for all subsequent temperature measurements during the treatment period.

The primary efficacy outcome was the percentage of patients in the Caldolor 400 mg group with fever reduction, defined as a temperature "<101.0°F (38.3°C)", 4 h after

administration of the first dose of study medication, compared to the corresponding percentage in the placebo group.

There are no regulatory guidelines relating to efficacy outcomes in studies of antipyretic medications. Published clinical studies have investigated a range of outcomes such as:

- the percentage of patients whose temperature decreased below a set threshold over a predefined time period;
- the percentage of patients whose temperature decreased by a set amount over a predefined time period;
- the mean, maximum or minimum temperature over a predefined time period;
- the rate of temperature change during a predefined time period;
- cumulative measures of effect on body temperature such as the area under the temperature or change-in-temperature versus time curve over a predefined time period or the weighted sum of temperature measurements at different time points.

Indirect efficacy measures such as the time to first use of rescue treatment have also been studied. Depending on the focus of the trial, the time period over which efficacy is assessed may be a single dose interval or may span several doses. For example, the PI for IV paracetamol (Perfalgan) states that in the pivotal antipyretic study supporting the registration of that product, the primary efficacy outcome was the mean change in body temperature at several time points from 0.5 to 6 h after a single dose, compared to placebo. However, that study also had a range of secondary efficacy outcomes encompassing most of the types described above.

The thresholds for declaring a patient to be febrile and for subsequently declaring fever to have responded to treatment have also varied across studies. The temperature for declaring a therapeutic response is often lower than the temperature required for the initial diagnosis of fever but it is not uncommon for the values to be the same in any one trial, as was the case in CPI-CL-004. *Harrison's Principles of Internal Medicine* defines a fever as an oral temperature >37.2°C (>98.9°F) in the morning or >37.7°C (>99.9°F) in the afternoon, these being the upper 99th percentiles for normal body temperature at the respective times of day[11]. The same text notes that rectal temperature (core temperature) is generally about 0.4°C higher than oral temperature, and that for most fevers, body temperature increases by 1°-2°C. Given these factors, the core temperature of 101°F (about 38.3°C) that was used for diagnosing fever in CPI-CL-004 was not particularly stringent. For comparison, the PI for Perfalgan states that in the pivotal antipyretic study, which was conducted in children, the minimum temperature for diagnosing fever was 38.5°C.

Similarly, the use of the same temperature for diagnosing a fever and declaring a treatment response meant that a response would have been relatively easy to obtain, particularly when one realises that patients were also receiving treatment (such as antibiotics, antimalarials) for the underlying cause of the fever. This was reflected in a substantial placebo response, particularly over the full 24 h treatment period. For comparison, in the pivotal study for Perfalgan the minimum temperature for diagnosing fever was 38.5°C but the temperature for declaring a treatment response (one of the secondary endpoints) was 38.0°C. This shortcoming of CPI-CL-004 was to some extent addressed in the additional analyses requested by the FDA, which examined the time to reach a temperature <100°F and <99°F.

[11] Dinarello CA, Porat R. Fever and Hyperthermia. In: Fauci AS, Longo DL, Kasper DL et al, eds. Harrison's Principles of Internal Medicine 17th Edition. (via STAT!Ref Online Electronic Medical Library. http://online.statref.com/document.aspx?fxid=55&docid=131).

Despite these issues, the selected criteria were nevertheless sufficient to demonstrate a statistically significant difference between Caldolor and placebo, and as previously noted the clinical relevance of even a large temperature decrease, in terms of patient outcomes, is unclear. An exception would be in children, where temperature reduction also reduces the risk of a febrile convulsion but that patient group is not relevant to the proposed use of Caldolor, which is restricted to adults.

In this multi-national study, temperatures were measured and recorded in either °F or °C, according to conventional practice in each country. The protocol defined the temperature threshold for achieving fever reduction as "101.0°F (38.3°C)" but these two values are not quite the same (101.0°F actually converts to 38.333333…°C). The definition of a treatment failure was also ambiguously expressed in the protocol as "103.0°F (39.4°C)" (103°F actually converts to 39.444444…°C). When the data from different countries were combined for analysis, slightly different results were obtained for some outcomes, depending on whether the data were first converted to °F and then compared to the °F threshold, or converted to °C and then compared to the °C threshold. However the two methods produced identical results for the primary outcome and only minor variations in the main secondary analysis of the percentage of patients in the Caldolor 100 mg and 200 mg groups whose fever was reduced 4 h after the first dose. The impact of the choice of method on other temperature outcomes was not reported but would presumably also be minor.

Sample size

Data from a published study of IV ibuprofen in sepsis patients were used to provide information about treatment differences in patients treated with 800 mg IV ibuprofen or placebo. At 4 h after administration of the first dose, 78.2% of the patients who received IV ibuprofen and 41.8% of the patients who received placebo had temperatures below 101.0°F (38.3°C). On the basis of these data, a sample size of 30 patients per treatment group in the Intent to Treat (ITT) analysis was calculated to provide 80% power, at the significance level of α=0.05, to detect this same treatment difference (approximately 37%).

Randomisation and blinding methods

Patients who met all the inclusion and exclusion criteria during the Screening/Baseline Period were randomised to one of the four study treatments in a 1:1:1:1 ratio. Randomisation was by site and was stratified on the basis of the severity of the patient's condition (critically ill or non-critically ill). Opaque randomisation envelopes that had been centrally prepared and provided to each site were opened in sequential order by study pharmacists who thus became unblinded to treatment allocation. For the active treatment arms, the pharmacists then added the required dose of Caldolor to a 100 mL bag of normal saline. Patients in the placebo group received a 100 mL bag of normal saline with no additive but pharmacists were instructed to puncture the additive port to maintain the double-blind for investigators and patients, who were not informed which treatment had been allocated.

The randomisation and blinding methods appear adequate. Although the infusion bags were transparent, Caldolor injection is described as "colourless to slightly yellow" and any colour would probably not have been discernable after dilution. The small volume difference between the four study treatments is not likely to have been evident to the investigators or patients. Dilution of Caldolor in 100 mL of normal saline and infusion over 30 minutes led to a low incidence of injection site AEs that was similar to the incidence in the placebo group and that should not have acted as a source of unblinding.

Analysis populations

The Safety Analysis Population (SAP) comprised all randomised patients who received at least one dose of study medication.

The Intention-To-Treat (ITT) population included all patients from the safety population who had a baseline assessment and at least one post-baseline evaluation of the primary endpoint.

The Efficacy-Evaluable Population (EEP) at Hour 4 included all patients from the ITT population who had not received any excluded concomitant medication within the 4 h prior to first administration. The EEP at Hour 24 included all patients who had received at least 5 doses of study medication with no excluded concomitant medication(s) within the 24-h treatment period.

Statistical tests

All statistical tests were two-sided, with p-values less than 0.05 for treatment differences and less than 0.10 for interaction effects considered significant.

The principle analyses were performed in the ITT population and supportive analyses were performed in the EEP. These efficacy analyses were to be performed without regard to illness severity stratum (critically ill or not critically ill at the time of randomisation) but the protocol also provided for optional analyses to be performed separately on each illness stratum. These were not available in the main study report but were provided in the *Integrated Summary of Efficacy* (ISE). Additional analyses requested by the FDA were also included in the submission.

Missing values were imputed using the last-observation-carried-forward (LOCF) method. For patients declared as treatment failures and for patients who received corticosteroids or rescue treatment, temperature measurements subsequent to treatment with any corticosteroid or rescue treatment were substituted with the mean of the treatment group temperature for that corresponding time point. Linear interpolation was used to estimate the time to afebrility when a patient's temperature was above 101.0°F at one time point and below 101.0°F at the next time point.

The use of a critical p-value of 0.05 for the between-treatment comparison of the primary efficacy outcome is acceptable. Although there were 3 Caldolor dose groups (and thus 3 potential comparisons with placebo) multiplicity was avoided by using only one of these (the 400 mg versus placebo comparison) as the primary outcome. As discussed later, however, this approach has implications for the sponsor's proposal that the 200 mg dose should also be approved.

Participant flow

The report did not state the number of prospective participants who were screened. A total of 123 patients were randomised and progressed as follows:

- SAP: 120 patients received study medication and were included in the SAP. The 3 patients who did not receive study medication were discontinued prior to dosing due to poor venous access (n=1) or temperature drop to <101.0°F before the first dose could be given (n=2).
- ITT: All 120 patients in the SAP were included in the ITT population.
- EEP: The EEP at 4 h included 119 patients and excluded 1 placebo recipient who had received rescue medication (paracetamol) due to treatment failure. The EEP at 24 h included 107 patients and excluded 13 patients: 1 Caldolor 400 mg and 3 placebo recipients who had received rescue treatment due to treatment failure; 3 Caldolor 100 mg and 3 placebo recipients who received excluded concomitant medications but were not treatment failures; 1 Caldolor 100 mg, 1 Caldolor 40 mg and 1 placebo recipient

who received <5 doses of study medication, having discontinued treatment due to an AE or as a precaution to prevent an AE.

- A total of 109 patients completed the study: 108 of these received all 6 doses of study medication and 1 patient missed the third dose of study medication (Caldolor 400 mg) due to a nursing error.

Table 8 summarises the disposition of patients according to treatment group and analysis population, with a further breakdown according to illness severity stratum for the ITT population.

Table 8. CPI-CL-004: Patient disposition.

Population	Placebo	Caldolor			TOTAL
		100 mg	200 mg	400 mg	
Screened	nr	nr	nr	nr	nr
Randomised	nr	nr	nr	nr	123
SAP	28	31	30	31	120
ITT	28	31	30	31	120
Critical	13 (46%)	14 (45%)	12 (40%)	14 (45%)	53 (44%)
Non-critical	15 (54%)	17 (55%)	18 (60%)	17 (55%)	67 (56%)
EEP - 4 hs	27	31	30	31	119
EEP - 24 hs	21	27	30	29	107
Completed	23	27	30	29	109

Amongst the ITT population, 78 patients were enrolled at US centres, 40 in Thailand, and 2 in Australia.

A total of 29 patients in the ITT population should by protocol have been excluded from study participation: 21 required the use of potentially nephrotoxic antibiotics at study entry; 3 had received corticosteroids at baseline and during the treatment period; 1 was found to have been allergic to aspirin (not known until after dosing with study drug); 1 did not have a documented pregnancy test; 1 received antipyretic treatment within the 8 h prior to the first dose of study medication (an exclusion criterion that was later reduced to 4 h by a protocol amendment and under which there would not have been a deviation); 1 was found to have a brain injury secondary to pre-baseline trauma (not identified until Study Day 2) and 1 was only 17 years of age. Four patients were found to have been randomised to the wrong illness stratum but all analyses were performed on the basis of the corrected stratum.

A total of 10 patients continued study treatment despite receiving rescue treatment during the study period and there were treatment administration errors in 4 patients (3 timing errors and 1 missed dose).

These protocol deviations should not have materially affected the assessment of efficacy but the use of potentially nephrotoxic antibiotics and use of rescue medication may have impacted on the safety assessment. The use of rescue treatment during the study would

not have affected the efficacy assessment because of the statistical methods for handling temperature measurements after the use of rescue medication.

Baseline data

The four treatment groups in the ITT population were similar in respect of their baseline characteristics. Overall, about half of the patients (n=58) were Caucasian and one-third (n=40) were Asian; 44% were critically ill and 56% were not. The mean age was 37.8 years (range 17-89). Mean baseline temperatures were 38.9°C, 39.1°C, 39.1°C and 39.2°C and in the placebo, Caldolor 100 mg, 200 mg, and 400 mg groups, respectively.

Two notable features of the ITT population were the high proportion of patients with malaria (31%) compared to the patient population that is likely to receive Caldolor if it is registered in Australia and a high number of males compared to females (88 versus 32). The patients with malaria all came from the Thai study centre. As previously noted, malaria is one of the standard models for testing the efficacy of antipyretic treatments and the inclusion of patients with malaria does not adversely affect the generalisability of the efficacy results. The reason for the predominance of males in the study is not clear and was not explored in the study report but the gender imbalance was consistent across the 4 treatment groups and should not invalidate the efficacy results.

Results for the primary efficacy outcome

At 4 hs, in the ITT population, 24 of 31 (77%) patients in the Caldolor 400 mg group, compared to 9 of 28 (32%) in the Placebo group had a temperature <101.0°F (p=0.0005). The proportions were similar in the EEP (77% versus 30%, p=0.0003).

Caldolor 400 mg was superior to placebo in respect of the primary efficacy outcome.

Results for other efficacy outcomes

The results for other efficacy outcomes in the ITT population are summarised in Table 9. Randomisation in CPI-CL-004 was stratified according to severity of illness, and efficacy results for the critically ill and non-critically ill strata are summarised in Table 10. Mean temperatures over time in the ITT population are shown in Figure 2.

Table 9. CPI-CL-004: Efficacy results. ITT population. Table continued across 2 pages.

	Placebo N=28	Caldolor 100 mg N=31	Caldolor 200 mg N=30	Caldolor 200 mg N=30
Temp <101°F at 4 h *n (%)* *CMH p-value*	9 (32%)	**20 (65%)** **p=0.0138**	**22 (73%)** **p=0.0018**	**(Primary)** **24 (77%)** **p=0.0005**
Temp <38.3°C at 4 h *n (%)* *CMH p-value*	9 (32%)	**19 (61%)** **p=0.0264**	**21 (70%)** **p=0.0043**	**(Primary)** **24 (77%)** **p=0.0005**
Treatment failures at 24 h *n (%)* *CMH p-value*	9 (32%)	8 (26%) p=0.587	4 (13%) p=0.305	**4 (13%)** **p=0.041**
Time to treatment failure (h) § *mean ± SE* *log-rank p-value*	5.70 ± 1.97	7.39 ± 1.39 p=0.7544	10.29 ± 3.25 p=0.2221	10.75 ± 2.75 0.3899

	Placebo N=28	Caldolor 100 mg N=31	Caldolor 200 mg N=30	Caldolor 200 mg N=30
Time to afebrility (temp <101°F) (h) § *mean ± SE* *log-rank p-value*	8.47 ± 1.61	3.67 ± 1.00 p=0.0187	4.40 ± 1.34 p=0.0476	3.61 ± 1.06 p=0.0137
Time to temp <100°F in the first 24 hs) (h) † *median* *log-rank p-value*	13.24	**4.67** **p=0.0232**	**2.75** **p=0.0295**	**3.63** **0.0101**
Time to temp <99°F in the first 24 hs) (h) † *median* *log-rank p-value*	17.17	17.55 p=0.8134	8.11 0.2444	8.18 0.0610
Temp. decrease at 4 h (°C) ‡ *mean ± SD* *mean treatment - placebo diff.* *(95% CI for mean trt - plac diff.)*	0.31 ± 1.02	**1.04 ± 0.73** **0.72** **(0.19, 1.26)**	**1.14 ± 0.82** **0.83** **(0.29, 1.37)**	**1.47 ± 0.88** **1.16** **(0.62, 1.69)**
Temp. decrease at 24 h (°C) ‡ *mean ± SD* *mean treatment - placebo diff.* *(95% CI for mean trt - plac diff.)*	1.15 ± 1.32	1.72 ± 1.11 0.57 (-0.14, 1.28)	1.74 ± 1.04 0.59 (-0.12, 1.31)	**1.93 ± 1.11** **0.78** **(0.07, 1.49)**
Maximum temperature decrease during 0-4 h (°C) ‡ *mean ± SD* *mean treatment - placebo diff.* *(95% CI for mean trt - plac diff.)*	0.68 ± 0.76	**1.31 ± 0.80** **0.62** **(0.11, 1.13)**	**1.38 ± 0.79** **0.70** **(0.19, 1.21)**	**1.60 ± 0.91** **0.92** **(0.41, 1.43)**
Maximum temperature decrease during 0-24 h (°C) ‡ *mean ± SD* *mean treatment - placebo diff.* *(95% CI for mean trt - plac diff.)*	1.76 ± 1.12	2.33 ± 1.06 0.44 (-0.25, 1.13)	2.20 ± 1.06 0.57 (-0.12, 1.25)	**2.55 ± 1.18** **0.78** **(0.10, 1.47)**
AUC-T_{0-4} (°C×h) ‡ *mean ± SD* *mean treatment - placebo diff.* *(95% CI for mean trt - plac diff.)*	6.86 ± 2.45	**5.31 ± 2.41** **-1.54** **(-0.04, -3.04)**	**5.04 ± 2.59** **-1.82** **(-0.30, -3.33)**	**4.81 ± 2.25** **-2.05** **(-0.55, -3.55)**
AUC-T_{0-24} (°C×h) ‡ *mean ± SD* *mean treatment - placebo diff.* *(95% CI for mean trt - plac diff.)*	30.52 ± 13.47	**22.03 ± 12.83** **-8.50** **(-0.46, -16.53)**	**18.60 ± 14.77** **-11.92** **(-3.82, -20.02)**	**14.43 ± 10.56** **-16.10** **(-8.06, -24.13)**

P-values are for pairwise comparisons with placebo. Results with p<0.05 are shown in bold. The primary efficacy outcome is shown in red. § The reported means do not account correctly for patients who were censored (that is, who remained febrile at the last observation in the 24 h treatment period). However, the p-values are based on the log-rank test which accounts for censoring, and are valid. † FDA-requested analysis. ‡ Results for these temperature outcomes were provided in both °C (or °C×h) and °F (or °F×h). The results in °C (or °C×h) are shown here, reflecting the units that are used in Australia.

Table 10. CPI-CL-004: Efficacy results according to illness severity stratum. ITT population. Table continued across 2 pages.

	Illness stratum	**Placebo**	**Caldolor 100 mg**	**Caldolor 200 mg**	**Caldolor 400 mg**
	Critical	*N=13*	*N=14*	*N=12*	*N=14*
	Non-critical	*N=15*	*N=17*	*N=18*	*N=17*
Temp <101°F at 4 h (From study report) *n (%); CMH p-value*	Critical	1 (8%)	**10 (71%)** **p=0.0010**	**6 (50%)** **p=0.0211**	**8 (57%)** **p=0.0075**
	Non-critical	8 (53%)	10 (59%) p=0.7585	**16 (89%)** **p=0.0245**	**16 (94%)** **p=0.0089**
Temp <38.3°C at 4 h (From study report) *n (%) CMH p-value*	Critical	1 (8%)	**9 (64%)** **p=0.0028**	**6 (50%)** **p=0.0211**	**8 (57%)** **p=0.0075**
	Non-critical	8 (53%)	10 (59%) p=0.7585	15 (83%) p=0.0660	**16 (94%)** **p=0.0089**
Time to afebrility (h) (From ISE) † *mean ± SD;* *log-rank p-value* *hazard ratio*	Critical	8.4 ± 1.76	5.7 ± 1.62 p=0.059 HR = 2.08		6.0 ± 1.91 p=0.117 HR = 1.40
	Non-critical	6.3 ± 1.77	2.7 ± 0.68 p=0.144 HR = 1.59		**1.3 ± 0.30** **p=0.010** **HR = 1.70**
Temp. decrease at 4 h (°C) (From ISE) †‡ *mean ± SD* *median treatment - placebo diff.* *(95% CI for median trt - plac diff.)*	Critical	-0.1 ± 0.91	**0.7 ± 0.59** **0.7** **(0.3, 1.3)**		**0.8 ± 0.77** **0.8** **(0.3, 1.6)**
	Non-critical	0.6 ± 1.02	**1.4 ± 0.76** **0.7** **(0.1, 1.3)**		**2.0 ± 0.59** **1.3** **(0.7, 2.0)**
Temp. decrease at 24 h (°C) (From ISE) †‡ *mean ± SD* *median treatment - placebo diff.* *(95% CI for median trt - plac diff.)*	Critical	0.7 ± 1.23	1.1 ± 0.84 0.6 (0.0, 1.1)		**1.3 ± 0.60** **0.9** **(0.1, 1.5)**
	Non-critical	1.5 ± 1.30	2.2 ± 0.96 0.7 (-0.2, 1.4)		2.4 ± 1.21 -0.9 (-0.2, 1.17)

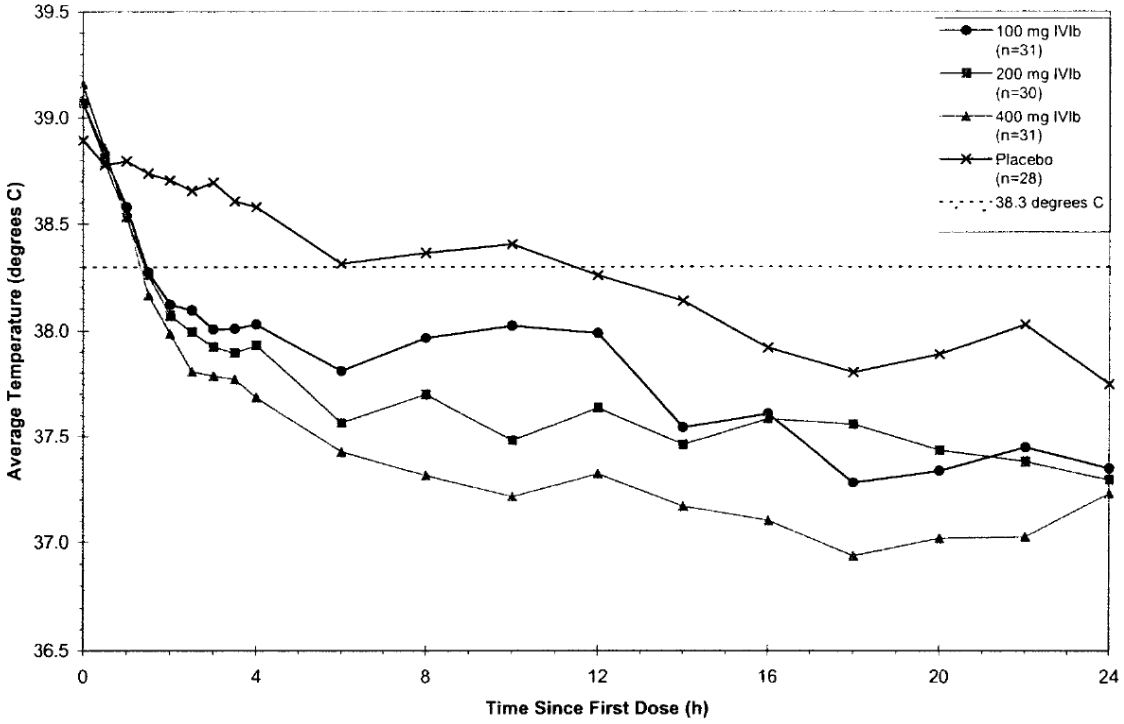
Table 10. CPI-CL-004: Efficacy results according to illness severity stratum. ITT population. (continued)

	Illness stratum	Placebo	Caldolor 100 mg	Caldolor 200 mg	Caldolor 400 mg
	Critical	*N=13*	*N=14*	*N=12*	*N=14*
	Non-critical	*N=15*	*N=17*	*N=18*	*N=17*
Maximum temperature decrease during 0-4 h (°C) (From ISE) †‡ *mean ± SD* *median treatment - placebo diff.* *(95% CI for median trt - plac diff.)*	Critical	0.4 ± 0.59	**0.9 ± 0.73** **0.5** **(0.1, 0.9)**		**0.9 ± 0.72** **0.5** **(0.2, 0.9)**
	Non-critical	1.0 ± 0.80	**1.7 ± 0.66** **0.8** **(0.2, 1.2)**		**2.2 ± 0.65** **1.2** **(0.6, 1.8)**
Maximum temperature decrease during 0-24 h (°C) (From ISE) †‡ *mean ± SD* *median treatment - placebo diff.* *(95% CI for median trt - plac diff.)*	Critical	1.2 ± 1.07	1.6 ± 0.94 0.5 (-0.1, 1.0)		1.7 ± 0.74 0.7 (-0.1, 1.6)
	Non-critical	2.2 ± 0.95	2.7 ± 0.86 0.5 (-0.1, 1.1)		**3.2 ± 1.04** **-0.9** **(0.1, 1.8)**
AUC-T_{0-4} (°F×h) (From ISE) †‡ *mean ± SD* *median treatment - placebo diff.* *(95% CI for median trt - plac diff.)*	Critical	13.1 ± 2.88	**9.6 ± 4.01** **-3.8** **(-6.3, -1.3)**		**7.6 ± 4.76** **-4.1** **(-8.2, -0.4)**
	Non-critical	11.7 ± 5.42	9.1 ± 4.84 -2.6 (-5.9, 0.5)		**7.6 ± 4.76** **-4.1** **(-8.2, -0.4)**
AUC-T_{0-24} (°F×h) (From ISE) †‡ *mean ± SD* *median treatment - placebo diff.* *(95% CI for median trt - plac diff.)*	Critical	64.7 ± 24.69	**45.5 ± 26.69** **-22.3** **(-39.5, -1.9)**		**38.7 ± 18.25** **-29.5** **(-46.7, -10.1)**
	Non-critical	46.5 ± 21.14	**30.0 ± 21.50** **-18.5** **(-33.2, -2.9)**		**15.5 ± 12.22** **-36.0** **(-46.3, -19.3)**

P-values are for pairwise comparisons with placebo. Results with p<0.05 are shown in bold. † Results according to illness stratum were not provided in the CPI-CL-004 study report. The ISE reported results according to illness stratum but data were combined for the Caldolor 100 mg and 200 mg dose groups. ‡ In the CPI-CL-004 study report, results for these temperature outcomes were provided in both °C (or °C×h) and °F (or °F×h). The ISE included only one set of results for each outcome and the units of measurement were not stated. Comparison with the results in the CPI-CL-004 study report showed that the ISE gave results in °C for temperature change (converted to temperature decrease in this table for consistency with the study report) and for maximum temperature change (converted to maximum temperature decrease in this table for consistency with the study report). However, the ISE results for AUC-T_{0-4} and AUC-T_{0-24} were in °F×h.

The CPI-CL-004 study report did not include results for the number and percentage of treatment failures at 24 h or for the time to treatment failure according to illness severity stratum. The ISE did report stratified results for these outcomes but the ISE analyses used a definition of treatment failure that differed from the one that was specified in the CPI-CL-004 study protocol.

Figure 2. CPI-CL-004: Core body temperature over time, ITT population.



Caldolor 400 mg was superior to placebo in respect of all but one of the other prespecified efficacy outcomes (time to treatment failure, which showed a non-significant increase in favour of Caldolor 400 mg).

In the Caldolor 100 mg and 200 mg groups, the percentage of patients with fever reduction 4 h after the first dose (an outcome that corresponds to the primary outcome in the 400 mg dose group), was significantly higher than in the placebo group, using a critical p-value of 0.05 (Table 11).

Table 11. CPI-CL-004: Outcomes in the Caldolor 100 mg and 200 mg q4h dose groups that correspond to the primary outcome in the Caldolor 400 mg q4h dose group - ITT population.

	Placebo *N=28*	Caldolor 100 mg *N=31*	Caldolor 200 mg *N=30*	Caldolor 400 mg *N=31*
Temp <101°F at 4h				
n (%)	9 (32%)	20 (65%)	22 (73%)	24 (77%)
CMH p-value		p=0.0138	p=0.0018	p=0.0005
Temp <38.3°C at 4h				
n (%)	9 (32%)	19 (61%)	21 (70%)	24 (77%)
CMH p-value		p=0.0264	p=0.0043	p=0.0005

However, there was a clear dose-response relationship for this outcome, with the percentage of responders rising from 32% in the placebo group to 61% for Caldolor 100

mg, 70% for Caldolor 200 mg and 77% for Caldolor 400 mg. Moreover, the sponsor has proposed approval of a dose regimen of 100-200 mg every 4 h *in addition to* the regimen of 400 mg q4h that corresponds to the primary outcome in this study. To support the approval of all 3 dose regimens requires that efficacy be demonstrated in the ITT population against the primary efficacy outcome criteria for all three regimens. This in tum means that allowance needs to be made in the analysis for the assessment of 3 simultaneous primary outcomes. A simple and conservative method of allowing for this multiplicity would be to apply the Bonferroni correction to the critical p-value. Using this method, the critical p-value becomes 0.05/3, that is, α=0.0167. It should be noted that this criterion has to be met for *both* definitions of the primary outcome in a dose group (temperature <101°F at 4h and temp < 38.3°C at 4 h), otherwise the critical p-value would need to be further reduced to 0.0083 to allow for 6 comparisons (3 doses and 2 definitions).

Assessed against this critical p-value of 0.0167, the ITT comparison with placebo remains significant for the Caldolor 400 mg dose and the 200 mg dose but not for the 100 mg dose.

A dose-response relationship was seen for other secondary efficacy assessments during the 4 h period after the first dose, although the difference between the Caldolor 100 mg and 200 mg dose groups and placebo, while always favourable, was not always statistically significant (at the α=0.05 level). In efficacy assessments that were performed across the full 24-h treatment period, all three Caldolor dose groups were numerically superior to placebo but, with the exception of AUC-T_{0-24}, the difference was statistically significant (at the α=0.05 level) only for the Caldolor 400 mg group and a dose-response relationship was not always evident. To some extent this probably represents a "swamping" of the smaller treatment effect in the lower dose groups by temperature changes resulting from treatment of the underlying condition or occurring as part of the natural history of the underling condition.

The *clinical* relevance of these statistically significant effects is not clear. The primary outcome used the same threshold to declare a treatment success as was used to declare a fever at enrolment, so achievement of the primary outcome did not necessarily equate to a clinically meaningful temperature reduction in an individual patient. An alternative outcome that has more intuitive clinical relevance would be the percentage of patients whose temperature was normalised following study treatment. In terms of the available outcomes, the closest to this is a *post hoc* analysis, requested by the FDA, of the time to temperature <99°C. In that analysis, favourable trends were seen for all Caldolor dose groups compared to placebo but these were not statistically significant (even at the α=0.5 level).

In the analysis of efficacy according to illness stratum, the effect of Caldolor was consistently lower in critically-ill patients than in those who were not critically ill. The sponsor has proposed that this is explained by lower plasma ibuprofen concentrations in the critically ill patients and that it justifies the availability of a higher (800 mg) dose for use in critically ill patients. However, Caldolor 400 mg q4h *was* significantly superior to placebo in the critically ill subgroup. Furthermore, while there was a dose-response relationship in the *non*-critically ill subgroup, there was very little evidence of a dose-response relationship in the critically ill patients. This suggests that increasing the dose further in the critically ill may not actually achieve the desired improvement in response. Finally, the use of high doses of ibuprofen or other NSAIDs in critically-ill patients, who are already at increased risk of compromised renal function, raises safety concerns because of the potential adverse effects of ibuprofen on the kidney. Overall, a recommendation to routinely increase the dose to 800 mg when treating fever in critically ill patients is not justified by the data.

CPI-CL-006

Study design, objectives, location and dates

CPI-CL-006 was a randomised, double-blind, placebo-controlled trial that evaluated the efficacy and safety of multiple doses of Caldolor 400 mg for the treatment of fever in hospitalised adults with uncomplicated falciparum malaria. The study was conducted at a single centre in Thailand from April to July 2002.

Inclusion and exclusion criteria

CPI-CL-006 enrolled hospitalised adults with uncomplicated falciparum malaria and a fever >38.0°C (100.4°F), based on the 2 highest temperature measurements at least 1 h apart during the 12 h prior to the first dose of study medication. Prospective patients were excluded if they had received an antipyretic drug within the last 8 hs, had a contraindication or major precaution to NSAID use (such as known NSAID allergy, platelet abnormalities, bleeding risk, renal impairment), or whose fever was due to certain causes for which NSAID treatment would not be expected to be useful (neurogenic fever, blood or drug reaction).

All study participants were to have falciparum malaria. As noted for CPI-CL-004, this means that the study population does not reflect the likely usage of Caldolor in Australia. It serves as an adequate model for demonstrating antipyretic efficacy but not for assessing safety in an Australian context.

Screening temperatures were taken up to 2 h before the first dose of study treatment, and unlike CPI-CL-004, the protocol did not require patients to be febrile at the time of (or soon before) the first dose. In actuality, however, all patients had a temperature ≥38.0°C at the time of the first dose.

The exclusion criteria were almost the same as in CPI-CL-004 and reflect the standard precautions and contraindications for ibuprofen.

Study treatments

Caldolor 400 mg or placebo were administered IV over 30 minutes, every 6 h for the first 3 days (72 hs) and then 6-hly as required for a further 2 days to treat a fever greater than 38.0°C (100.4°F). Each dose of Caldolor was diluted in 100 mL of normal saline.

The IV catheter used for administration of study medication was flushed with normal saline before and after each infusion. If a central venous catheter was available, that route of administration was preferred, however, a peripheral IV line with good blood return was acceptable.

In addition, standard artemisinin-based combination anti-malarial therapy (ACT) was initiated once study treatment had commenced and was continued throughout the study.

Antipyretic medications (including aspirin, other NSAIDs and paracetamol) and anti-pyretic procedures (including cold packs, cooling blankets and alcohol baths) were not permitted within 8 h before the start of study medication. Corticosteroids were not permitted during the study. Once study medication had been commenced, the use of cold packs, cooling blankets, alcohol baths, or other similar treatments was only permitted as rescue treatment following treatment failure. Treatment failure was defined as a temperature >41.1°C (106.0°F) a minimum of 2 h following the first dose of study medication, or a temperature >39.4°C (103.0°F) a minimum of 2 h after the second or subsequent doses of study medication.

The study report did not state that concomitant antipyretic medications (as distinct from physical measures) were prohibited but the listing of concomitant medications shows that such medications were not given. The use of antimalarial therapy would tend to reduce

the apparent antipyretic effect of Caldolor over the 3-day assessment period due to resolution of the underlying infection and associated fever in both treatment groups.

Efficacy variables and outcomes

The main efficacy variable was core body temperature. Core temperature was obtained using the tympanic method at Hour 0 (immediately before the first dose of study medication), then at Hours 1, 2, 3, 4, 8, 12, 16 and 20 on Day 1 and then 4 hly on Days 2 to 5.

A secondary "efficacy" variable was parasite clearance time, defined as the time from the start of study treatment to the time of the first negative screen result. Blood samples for malarial parasite count were taken at baseline then 6 hourly on each Day (1-5) until the first negative screen.

The primary efficacy outcome was the area above the temperature 37.0°C (98.6°F) versus time curve from 0 to 24 h after the start of treatment (AUC-T_{0-24}). This was calculated using the linear trapezoidal method. Temperatures below 37.0°C (98.6°F) did not contribute to AUC-T. If a patient's final temperature measurement was missing, the last available temperature measurement was carried forward. If any intermediate temperature measurements were missing during the treatment period, linear interpolation between the previous (including baseline) and following available data points was used to assign a value.

Other efficacy outcomes included:

- Area above the temperature 37.0°C (98.6°F) versus time curve from 0 to 4 h after the start of treatment (AUC-T_{0-4})
- Area above the temperature 37.0°C (98.6°F) versus time curve from 24 to 72 h after the start of (AUC-T_{24-72})
- Number and percentage of treatment failures, as previously defined, during the 5 day treatment period.
- Parasite clearance time, as defined above.

The primary efficacy outcome and the other temperature-based outcomes are acceptable means of demonstrating that the effect of Caldor on body temperature is statistically superior to that of placebo. However, they do not allow an assessment of whether the statistically significant effects are clinically meaningful in terms of the magnitude of the effect in an individual patient.

Parasite clearance time was cast as an efficacy outcome in this study but it is not actually relevant to the efficacy of ibuprofen as an antipyretic agent. It is relevant to a potential safety concern regarding the use of antipyretic agents in patients with malaria: some studies (including this one) have shown that such treatment may be associated with delayed parasite clearance. However, it has not been shown that this effect is clinically important[12] and it has even been argued that it may actually reflect reduced parasite cytoadherence and thus be beneficial.[13]Current World Health Organization guidelines recommend the use of antipyretic agents in patients with malaria despite this finding.[14]

[12] Meremikwu MM, Logan K, Garner P. Antipyretic measures for treating fever in malaria. Cochrane Database of Systematic Reviews 2000, Issue 2. Art. No.: CD002151. DOI: 10.1002/14651858.CD002151. Accessed 17 Jan 2011.

[13] Kakkilaya BS. Treatment of Uncomplicated P. falciparum Malaria. http://www.malariasite.com/malaria/Treatment4.htm. (accessed 17 Jan 2011).

[14] World Health Organization. Guidelines for the treatment of malaria. Second edition. Geneva: World Health Organization, 2010. http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf. (accessed 17 Jan 2011).

Finally, while it might possibly be relevant to the use of Caldolor specifically in patients with malaria, it does not represent a safety issue that would be relevant to the most of the anticipated usage of Caldolor in Australia.

Sample size

A sample size of 60 patients (30 per treatment) was planned. Based on incomplete data from a published study, it was hoped that this would be sufficient to detect a between-treatment difference in AUC-T_{0-24} of 12°C×h. An interim analysis was originally planned to adjust the sample size if necessary but was cancelled prior to unblinding.

Randomisation and blinding methods

Randomisation to Caldolor 400 mg or placebo was on a 1:1 basis. Randomisation and blinding methods were the same as in CPI-CL-004.

Analysis populations

The Safety Analysis Population (SAP) comprised all randomised patients who received at least one dose of study medication.

The ITT population included all patients from the safety population who had a baseline assessment and at least one post-baseline evaluation of the primary endpoint.

The EEP included all patients from the ITT population who had no major protocol violations with regard to inclusion and exclusion criteria, and who had the required primary efficacy assessments (temperature measurements in the first 24 h after the start of study treatment). If 2 or more consecutive temperature measurements were missing in the first 24 hs, the patient was not eligible for inclusion in the EEP.

Statistical methods

All statistical tests were two-sided, with p-values less than 0.05 for treatment differences considered significant.

The primary outcome was to be analysed in the ITT population with a supportive analysis in the EEP. Secondary outcomes were to be analysed only in the EEP. However, the EEP included all 60 randomised patients, so all outcomes were, in effect, analysed in the ITT population. Missing temperature values were imputed by linear interpolation or LOCF as previously described for the primary endpoint. Patients who received rescue treatment were withdrawn from study medication and temperature measurements subsequent to recue treatment were substituted with the mean of the treatment group temperature for that corresponding time point.

Participant flow

The study report did not state the number of prospective participants who were screened. A total of 60 patients were randomised and progressed as follows:

SAP: 60 patients received study medication and were included in the SAP.

ITT: All 60 patients in the SAP were included in the ITT population.

EEP: The EEP included all 60 patients from the ITT.

A total of 59 patients completed the entire study. One patient in the Caldolor 400 mg group completed the 5-day treatment period but filed to return from the Day 21 follow-up.

Table 12 summarises the disposition of patients according to treatment group and analysis population.

Table 12. CPI-CL-006: Patient disposition.

Population	Placebo	Caldolor 100 mg	TOTAL
Screened	nr	nr	nr
Randomised	30	30	60
SAP	30	30	60
ITT	30	30	60
EEP	30	30	60
Completed 5-day treatment period	30	30	30
Completed study	30	29	60

nr = not reported.

All 60 patients in the ITT population complied with the entry criteria. One patient in the placebo group continued study medication despite receiving rescue treatment (tepid sponge that was performed in error at 3 h after the first dose when the patient's temperature was 39.2°C instead of the required 41.1°C). A second placebo recipient did not receive rescue therapy and continued to receive study treatment, in violation of the protocol, when her temperature exceeded 39.4°C after the second dose. Clinical laboratory tests were supposed to be performed On Days 0 to 7, 14 and 21 but instead were omitted in all patients on Days 1 to 5. The last protocol deviation was during data entry: data were entered once then double-checked instead of being double-entered as specified in the protocol.

These protocol deviations should not have materially affected the assessment of efficacy. Omission of the planned laboratory tests on Days 1 to 5 will have reduced the available safety data.

Baseline data

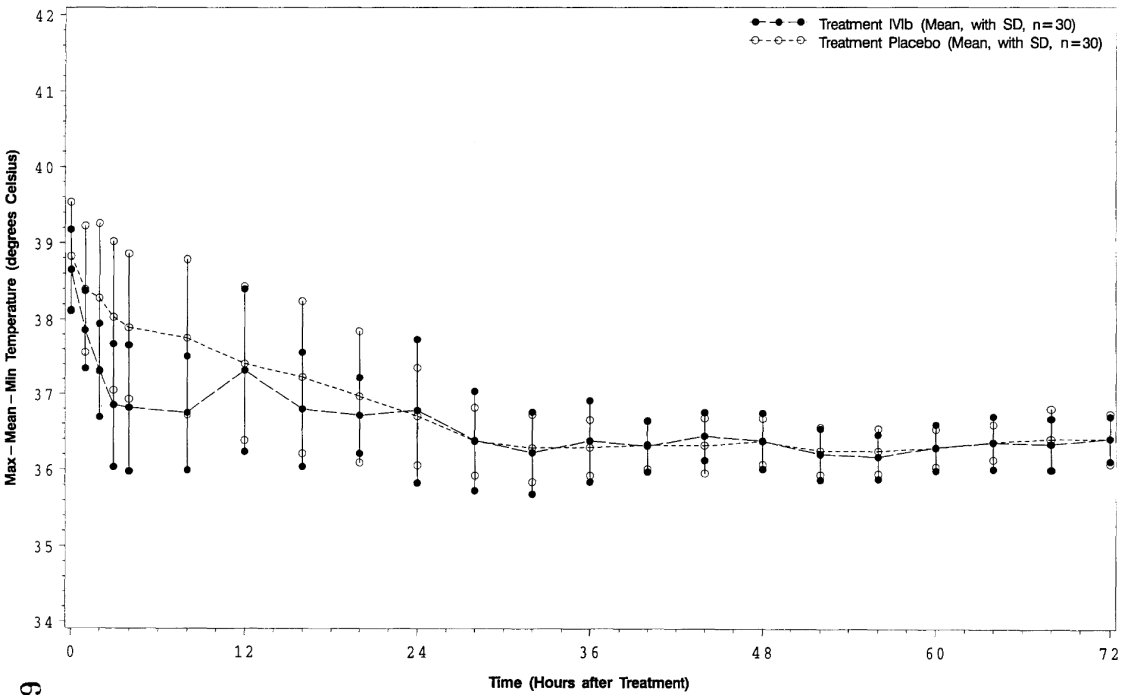
The two treatment groups were similar with respect to baseline characteristics. All patients were Asian, with a mean age of 32.4 years (range 18-54) in the Caldolor group and 27.8 years (range 18-52) in the placebo group. As in CPI-CL-004, males predominated in both treatment groups (24 males and 6 females per group). The mean baseline temperature was 38.7°C (range 38.2-39.5) in the Caldolor group and 38.8°C (range 38.2-40.0) on the placebo group.

The reason for the predominance of males is not clear and was not explored in the study report but the gender imbalance was the same in the two treatment groups and should not invalidate the efficacy results.

Results for the primary efficacy outcome

The AUC-T_{0-24} was 7.49 ± 7.94 °C×h in the Caldolor 400 mg group and 16.44 ± 11.60 °C×h in the placebo group. The effect of baseline temperature on AUC-T_{0-24} was statistically significant, with AUC-T_{0-24} increasing by 6.75°C×h for every 1°C increase in baseline temperature. After adjustment for baseline temperature, the between-treatment difference in mean AUC-T_{0-24} was -8.14°C×h, which was statistically significant (p=0.0019). Mean temperature profiles over time for the Caldolor and placebo groups are shown in Figure 3.

Figure 3. CPI-CL-006: Core body temperature from 0 to 72 h after the first dose of study treatment, ITT population.



Caldolor produced a statistically significant reduction, compared to placebo, in the primary outcome of AUC-T_{0-24}. The magnitude of the reduction was less than the anticipated value of 12°C×h but this is not important because the clinical relevance of any amount of temperature reduction (in terms of eventual patient outcomes) is unknown.

Results for other efficacy outcomes

Caldolor 400 mg significantly reduced area above the temperature 37.0°C (98.6°F) versus time curve from 0 to 4 h after the start of treatment (AUC-T_{0-4}) and area above the temperature 37.0°C (98.6°F) versus time curve from 0 to 72 h after the start of treatment (AUC-T_{0-72}) but had no effect on area above the temperature 37.0°C (98.6°F) versus time curve from 24 to 72 h after the start of treatment (AUC-T_{24-72}). Caldolor significantly reduced the time to temperature <100°F and time to temperature <99°F (FDA-requested *post hoc* analyses).

Treatment failure was uncommon in both groups, 2 patients (6.7%) in the Caldolor group and 3 (10%) in the placebo group, and the between-treatment difference was not statistically significant.

Malaria parasite clearance time was significantly increased in the Caldolor group (median 32.0 h compared to 24.0 h in the placebo group; median between-treatment difference 8.0 hs; p=0.0025).

The secondary outcomes show that all of the effect of Caldolor 400 mg was apparent in the first 24 h of treatment, with no difference compared to placebo thereafter. As can be seen from Figure 3, this was because the fever had resolved in both groups by 24 hs, presumably due to the successful treatment of malaria with ACT.

The increase in malaria parasite clearance time in the Caldolor group is consistent with some other studies of antipyretic agents in patients with malaria. While the clinical relevance of this effect in patients with malaria is unclear, it is not relevant to the use of Caldolor in fever due to other causes, which would represent most of the expected usage in Australia.

Other efficacy studies

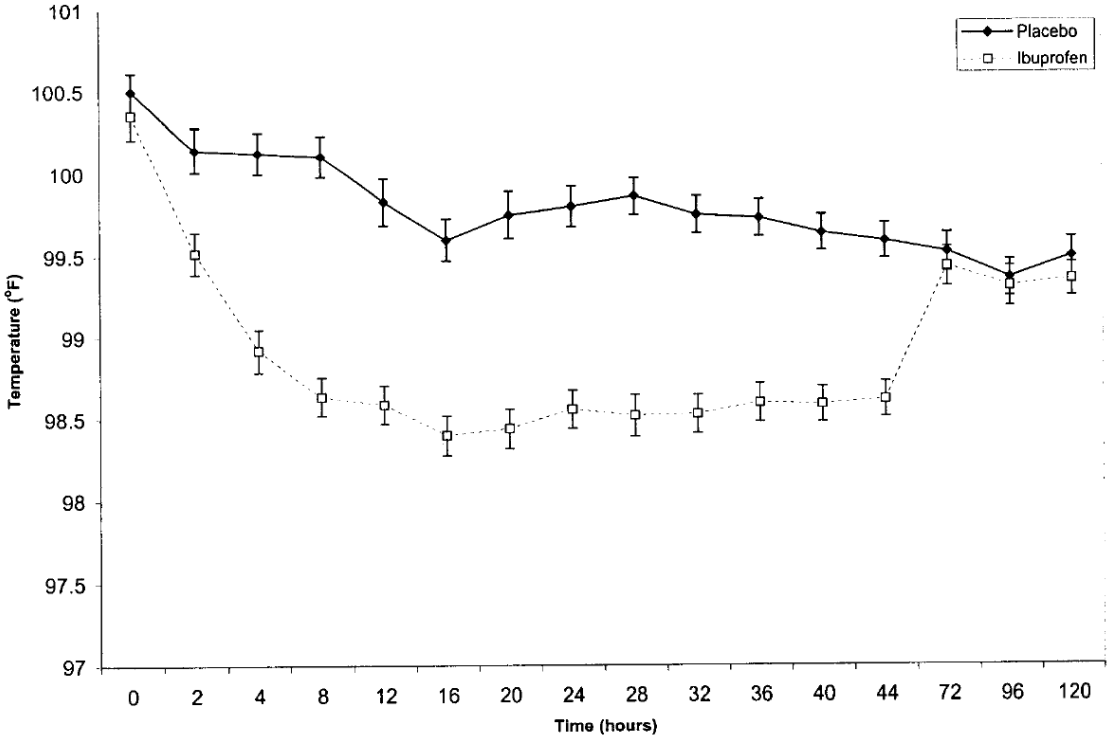
IND 32803

IND 32803 was an investigator-initiated, randomised, double-blind, placebo-controlled study of IV ibuprofen in patients with severe Sepsis Syndrome. Patients received ibuprofen 10 mg/kg up to a maximum of 800 mg, q6h for 8 doses (40 hs). The study, which was primarily designed to assess the effect of ibuprofen on 30-day mortality in this patient group, was conducted in the USA and Canada from November 1989 to April 1995 and used a developmental formulation of IV ibuprofen (see above). Although patients were required to be either febrile (core temperature ≥38.3°C or 101°F) or hypothermic (core temperature ≤35.5°C or 96°F) at screening, about half had become "normothermic" (>35.5 to <38.3°C or >96 to <101°F) by the time study drug was started. A potential confounder was that the study permitted the use of non-study treatments (paracetamol and cold packs) to treat fever. Lastly, the effect of ibuprofen on body temperature was only one of a number of secondary outcomes, with no statistical adjustment for multiplicity.

Nevertheless, from Hour 2 until the end of study treatment, body temperature was significantly reduced in ibuprofen recipients compared to placebo recipients, in the overall study population (Figure 4), in patients who were febrile at baseline (Figure 5), and in patients who were "normothermic" (although on average slightly febrile) at baseline (Figure 6). These differences occurred despite a significantly lower use of paracetamol in the ibuprofen group compared to placebo. The use of cooling blankets was limited (<3% after baseline) and similar in the ibuprofen and placebo groups.

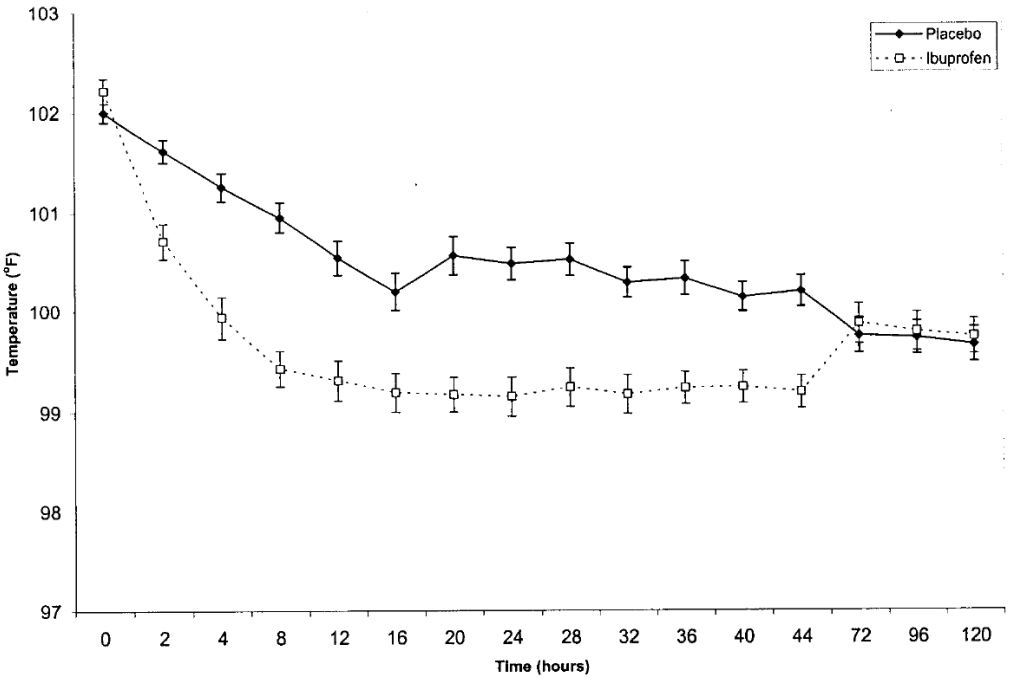
Overall, the findings are consistent with and supportive of the data from the two pivotal studies.

Figure 4. IND 32803: Core body temperature (mean ± SE) over time, all enrolled patients.



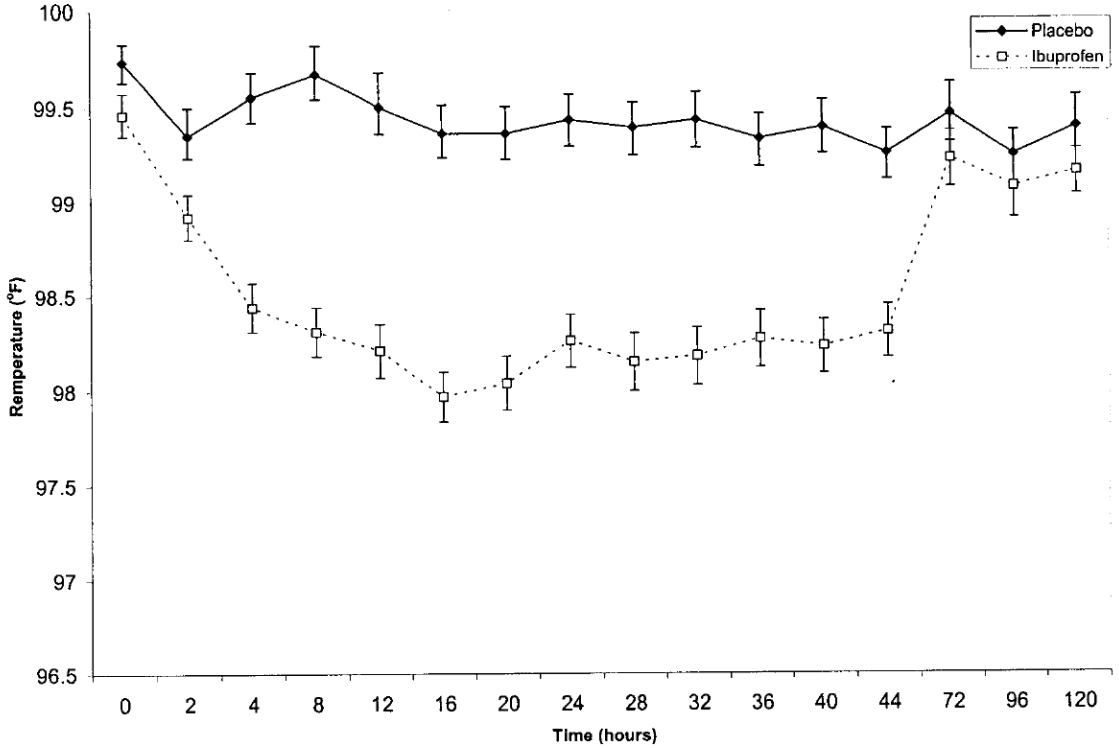
Data for each time point are from all enrolled patients who had an observation at that time point.

Figure 5. IND 32803: Core body temperature (mean ± SE) over time in patients who were febrile at baseline.



Data for each time point are from all patients who were febrile (≥101°F) at baseline and had an observation at that time point.

Figure 6. IND 32803: Core body temperature (mean ± SE) over time in patients who were "normothermic" at baseline.



Data for each time point are from all patients who were "normothermic" (>96°F and <101°F) at baseline and had an observation at that time point.

Analyses performed across trials (pooled analyses and meta-analyses)

The submission included an Integrated Summary of Efficacy for the fever indication but it described and analysed each study separately. A pooled efficacy analysis or meta-analysis was not performed and would not have been appropriate given the differences in study design and efficacy endpoints.

Evaluator's conclusions on clinical efficacy for the treatment of fever

The submission permits the following conclusions regarding the efficacy of Caldolor for the treatment of fever.

In non-critically ill adults:

- Caldolor administered IV over 30 minutes at doses of 200 or 400 mg every 4 h or 400 mg every 6 h was shown to be superior to placebo for the short term treatment of fever.
- In such patients, there was a positive dose-response relationship but the use of doses above 400 mg q4-6h was not studied and the scope for higher doses to further improve efficacy is limited given the already high level of response that was seen at the 400 mg dose level.

In critically-ill adults:

- Caldolor 400 mg q4h was superior to placebo for the short term treatment of fever.
- The efficacy of Caldolor was less than in non-critically ill adults. This is possibly explained by lower dose-normalised ibuprofen concentrations in the critically-ill.

However, there was no evidence of a dose-response relationship in the critically ill, so increasing the dose beyond 400 mg q4h may not lead to an improvement in efficacy.

- A 6 h dose interval was not tested in critically ill patients. Lower ibuprofen concentrations and efficacy in the critically ill mean that extension of the dose interval to 6 h in such patients might not provide satisfactory pain relief over the entire dose interval. While this might in theory be countered by increasing the dose to 800 mg, neither the efficacy nor the safety of that approach were tested.

Medium to long-term efficacy in the treatment of fever was not studied.

Efficacy in children and adolescents (<18 years) was not studied.

The clinical relevance of the statistically significant differences between Caldolor and placebo is unclear, because the time to achieve a normal temperature (<99°F) was significantly reduced by Caldolor in only one of the two studies, and because temperature reduction in febrile patients has not been convincingly shown to improve clinical outcomes (morbidity and mortality).

Analgesia

The submission included 3 studies of the use of Caldolor for the management of pain: CPI-CL-008A, CPI-CL-008B and CPI-CL-008C. All 3 studies were pivotal and are sufficiently similar that they may be grouped for description in this evaluation report.

Pivotal efficacy studies

CPI-CL-008A, CPI-CL-008B and CPI-CL-008C

Study design, objectives, locations and dates

CPI-CL-008A, CPI-CL-008B and CPI-CL008C were double-blind, randomised, placebo-controlled, parallel-group, multicentre studies that examined the efficacy and safety of Caldolor as an adjunct to morphine for the treatment of post-operative pain in adults. CPI-CL-008A was conducted in Australia, the USA and the Republic of South Africa (RSA) between Feb 2005 and Sep 2006; CPI-CL-008B enrolled patients in the USA only, between Jan and Dec 2007; CPI-CL-008C was performed in the USA and RSA from Jun 2007 to April 2008.

Inclusion and exclusion criteria

All 3 studies included adults (age 18-70 years in 008A and B, 18-80 years in 008C) who were scheduled for elective single site surgery with an anticipated need for post-operative IV morphine analgesia for >24 h (008A and B) or >28 h (008C). CPI-CL-008A enrolled men and women undergoing orthopaedic, abdominal or gynaecological surgery; 008B enrolled women undergoing abdominal hysterectomy; 008C enrolled men and women undergoing elective hip or knee replacement, reconstruction or arthroplasty.

Some exclusion criteria removed potential confounders, such as: the use of use of pre- or intra-operative nerve or epidural [15] blocks; the use of NSAIDs during the 12 h before the first dose of study medication; and the use of other analgesics during the 24 h (008A and B) or 12 h (008C) before the first dose of study medication (with the exception of paracetamol, which was allowed until 6 h pre-operatively and tramadol, which was allowed up to midnight on the evening prior to surgery). Other exclusion criteria reflected the standard precautions and contraindications for ibuprofen, or administrative matters (such as unwillingness to comply with study procedures).

[15] This exclusion is also safety-related.

The studies included patients with visceral and somatic pain, and comply with TGA-adopted guidelines relating to the pain models that should be studied to support an indication for the treatment of moderate to severe acute nociceptive pain as an adjunct to opioids[16]. The caveat "as an adjunct to opioids" reflects the mode of use of Caldolor in the studies rather than a requirement of the guideline.

There were no studies of the use of Caldolor as *monotherapy* for the treatment of mild-to moderate pain, as per the first part of the proposed analgesia indication. Accordingly the demonstration of efficacy for that part of the indication relies on extrapolation from the available studies of Caldolor, supplemented by pharmacokinetic comparisons between Caldolor and oral ibuprofen.

Study treatments

In the first study, CPI-CL-008A, patients were randomised to receive Caldolor 400 mg, Caldolor 800 mg or placebo. On the basis of that trial, only the 800 mg dose was compared to placebo in studies CPI-CL-008B and 008C.

In CPI-CL-008 A and B, the first dose of study treatment was given near the end of surgery (after haemostasis, at the start of skin closure). Study treatment was then given every 6 h for 48 hs, then as required for pain every 6 h for up to 120 h (5 days) post-surgery. Study treatment could be stopped at any point after the first 24 h if pain resolved, IV access was lost or the patient was discharged.

In CPI-CL-008C, the first dose of study treatment was given just before the start of surgery (during induction of anaesthesia). Study treatment was then given every 6 h for 24 h After Dose 5, study treatment was given every 6 h as required for pain for up to 5 days post-surgery. Study treatment could be stopped at any point after the first 24 h if pain resolved, IV access was lost or the patient was discharged.

All study treatments were infused IV over 30 minutes via a peripheral or central line. In CPI-CL-008A, Caldolor was diluted in 200 or 250 mL normal saline solution (depending upon standard normal saline bags at the different study sites). In CPI-CL-008B and 008C, Caldolor was diluted in 250 mL normal saline solution. All study treatments were infused IV over 30 minutes.

In all three studies, patients had access to IV morphine during the post-operative study period, either on request or delivered by patient-controlled analgesia (PCA).

In practice, no patients completed the full 5 days of study treatment and the average treatment duration was only 2 days. In addition, efficacy was formally assessed only over the first 24 hs. This is sufficient, however, for an acute pain indication.

Efficacy variables and outcomes

The primary efficacy outcome in CPI-CL-008A and 008B was total morphine usage in the 24 h following the first dose of study treatment in the Caldolor treatment groups compared to placebo.

The primary efficacy outcome in CPI-CL-008C was the area under the pain intensity with movement versus time curve, from 6 to 28 h after the first dose of study treatment, in the Caldolor treatment group compared to placebo. Pain intensity was measured using a VAS with ends anchored at "No pain" and "Worst possible pain". VAS assessments were performed immediately following surgery (as soon as the patient was able to complete an assessment) and at Hours 6, 8, 12, 16, 20, 24 and 28. Patients were instructed to "Put a mark on the line at the point that best describes how much pain you are having right now".

[16] CPMP/EWP/612/00 Note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain. http://www.tga.gov.au/docs/pdf/euguide/ewp/061200final.pdf.

Consumption of rescue medication (in this case morphine) and area under the pain-intensity versus time curve are standard efficacy outcomes in pain studies and consistent with the relevant TGA-adopted guideline[16]. The VAS is a standard method of assessing pain. The length of time over which the primary outcomes were assessed is consistent with an acute pain indication.

Sample size

CPI-CL-008A was conducted first, to determine the most appropriate dose of Caldolor for the treatment of post-operative pain. Initially, 225 patients were to be randomised to placebo, 400 mg Caldolor q6h, or 800 mg Caldolor q6 h. After approximately 75% of these (168 patients) had completed the study, an analysis of variance was conducted without breaking the blind and without dividing the information by groups. An independent statistician responsible for running this analysis recommended that the sample size be increased to provide a total EEP of not less than 360. A total of 406 participants were actually randomised, leading to an EEP of 342.

Based on the results of CPI-CL-008A, CPI-CL-008B used only the Caldolor 800 mg q6h regimen and was planned to include 145 patients per group in the EEP (290 total) with the expectation of providing 90% power to detect a 20% reduction in morphine use in the Caldolor group compared to placebo, at a significance level of 0.05.

Based on the results of CPI-CL-008A, CPI-CL-008C had a planned sample size of 67 per group, which was expected to provide 90% power to detect a 20% reduction in pain-AUC with movement in the Caldolor group compared to placebo, at a significance level of 0.05.

Randomisation and blinding methods

Randomisation in the pivotal studies was by means of sealed envelopes containing treatment assignments that were prepared centrally and provided to each study site pharmacy. Randomisation to the treatment groups in each study was on a 1:1 basis. Randomisation was stratified by weight (≤75 kg and >75 kg) and age (≤45 years and >45 to 70 years in CPI-CL-008A and B; ≤45 years and >45 to 80 years in 008C).

All three studies were double-blind. As in the fever studies, the pharmacists who prepared the study medication were aware of the treatment allocation but were instructed to puncture the additive port of the placebo normal saline bags to maintain the double blind for patients, investigators and nursing staff.

Analysis populations

In CPI-CL-008A and B, analyses were performed in the following populations:

- ITT population: All randomised patients who received at least a partial dose of study medication.
- EEP: Patients from the ITT population who received the first 4 doses of study medication within ± 60 minutes of the scheduled time.
- Abdominal hysterectomy (AH) population (CPI-CL-008A): Women from the EEP who underwent abdominal hysterectomy.

In CPI-CL-008C, analyses were performed in the following populations:

- All-treated (AT) population: All randomised patients who received at least one dose of study medication.
- ITT population: Patients from the AT population who received at least one *post-surgical* dose of study medication or at least one dose of morphine for break-through pain.

- EEP: Patients from the ITT population who received the first 4 doses of study medication within ± 60 minutes of the scheduled time and who had the 6-h and 24-h VAS pain on movement assessments.

In CPI-CL-008C, the first dose of study treatment was given intraoperatively, so the AT population corresponds to the conventional definition of the ITT population or Full Analysis Set. However, the primary efficacy assessment was conducted during the 22-h period after the first scheduled post-operative dose of study medication, so the ITT population includes all of the patients who were eligible to be assessed for the primary efficacy outcome.

Statistical methods

In CPI-CL-008A and B, the primary efficacy outcome was analysed in the ITT population, the EEP and (for 008A) in the AH population. Secondary efficacy outcomes were analysed in the ITT and EEP populations. Analyses were performed without regard for stratification at the time of randomisation.

In CPI-CL-008C, the primary and secondary efficacy outcomes were analysed in the AT population, the ITT population and the EEP.

The statistical methods used to analyse each efficacy outcome were summarised in the study report.

As previously noted, CPI-CL-008A was conducted first, to determine the optimal dose of Caldolor for the management of post-operative pain. Dose selection for subsequent studies was to be based on a significance level of $p \leq 0.05$ when comparing each Caldolor dose level to placebo and $p \leq 0.10$ when comparing the two Caldolor dose levels, as follows:

- If efficacy was demonstrated for the primary outcome when Caldolor was compared to placebo ($p \leq 0.05$) but no statistically significant difference was seen between the 400 mg and 800 mg dose levels ($p > 0.10$), the lower dose of 400 mg was to be selected for subsequent studies.
- If significant safety concerns were evident with the 800 mg dose and not observed with the 400 mg dose, the 400 mg dose could be selected for subsequent studies even if the 800 mg dose was shown to be more efficacious than the 400 mg dose ($p \leq 0.10$).

The prespecified statistical tests were appropriate. The ITT analyses from CPI-CL-008A and B and the AP and ITT analyses from CPI-CL-008C are the most relevant for assessing the efficacy of Caldolor. Results from the EEP and AH populations exclude patients whose study medication was given outside the specified time window and are likely to overestimate the efficacy of Caldolor in actual clinical practice.

Participant flow

Table 13 shows the number of patients who were enrolled, randomised, included in the various analysis populations and completed the three pain studies. The number of potential patients who were screened for the three studies was not reported.

Table 13. CPI-CL-008 A, B and C: Patient disposition.

Population	008A			008B		008C	
	Placebo q6h	Caldolor 400 mg q6h	Caldolor 800 mg q6h	Placebo q6h	Caldolor 800 mg q6h	Placebo q6h	Caldolor 800 mg q6h
Screened	nr	nr	nr	nr	nr	nr	nr
Randomised	134	134	138	153	166	92	106
AT	na	na	na	na	na	86	99
ITT	134	134	138	153	166	84	95
EEP	115	111	116	137	150	64	77
AH	58	50	53	137*	150*	na	na
Discontinued	134	134	138	153	166	86	99
Completed	0	0	0	0	0	0	0

nr = not reported; na = not applicable; * No 'AH' population was defined but all patients in 008B had undergone abdominal hysterectomy.

In CPI-CL-008A, B and C, all patients had study medication discontinued prior to Day 5. Most early discontinuations were due to cessation of IV access and/or commencement of oral analgesia.

Protocol violations

In CPI-CL008A, protocol violations were recorded in 86 (64%), 88 (66%) and 95 (69%) of the patients randomised to placebo, Caldolor 400 mg and Caldolor 800 mg, respectively. These violations most commonly involved errors in the timing of study drug administration (more than 1 h before or after the scheduled time), or the receipt of restricted medications. Other protocol violations involved failure to observe exclusion criteria, consenting errors and randomisation according to the wrong age or weight stratum. Amongst the 17 randomised patients who should have been excluded due to factors such as creatinine clearance <60 mL/min, history of asthma or allergy to NSAIDs, anaemia and inability to close the surgical would, none experienced AEs that were related to the failure to observe the exclusion criteria.

In CPI-CL-008B, protocol violations were recorded in 36 (24%) and 32 (19%) of the patients randomised to placebo and Caldolor 800 mg, respectively. By far the majority of these involved the administration of restricted medications. Two patients with creatinine clearance <60 mL/min were randomised to placebo.

In the AT population of CPI-CL-008-C, protocol violations were recorded in 32 (37%) and 30 (30%) of the placebo and Caldolor 800 mg groups, respectively. The most common violations were administration of restricted medications and administration of study drug a more than 1 h before or after the scheduled time.

Each type of protocol violation was evenly distributed across the treatment groups within each study. Because of this, the violations are not expected to have materially affected the efficacy conclusions.

Baseline data

In CPI-CL-008A, the majority of patients were female (79%), and Caucasian (86%). The mean age was 45 years. A total of 295 patients (73%) underwent abdominal surgery, of whom 161 (40% of the ITT population) were women who had an abdominal hysterectomy; 111 patients (27%) had orthopaedic surgery. Each of the three geographical regions (USA, Australia and the RSA) contributed about one-third of the ITT population.

In CPI-CL-008B, all of the patients were women who underwent an abdominal hysterectomy in the USA. The mean age was 42 years. About half of the patients (55%) were Black, 39% were Caucasian and 6% were Hispanic.

In CPI-CL-008C, the majority of patients were female (65%), and Caucasian (86%). The mean age of 61 years was higher than in the other studies. Some 71% of the patients were enrolled in the USA and the remainder in the RSA. 50% of the patients underwent knee replacement; 22% hip replacement; 19% knee arthroplasty and 9% hip arthroplasty.

Baseline (pre-treatment) pain severity was not measured in any of the studies, as the first dose of study medication was given before the patients were conscious of pain in 008A and B and before the onset of pain in 008C. However, the types of surgery that were undertaken would be expected to produce moderate to severe pain in the absence of analgesia.

Results for the primary efficacy outcome

An FDA inspection identified concerns regarding the primary outcome data from one site that participated in both CPI-CL008A and B. Most of these issues involved CPI-CL-008B. According to the publicly available FDA reviews, there were discrepancies between the source documents and the submitted data listings for the primary endpoint (24-h morphine usage) for 4 patients. One of the patients was in enrolled in 008A and the other 3 in 008B. Also, the treatment assignments of 2 patients enrolled in 008A were unblinded to the study staff and 2 ineligible patients were enrolled in 008B.

These findings led the FDA to request a reanalysis of the primary outcome data from CPI-CL-008B, excluding all data from the site concerned. The FDA statistical reviewer also performed a reanalysis that excluded only the 5 patients with suspect data for the primary outcome.

The reanalyses did not alter the study conclusions. The exclusion of data from Site 2 in CPI-CL-008B slightly reduced the between-treatment difference for the primary endpoint and raised the corresponding p-value, which nevertheless remained well below 0.05. Other outcomes were not affected. For completeness, both the original analysis and the reanalyses will be presented in this report.

Morphine usage

Total morphine usage in the 24 h following the first dose of study medication (which was given intra-operatively at the initiation of skin closure) was the primary efficacy outcome in CPI-CL-008A and B. In CPI-CL-008A, only Caldolor 800 mg q6h and *not* Caldolor 400 mg q6h was significantly superior to placebo at the α=0.05 level in respect of this outcome (Table 14).

Table 14. CPI-CL-008A: Primary efficacy outcome. Total morphine usage in the 24 h after the first dose of study medication (ITT population).

	Placebo q6h *N=134*	Caldolor 400 mg q6h *N=134*	Caldolor 800 mg q6h *N=138*
Morphine usage (mg)			
mean ± SD	48.9 ± 27.7	46.3 ± 29.4	43.8 ± 33.7
median	45.3	44.0	35.5
range	0.0 - 144.0	3.0 - 198.25	0.0 - 221.3
Transformed morphine usage (mg) *			
LS mean (SE)	223.0 (13.8)	208.5 (13.6)	190.6 (13.1)
LS mean difference versus placebo (95% CI)	-	-14.4 (-44.4, 15.5)	-32.4 (-62.1, -2.6)
P-value versus placebo †	-	0.458 (NS)	0.030

* Data were transformed using the rank transformation (a non-parametric test), because the raw, log-transformed and Box-Cox-transformed data were found to be non-normally distributed. † Linear 4-way ANOVA with fixed effects for age group, weight group, randomisation centre and treatment group.

The statistical analysis was adjusted for multiplicity (testing two separate Caldolor dose levels versus placebo) using Dunnett's method. Dunnett's method reports adjusted p-values that should be compared with the usual critical p-value of 0.05. The results therefore demonstrate a significant effect in the Caldolor 800 mg group and no significant effect in the Caldolor 400 mg group, *in the rank-transformed data*.

However, the FDA statistical reviewers did not accept this analysis and the FDA-approved PI states that statistically significant efficacy was not demonstrated for either dose in this study. A central point of the FDA reviewers' argument is that the statistical analysis plan provided for the analysis of raw data in the first instance, followed by log-transformed data and then Box-Cox transformed data if the data at each preceding step were not normally distributed. The non-parametric analysis based on rank-transformed data was not prespecified (even though one can argue that its use is logical given the non-normality of the raw, log-transformed and Box-Cox transformed data). Furthermore, the preplanned analyses *failed to* show a significant effect on morphine usage for either Caldolor dose level, and the practice of resorting to an unplanned analysis to provide a different (rather than a confirmatory) result is not acceptable. Finally, the FDA statistical reviewers noted that the violation of normality that was used as the excuse for discarding the planned analyses should not be important when the sample size is sufficiently large (as it was in this study). Thus, there is no strong reason for accepting the non-parametric analysis in preference to the planned analyses and the study should therefore be regarded as inconclusive.

The FDA reviewer's arguments are cogent and have not been refuted by the sponsor. While the study results are sufficient to justify exploration of the 800 mg dose in subsequent studies, the proposed PI statement that the 800 mg dose significantly reduced morphine consumption in this study should not be allowed.

Study CPI-CL-008B therefore examined only Caldolor 800 mg q6h and found that regimen to be significantly superior to placebo (Table 15). Caldolor 800 mg reduced mean morphine usage by about 10% in CPI-CL-008A and 15% in CPI-CL-008B.

Table 15. CPI-CL-008B: Primary efficacy outcome. Total morphine usage in the 24 h after the first dose of study medication (ITT population, including and excluding patients from Site 2).

	All patients		Excluding Site 2	
	Placebo q6h	Caldolor 800 mg q6h	Placebo q6h	Caldolor 800 mg q6h
	N=153	*N=166*	*N=138*	*N=142*
Morphine usage (mg)				
mean ± SD	55.9 ± 20.6	47.3 ± 25.6	57.0 ± 20.8	49.4 ± 25.9
median	54.0	43.5	55.5	45.3
range	14.5 - 114.0	4.0 - 143.3	14.5 - 114.0	4.0 - 143.3
Transformed morphine usage (mg) *				
LS mean (SE) †	13.6 (0.4)	12.1 (0.4)	14.4 (0.5)	12.9 (0.5)
LS mean difference (95% CI) †	-1.50 (-2.25, -0.74)		-1.47 (-2.47, -0.46)	
p-value †	<0.001		0.004	

CPI response to FDA Information Request Received 19 May 2009, page 1. * Data were transformed using the prespecified Box-Cox transformation because the raw data were found to be non-normally distributed. † The "all patients" analysis is based on a linear ANOVA model with fixed effects for age group, weight group, randomization centre, and treatment group. The analysis excluding Site 2 is based on a linear ANOVA model with fixed effects for age group, weight group, randomization centre, treatment group, and treatment by age group, treatment by weight group, and weight group by centre interactions. The p-values and 95% confidence intervals are based on the difference in LS Means from the corresponding final ANOVA model.

Corresponding results were seen in the EEPs of both CPI-CL-008A and B and in the AH subpopulation of 008A.

In the AT and ITT populations and the EEP of CPI-CL-008C, Caldolor 800 mg q6h significantly reduced mean morphine usage by around 30 to 33% compared to placebo during the 28 h after the first dose of study medication (given pre-operatively at the induction of anaesthesia), although this was not the primary outcome in that study.

AUC-VAS with movement

In CPI-CL-008C, the primary outcome was the AUC-VAS with movement during the period from 6 to 28 h after the first dose of study medication (which was given pre-operatively at the induction of anaesthesia). Caldolor 800 mg q6h was significantly superior to placebo in respect of this outcome in the AT and ITT populations (Table 16) and in the EEP.

Table 16. CPI-CL-008C: Primary efficacy outcome. AUC-VAS$_{6-28}$ with movement (AT and ITT populations).

AUC-VAS$_{6-28}$	AT population		ITT population	
	Placebo q6h	Caldolor 800 mg q6h	Placebo q6h	Caldolor 800 mg q6h
	N=86	*N=99*	*N=84*	*N=956*
mean ± SD	1307.8 ± 388.7	970.1 ± 422.2	1307.8 ± 393.3	970.2 ± 431.0
median	1304.6	946.2	1304.6	932.7
LS mean (SE)	1326.1 (82.0)	1005.0 (81.5)	1327.6 (85.6)	1006.7 (83.9)
LS means difference (95% CI)	-321.1 (-436.7, -205.4)		-320.9 (-440.7, -201.1)	
p-value †	<0.001		<0.001	

† Linear 4-way ANCOVA with fixed effects for age group, weight group, randomisation centre and treatment group. Raw data were found to be normally distributed and were therefore analysed without transformation.

The results for corresponding (but non-primary) outcomes in the other studies were as follows: In both CPI-CL-008A and 008B, Caldolor 800 mg q6h significantly reduced AUC-VAS$_{0-24}$, AUC-VAS$_{6-24}$ and AUC-VAS$_{12-24}$ on movement, compared to placebo. In CPI-CL-008A, Caldolor 400 mg q6h significantly reduced AUC-VAS$_{0-24}$, AUC-VAS$_{6-24}$ and AUC-VAS$_{12-24}$ on movement, compared to placebo but the effect was noticeably less than that of the 800 mg dose.

The primary outcomes in all three studies and the corresponding secondary outcomes showed that Caldolor 800 mg q6h is efficacious as an adjunct to morphine for the short term management of moderate to severe post-operative pain. Satisfactory efficacy was *not* demonstrated for Caldolor 400 mg q6h in this situation.

Results for other efficacy outcomes

In CPI-CL-008A, Caldolor 400 mg q6h and 800 mg q6h significantly reduced AUC-VAS at rest, consistent with their effect on AUC-VAS with movement. Similarly, Caldolor 800 mg q6h significantly reduced AUC-VAS at rest in CPI-CL-008B and C and AUC-VRS at rest in CPI-CL-008C.

When Caldolor 800 mg was started preoperatively in CPI-CL-008C the VAS pain scores at rest and with movement were significantly reduced "immediately post-surgery" compared to placebo. This measurement was performed as soon as patients had recovered sufficiently from the anaesthetic to provide a pain assessment. When Caldolor 800 mg was started at the end of surgery in CPI-CL-008A, the mean VAS pain score was numerically reduced compared to placebo, from the first post-surgical observation (1 h after the first dose) but the difference did not become statistically significant until 9 h after the first dose (that is, 3 h after the second dose). In CPI-CL-008B, when Caldolor 800 mg was also started at the end of surgery, the mean VAS pain score was essentially the same as in the placebo group until 6 h after the first dose and did not become significantly lower until 15 h after the first dose. Overall, the data suggest that starting Caldolor preoperatively instead of at the end of surgery may provide earlier pain relief but this conclusion is based on a cross-study comparison and remains unproven.

Short term persistence of efficacy was demonstrated according to the principal treatment periods in each study: 48 h in CPI-CL-008A, 24 h in 008B and 28 h in 008C. After these time points, the use of Caldolor was optional and the number of patients who remained on study treatment was too low to provide meaningful data.

Neither Caldolor dose regimen had a significant effect on the number of treatment failures, time to return of GI motility, time to resumption of liquid or solid intake, or length of hospital stay. The time to ambulation was significantly reduced in the Caldolor 800 mg q6h group of CPI-CL-008B but not in CPI-CL-008C or in either Caldolor dose group of CPI-CL-008A.

In respect of the "combined safety assessment" of opioid-related AEs, Caldolor 400 mg q6h was associated with a significantly reduced incidence of these AEs compared to placebo in the ITT population of CPI-CL-008A but this was not confirmed in the EEP. Caldolor 800 mg q6h did not significantly reduce the incidence of opioid-related AEs in any of the analysis populations across all three studies.

Other efficacy studies

Not applicable.

Analyses performed across trials (pooled analyses and meta-analyses)

Efficacy results from the Caldolor 800 mg dose groups in CPI-CL-008A and B were combined in the *Integrated Summary of Efficacy*. Most aspects of the design and conduct of CPI-CL-008A and B were identical, which supports combining the studies for analysis. However, the baseline characteristics of the patients were dissimilar (008B enrolled only women undergoing abdominal hysterectomy with a markedly different ethnic distribution to 008A) and morphine usage was noticeably lower in the placebo group of 008A than the placebo group of 008B. The combined analysis used individual patient data and the effect of study treatment was adjusted for age group, weight group and randomisation centre. However, given the abovementioned differences between the study populations the analysis should also have adjusted for gender, surgery type and race (unless these could be shown to have no significant impact on the efficacy outcomes). Another shortcoming of the combined analysis is that it included data from the study site at which the FDA identified irregularities in the documentation of data for the primary outcome.

In any case, the combined analysis did not provide any useful additional information. The effect of Caldolor 800 mg on total morphine usage and AUC-VAS was statistically significant (as expected from the individual studies) and the effect of Caldolor 800 mg on the secondary efficacy endpoints (time to return of GI motility, resumption of fluid or solid intake, resumption of ambulation and length of hospital stay) remained non-significant. Of potential interest was the observation, amongst multiple subgroup analyses of the combined data from CPI-CL-008A and B that the effect of Caldolor 800 mg on total morphine usage was noticeably less in men than in women. However, this is probably a statistical artefact as the finding was not duplicated in CPI-CL-008C and there was no gender difference in the effect of Caldolor 800 mg on AUC-VAS.

Evaluator's conclusions on clinical efficacy for the management of pain

General comments

The analgesia indications sought for Caldolor are very broad. They cover both monotherapy and combination therapy (with opioids), and if approved would infer usage in a broad range of pain states, acute and chronic pain, nociceptive and neuropathic pain and primary dysmenorrhoea, that are regarded under the relevant guideline as distinct indications that each require separate proof of efficacy.

Management of mild to moderate pain

None of the submitted studies directly examined the use of Caldolor as monotherapy for the management of mild to moderate pain. However:

- Oral ibuprofen is approved in Australia for the treatment of various types of pain, namely "Rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, primary dysmenorrhoea and acute and/or chronic pain states in which there is an inflammatory component". Bioequivalence of Caldolor to an Australian-registered oral ibuprofen product has not been directly demonstrated but as discussed above, the pharmacokinetics of Caldolor when given as a 30 minute infusion are such that it is reasonable to conclude that it should be at least as efficacious as the same dose of an Australian-registered oral product.
- In three pivotal studies, Caldolor 800 mg q6h produced a statistically significant reduction in pain scores in patients with *moderate-to-severe* post-operative pain as well as (in spite of) a reduction in morphine consumption. The duration of these studies was limited to 48 hs.

Accordingly, it is reasonable to conclude that Caldolor would have some efficacy as monotherapy for the management of mild to moderate acute nociceptive pain. The lack of monotherapy studies means that the magnitude of the effect of Caldolor as monotherapy, and thus the clinical relevance of that effect, has not been directly determined but is assumed to be satisfactory on the basis of the pharmacokinetic comparison to oral ibuprofen.

Efficacy of Caldolor as monotherapy for the treatment of non-nociceptive (neuropathic) pain has not been demonstrated and the use of NSAIDs for neuropathic pain is generally not recommended[17,18].

Efficacy for the treatment of chronic pain has also not been directly demonstrated. Given the approval of oral ibuprofen for "chronic pain with an inflammatory component", the efficacy of Caldolor for the treatment of "chronic pain with an inflammatory component" could be inferred on pharmacokinetic grounds. However, the use of an IV product such as Caldolor for chronic pain would be clinically appropriate only in very exceptional circumstances and it is recommended that the Caldolor pain indication should specify short term use.

Management of moderate to severe pain as an adjunct to opioid analgesics

The approved indications for oral ibuprofen do not exclude combination use with opioids. Nor, however, do they specifically mention it, as is proposed for Caldolor. On that basis, this aspect of the proposed Caldolor indication cannot be extrapolated on pharmacokinetic grounds but must rely on the submitted efficacy studies.

All three of the submitted analgesia studies investigated the use of Caldolor as an adjunct to opioid analgesia (morphine) for the short term management of moderate to severe postoperative pain. The types of surgery involved were elective orthopaedic surgery, abdominal surgery and hysterectomy, thus covering both somatic and visceral *nociceptive* pain in accordance with the relevant TGA-adopted EU guideline.

[17] International Association for the Study of Pain. Pharmacological management of neuropathic pain. Pain clinical updates. 2010;XVIII(9),1-7. http://www.iasp-pain.org/AM/AMTemplate.cfm?Section=Home&SECTION=Home&CONTENTID=12215&TEMPLATE=/CM/ContentDisplay.cfm

[18] McQuay H. Dealing with pain. In: Warrell DA, Firth JD, Cox TM, eds. Oxford Textbook of Medicine. Oxford/New York. Oxford University Press. 2010. (via STAT!Ref Online Electronic Medical Library. http://online.statref.com/document.aspx?fxid=94&docid=4621

The primary outcomes in all three studies, together with the corresponding VAS pain score and morphine use secondary outcomes, satisfactorily demonstrated that Caldolor 800 mg q6h is superior to placebo for the short term (up to 48 hs) management of moderate to severe post-operative pain as an adjunct to morphine. Efficacy was demonstrated when Caldolor 800 mg was started just before the start of surgery and also when it was started at the end of surgery but the data do not permit a firm conclusion as to whether preoperative administration leads to earlier pain relief.

Given the common mechanism of action of opioids, one would expect efficacy to extend to coadministration of Caldolor with opioids other than morphine. On the basis of pathogenesis, one would also expect the results to extend to the management of other types of acute nociceptive pain as an adjunct to opioid analgesics.

The design of the studies, whereby pain severity could not be measured before treatment, means that the magnitude of the pain relief due to Caldolor in an individual patient cannot be determined. This, in turn, prevents an assessment of the number of patients who need to be treated with Caldolor to produce each additional patient with a clinically worthwhile pain reduction, compared to placebo.

The short duration of Caldolor use in the submitted studies (up to 48 hs, after which it was generally replaced by oral analgesia) means that the indication should refer to "short term" management of moderate to severe nociceptive pain.

Satisfactory efficacy for the management of moderate to severe post-operative pain as an adjunct to morphine was not shown for Caldolor 400 mg q6h.

Efficacy as an adjunct to opioids for the treatment of neuropathic pain or chronic pain has not been demonstrated.

Safety

Studies providing evaluable safety data

Safety data were collected in all of the submitted studies. Data from the company-sponsored studies were collated in an Integrated Summary of Safety (ISS). Data from the investigator-sponsored study in patients with sepsis syndrome (IND 32803), which had used a developmental formulation of IV ibuprofen, were summarised in the ISS but (appropriately) not combined with the data from the pivotal trials.

It is notable that the original evaluation of the safety data identified issues relating to the scope, analysis and presentation of the data that prevented an adequate assessment of the safety of Caldolor in the proposed usage, and thus of the benefit-risk balance. As a consequence, the sponsor responded with a document that included:

- Supplementary clinical data (primarily reanalyses of the original safety data) aimed at addressing issues raised in the original clinical evaluation;

This reanalysis of the safety data lead to the generation of a supplementary clinical evaluation report from which the key findings have been interspersed throughout the relevant sections of text under a suitable subject heading.

Pivotal efficacy studies

Indication: Fever

In the pivotal antipyretic studies, the following safety data were collected:

- General adverse events (AEs) were recorded up to Day 28 in CPI-CL-004 or Day 21 in CPI-CL-006. AE recording was to be "continuous" while patients remained in hospital

and via daily post-discharge telephone contact in patients who were discharged before these time points. The method of soliciting AEs was not specified.

- Laboratory tests were performed at baseline and at intervals up to Day 5 in CPI-CL-004 and Day 28 in CPI-CL-006. The tests included:
  - clinical chemistry (sodium, potassium, chloride, total carbon dioxide, glucose, blood urea nitrogen [BUN], creatinine, total bilirubin, albumin, total protein, aspartate aminotransferase [AST], alanine aminotransferase [ALT] and lactate dehydrogenase [LDH]);
  - haematology and coagulation (white blood cell count [WBC] and differential, haematocrit [Hct], haemoglobin [Hb], platelets, prothrombin time [PT] and activated partial thromboplastin time [APTT] [19]).
  - Investigators in CPI-CL-004 but not in CPI-CL-006, were asked to state whether any laboratory abnormalities were clinically significant.

Transfusion requirements were recorded until Day 5 in CPI-CL-004 only.

Indication: Pain

In the pivotal analgesia studies, the following safety data were collected:

- General AEs were recorded up to Day 14 in CPI-CL-008 A and B or Day 7 in CPI-CL-008C. AE recording was to be "continuous" while patients remained in hospital and via post-discharge telephone interviews on Day 14 (CPI-CL-008 A and B) or Day 7 (008C) in patients who were discharged before these time points. The method of soliciting AEs was not specified.
- In CPI-CL-008A and B, laboratory tests were performed at baseline and at 24, 48, 72, 120 and 168 h (7 days) after the first dose of study medication (with the final sample at study exit if this was occurred before 168 hs). The test types were as per the pivotal fever studies.
- In CPI-CL-008C, laboratory tests were only performed at baseline and 48 h after the first dose of study medication (or at discharge if this occurred before 48 hs). The tests were otherwise as per CPI-CL-008A and B, except that the international normalised ratio (INR) was determined as well as the PT.
- Investigators in all 3 pivotal pain studies were asked to state whether any laboratory abnormalities were clinically significant.
- Vital signs were assessed at baseline and at intervals until discharge from hospital.
- Transfusion requirements were recorded until Day 5 or hospital discharge in CPI-CL-008A and B and until hospital discharge in 008C.

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

[19]The study reports variously specified PTT and/or APTT, with the reports and protocols of CLI-008 A, B and C specifying PTT in one part of the documents but APTT in another. The two tests assess the same (intrinsic and common) coagulation pathways but their normal values are quite different (around 70 seconds for the PTT and 30 seconds for the APTT). However, the sample case report forms only referred to the APTT, the presentation of results in the submission consistently identified the test an APTT, and the normal ranges quoted in the individual patient data were consistent with the APTT rather than the PTT.

Dose-response and non-pivotal efficacy studies

The non-pivotal antipyretic Study IND 32803 provided data on AEs, laboratory tests and vital signs at baseline and up to 120 h (5 days) after the first dose of study medication, plus a final assessment of AEs at Day 30 or on hospital discharge.

Other studies evaluable for safety only

CPI-CL-003 was a randomised, double-blind, placebo-controlled, crossover study of the safety and tolerability of Caldolor 400 mg in healthy adult patients. Twelve patients received Caldolor 400 mg q4h for 3 doses and placebo q4h for 3 doses. Caldolor was diluted in 100 mL normal saline and infused over 30 minutes. The two study treatments were given on consecutive days and safety assessments (AEs, laboratory tests and vital signs) were performed until 12 h after the last dose of the second study treatment.

Clinical pharmacology studies

Adverse events and vital signs were recorded before each dose of study medication and at intervals after each dose in the Phase I studies. Baseline laboratory tests were performed in all Phase I subjects but post-treatment laboratory tests were only performed in 5 subjects after receipt of placebo, thus preventing any meaningful comparison with Caldolor (for which post-treatment results were available from 30 subjects).

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Patient exposure

Pivotal studies

In the 5 pivotal studies, 659 patients received Caldolor and 431 received placebo. Table 17 provides a breakdown according to study, illness severity stratum (in CPI-CL-004), presence of malaria (in the fever studies) and Caldolor dose group.

Table 17. Number of patients exposed to Caldolor in the pivotal studies.

Study	Placebo (N=431)	IVIb			
		< 400 mg (N=61)	400 mg (N=195)	800 mg (N=403)	Overall (N=659)
CPI-CL-004 (Fever)					
Critically Ill / No Malaria	13 (3%)	26 (43%)	14 (7%)	0 (0%)	40 (6%)
Non-critically Ill / No Malaria	5 (1%)	15 (25%)	7 (4%)	0 (0%)	22 (3%)
Critically Ill / Malaria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-critically Ill / Malaria	10 (2%)	20 (33%)	10 (5%)	0 (0%)	30(5%)
Total CPI-CL-004	**28 (6%)**	**61 (100%)**	**31 (16%)**	**NA**	**92 (14%)**
CPI-CL-006, All Malaria (Fever)	**30 (7%)**	**NA**	**30 (15%)**	**NA**	**30 (5%)**
CPI-CL-008A (Pain)	**134 (31%)**	**NA**	**134 (69%)**	**138 (34%)**	**272 (41%)**
CPI-CL-008B (Pain)	**153 (35%)**	**NA**	**NA**	**166 (41%)**	**166 (25%)**
CPI-CL-008C (Pain)	**86 (20%)**	**NA**	**NA**	**99 (25%)**	**99 (15%)**

"Overall" column for CPI-CL-008C corrected by evaluator. NA = not applicable. IVIb = Caldolor.

The duration of Caldolor treatment in the pivotal studies ranged from 1 to 5 days (mean ± SD, 2 ± 0.7 days). Table 18 summarises cumulative Caldolor dosage in the pivotal studies. The mean cumulative dose of Caldolor per patient in the pivotal studies was 3477 mg.

Table 18. Cumulative Caldolor dose in the pivotal studies according to dose group.

Cumulative Caldolor dose	Caldolor dose group			
	< 400 mg (N=61)	400 mg (N=195)	800 mg (N=403)	Overall (N=659)
Mean ± SD (mg)	879 ± 327	2661 ± 1195	4266 ± 1566	3477 ± 1770
Median (mg)	600	2400	4000	4000
Min (mg)	100	400	800	100
Max (mg)	1200	5200	13600	13600
<400 mg	2 (3%)	0	0	2 (<1%)
400 mg	0	12 (6%)	0	12 (2%)
≥400 to <1200 mg	29 (48%)	3 (2%)	20 (5%)	52 (8%)
≥1200 to <2400 mg	30 (49%)	65 (33%)	4 (<1%)	99 (15%)
≥2400 to <4800 mg	0	83 (43%)	295 (73%)	378 (57%)
≥4800 to <7200 mg	0	32 (16%)	63 (16%)	95 (14%)
≥7200 mg	0	0	21 (5%)	21 (3%)

Other studies

In the non-pivotal fever study IND 32803, 222 patients with sepsis syndrome received IV ibuprofen 10 mg/kg up a maximum of 800 mg, q6h for 8 doses (2 days)[20]. The mean ibuprofen dose was 645 mg, providing a mean cumulative ibuprofen dose of 5156 mg per patient.

In the three Phase I clinical pharmacology / tolerability studies, 60 healthy subjects received 1 to 3 doses of Caldolor. The mean cumulative dose of Caldolor was 674 mg per subject.

Adverse events

The study reports documented treatment-emergent adverse events (TEAEs).

All adverse events (irrespective of relationship to study treatment)

Pivotal studies

The pivotal studies covered distinct indications and patient populations, with the possibility that TEAEs might differ between the two sets of studies. TEAEs were assessed for the entire pivotal study population and separately for the pivotal fever and pain studies.

[20] 224 patients were randomised to ibuprofen but 2 of these did not receive any study drug.

Combined indications

For the combined (fever and pain) indications, TEAEs in the pivotal studies were reported in 557/659 (85%) of Caldolor recipients and 369/431 (86%) placebo recipients. Amongst the Caldolor recipients who experienced TEAEs, the maximum TEAE severity was mild in 55%, moderate in 36% and severe in 8%. Corresponding percentages amongst the placebo recipients were 57% mild, 38% moderate and 6% severe. The overall incidence of TEAEs was broadly similar across the range of Caldolor doses: 85% for doses <400 mg, 79% in patients treated with Caldolor 400 mg and 87% in those treated with Caldolor 800 mg. The most common TEAEs in patients treated with Caldolor (incidence ≥6%) were nausea, vomiting, constipation, flatulence, pruritus, headache and anaemia. The incidence of these TEAEs was comparable in the Caldolor and placebo groups.

The combined data are dominated by the much larger number of patients in the pain studies, potentially obscuring important differences between Caldolor and placebo in the fever studies. Also, the comparison of Caldolor dose groups is confounded by the differing mix of fever and pain patients in the different groups[21].

Despite its obvious relevance for a new IV formulation, patients in the pivotal studies were apparently not specifically questioned about infusion site pain or discomfort. Instead, infusion site reactions were documented only as part of the general recording of AEs. Infusion site reactions recorded in this manner were infrequent but slightly more common in the Caldolor group than the placebo group (3.0% versus 1.8%). Most such events were mild with a few being moderate in severity. There was no evident relationship to Caldolor dose level. [22]

Fever studies

In the pivotal fever studies, the maximum dose of Caldolor was 400 mg. TEAEs were reported in 73% of the Caldolor group and 64% of the placebo group. Table 19 summarises the most common TEAEs (incidence >3%) in the fever studies according to their System Organ Class (SOC).

[21] Sponsor comment: TEAEs were assessed for the entire pivotal study population and also separately for the pivotal fever and pain studies. Tables of numbers of patients experiencing TEAEs occurring in >3% of patients were provided separately for the pivotal fever and pain studies.

[22] Sponsor comment: The sponsor responded to this comment and the clinical evaluator of the Supplementary data has provided further comments on this issue below under *Findings Relating to TEAE's Following Evaluation of Supplementary Clinical Data Provided*.

Table 19. Pivotal fever studies: Number and percentage of patients with the most common TEAEs (incidence >3%) by SOC and study treatment.

System Organ Class Preferred Term	Placebo (N=58)	IVIb ≤ 400 mg (N=122)
Any Treatment-Emergent Event	37 (64%)	89 (73%)
Blood and lymphatic system disorders	11 (19%)	44 (36%)*
Anaemia	4 (7%)	22 (18%)
Eosinophilia	7 (12%)	22 (18%)
Leukopaenia	1 (2%)	4 (3%)
Lymphocytosis	2 (3%)	5 (4%)
Monocytosis	2 (3%)	2 (2%)
Neutropaenia	2 (3%)	8 (7%)
Thrombocythemia	0	6 (5%)
Cardiac disorders	0	5 (4%)
Gastrointestinal disorders	15 (26%)	25 (20%)
Abdominal pain	5 (9%)	8 (7%)
Diarrhoea	3 (5%)	8 (7%)
General disorders and administration site conditions	1 (2%)	9 (7%)
Multi-organ failure	1 (2%)	5 (4%)
Infections and infestations	7 (12%)	23 (19%)
Bacteraemia	0	4 (3%)
Pneumonia bacterial	0	6 (5%)
Injury, poisoning and procedural complications	1 (2%)	7 (6%)
Investigations	2 (3%)	18 (15%)*
Blood lactate dehydrogenase increased	1 (2%)	6 (5%)
Metabolism and nutrition disorders	10 (17%)	31 (25%)
Hypernatremia	0	5 (4%)
Hypoalbuminemia	1 (2%)	7 (6%)
Hypokalemia	5 (9%)	15 (12%)
Hypomagnesemia	1 (2%)	5 (4%)
Hypoproteinemia	2 (3%)	7 (6%)
Nervous system disorders	1 (2%)	14 (11%)*
Headache	0	4 (3%)
Psychiatric Disorders	0	4 (3%)
Respiratory, thoracic and mediastinal disorders	4 (7%)	15 (12%)
Skin and subcutaneous tissue disorders	2 (3%)	11 (9%)
Vascular disorders	1 (2%)	12 (10%)
Hypotension	1 (2%)	5 (4%)

IVIb = Caldolor * p<0.05. TEAS were noticeably more common with Caldolor than placebo in almost every SOC except, surprisingly, gastrointestinal disorders.

Most of the individual TEAEs in the above table were also more common with Caldor than placebo, again with the unexpected exceptions of abdominal pain and diarrhoea.

Of particular note, given the known safety issues associated with the use of NSAIDs, are the higher rates of cardiac and vascular disorders, infections, abnormal investigations and anaemia in the Caldor group. Caldolor also appeared to be associated with small but

potentially important increases in the risk of serious TEAEs such as neutropenia and multi-organ failure[23].

These comparisons are based on small numbers and may not be reliable. They are nevertheless concerning because the proposition that Caldolor is safe for the management of fever, particularly in very unwell patients (in whom experience with oral ibuprofen is limited), is based on these same small numbers.

Pain studies

In the pivotal pain studies, the Caldolor dose was either 400 mg or 800 mg. TEAEs were reported in 88% of the Caldolor 400 mg group, 87% of the Caldolor 800 mg group and 89% of the placebo group. Table 20 summarises the most common TEAEs (incidence >3%) in the pain studies according to their SOC.

During short-term use of Caldolor at doses up to 800 mg q6h as an adjunct to morphine for the treatment of postoperative pain, Caldolor did not increase the overall risk of TEAEs compared to placebo. TEAEs were reported by the majority of patients but were generally of the types that one would expect to see after surgery and/or the use of opioid analgesia. Statistically significant differences between Caldolor 400 mg and placebo in respect of some TEAEs were not replicated in the Caldolor 800 mg group and probably represent the play of chance.

The most common SOC for TEAEs in all patients was gastrointestinal disorders: TEAEs in this SOC were reported in 74% of Caldolor 400 mg recipients, 65% of Caldolor 800 mg recipients and 70% of placebo patients. Compared to placebo, Caldolor patients in the 400 mg dose group experienced statistically more abdominal discomfort, cough, infusion site irritation, and vaginal haemorrhage but these differences were not replicated in the Caldolor 800 mg dose group. Pyrexia was less common with Caldolor than placebo (7% for Caldolor 400 and 800 mg, compared to 13% for placebo).

The number of patients studied was only sufficient to exclude differences between placebo and Caldolor in respect of common adverse events. Differences in the incidence of uncommon, rare or very rare adverse effects would be missed in these studies and that part of the safety assessment must rely on extrapolation from experience with oral ibuprofen (which, it should be noted, is not specifically approved for the type of perioperative use that is expected to occur with Caldolor).

In addition, because Caldolor was only studied as an adjunct to morphine for post-operative pain relief, small but potentially important differences between Caldor and placebo in the risk of adverse events may have been obscured by the larger number of events arising as a consequence of the surgery itself and the use of morphine.

Finally, the overall risk of TEAEs and the risk of individual TEAE types in the Caldolor group, relative to placebo, was somewhat different to what was seen in the fever studies. This supports the argument that the safety data for Caldolor should not just be analysed for the combined fever and pain studies, but separately for the two indications.

[23] Sponsor comment: The incidence of neutropenia and multi-organ failure did not reach significance.

Table 20. Pivotal pain studies: Number and percentage of patients with the most common TEAEs (incidence >3%) by SOC and study treatment.

		IVIb	
System Organ Class Preferred Term	Placebo (N=373)	400 mg (N=134)	800 mg (N=403)
Any Treatment-Emergent Event	332 (89%)	118 (88%)	350 (87%)
Blood and lymphatic system disorders	19 (5%)	7 (5%)	19 (5%)
Anaemia	16 (4%)	5 (4%)	17 (4%)
Gastrointestinal disorders	262 (70%)	99 (74%)	261 (65%)
Constipation	60 (16%)	23 (17%)	58 (14%)
Dyspepsia	6 (2%)	6 (4%)	4 (1%)
Flatulence	44 (12%)	10 (7%)	50 (12%)
Nausea	209 (56%)	77 (57%)	205 (51%)
Vomiting	62 (17%)	30 (22%)	73 (18%)
General disorders and administration site conditions	66 (18%)	20 (15%)	62 (15%)
Pyrexia	47 (13%)	9 (7%)	30 (7%)*
Infections and infestations	17 (5%)	3 (2%)	17 (4%)
Injury, poisoning and procedural complications	17 (5%)	7 (5%)	15 (4%)
Investigations	60 (16%)	22 (16%)	68 (17%)
Body temperature increased	19 (5%)	0*	15 (4%)
Metabolism and nutrition disorders	14 (4%)	7 (5%)	14 (3%)
Hypokalemia	11 (3%)	5 (4%)	8 (2%)
Musculoskeletal and connective tissue disorders	17 (5%)	7 (5%)	15 (4%)
Nervous system disorders	49 (13%)	20 (15%)	58 (14%)
Dizziness	8 (2%)	8 (6%)*	17 (4%)
Headache	36 (10%)	12 (9%)	38 (9%)
Psychiatric disorders	24 (6%)	7 (5%)	23 (6%)
Insomnia	15 (4%)	4 (3%)	13(3%)
Renal and urinary disorders	22 (6%)	10 (7%)	32 (8%)
Urinary retention	12 (3%)	7 (5%)	19 (5%)
Reproductive system and breast disorders	19 (5%)	15 (11%)	14 (3%)
Vaginal haemorrhage	16 (4%)	13 (10%)*	13 (3%)
Respiratory, thoracic and mediastinal disorders	22 (6%)	10 (7%)	30 (7%)

IVIb = Caldolor. * p<0.05

Other studies

The report of the non-pivotal study IND 32803 in patients with sepsis syndrome summarised the number of TEAEs (65 ibuprofen and 62 placebo) but not the number of *patients* with TEAEs. However, the evaluator was able to construct a suitable summary table from the individual patient listings. TEAEs were reported in 52/224 (23%) of the patients who received ibuprofen, compared to 44/231 (19%) of those who received placebo.

The incidence of TEAEs was slightly higher with IV ibuprofen than with placebo but very low in both groups compared to the pivotal studies. This finding raises questions about the reliability of the TEAE data from IND 32803. It may reflect the clinical state of the study patients, many of whom were presumably too ill to self-report AEs. It could also represent poor compliance with AE recording during the study, or a tendency for investigators to ignore TEAEs that they did not regard as treatment-related. Although for further information concerning this, please refer to the section, 'Findings Relating to TEAE's

Following Evaluation of Supplementary Clinical Data Provided' where the evaluator indicates that although the absolute incidence of TEAEs in IND 32803 may be understated the relative comparison between IV ibuprofen should remain valid.

Amongst the individual AE types, hypotension was noticeably more common in IV ibuprofen recipients and GI bleeding was noticeably more common in the placebo group. The latter finding is unexpected and was not seen when treatment-related TEAEs were considered (see above).

In the Phase I studies, 28/60 (47%) subjects treated with Caldolor (200-800 mg) reported TEAEs. The maximum severity of TEAEs was mild in 17/28 (61%) and moderate in 11/28 (39%). The majority of Phase I TEAEs were infusion site reactions, which were reported in 22/60 (37%) of the Phase I subjects. Infusion site reactions were most common when undiluted Caldolor was administered in Study CPI-CL-001, particularly in the 400 and 800 mg dose groups where they were reported by 7/12 (58%) and 6/12 (50%) of the subjects, respectively. When Caldolor 400 mg was diluted and infused over 1 h in CPI-CL-003, only 1/12 (8%) of the subjects reported an infusion site reaction, "pressure above IV insertion site". When Caldolor was diluted but infused over 5-7 minutes in CPI-CL-011, 4/12 (33%) of the subjects reported infusion site reactions (all mild pain) during Caldolor infusion, compared to 0/12 during placebo infusion.

The next most common TEAE in Phase I Caldolor recipients was headache, which was reported in 8% of subjects after Caldolor infusion, compared to 6% after oral ibuprofen and 0% after infusion of placebo.[24]

Treatment-related adverse events (adverse drug reactions)

For each TEAE, the investigator was asked to provide an opinion as to whether the TEAE was causally related to study treatment. The resulting information was provided in summary tabular format as appendices to the ISS but only for both indications combined. The results were not discussed by the sponsor in the ISS or in the sponsor's *Clinical Overview* or *Summary of Clinical Safety*.

In the following discussion, "treatment-related" refers to TEAEs that were classified by the investigator as at least possibly related to study treatment.[25]

Pivotal studies

In the pivotal studies, TEAEs that were considered by the investigators to be at least possibly related to study treatment were reported in 29% of Caldolor recipients and 26% of placebo recipients. When broken down according to Caldolor dose, treatment-related TEAEs were significantly less common for Caldolor 100-200 mg than placebo, significantly more common for Caldolor 400 mg than placebo and there was no significant difference between Caldolor 800 mg and placebo.

Of note, there was one case of "acute hepatic failure" reported as a treatment-related TEAE in the Caldolor 800 mg group.

Because data for treatment-related TEAEs were combined for the two indications, one cannot determine whether the risk of such TEAEs with Caldolor (compared to placebo) differed between the indications. It is possible that the apparent excess of treatment-

[24] Sponsor comment: All instances of headache in Phase I trials occurred during Study CPI-CL-001 where the PK of oral ibuprofen was compared to IV infusion of Caldolor. During this study no IV placebo was administered. No other Phase I studies reported headache as a TEAE in treatment or placebo groups.

[25] Sponsor comment: It is important to note that: TEAEs were assessed for the entire pivotal study population and also separately for the pivotal fever and pain studies. Tables of numbers of patients experiencing TEAEs occurring in >3% of patients were provided separately for the pivotal fever and pain studies.

related TEAEs in the 400 mg dose group may be a chance association. Alternatively, it may represent an excess in patients treated with Caldolor for fever (an indication for which the 800 mg dose was not used). It seems unlikely that the findings merely represent a higher incidence of treatment-related TEAEs in patients who were critically ill (9% of the 400 mg dose group) given that there was no excess of treatment-related TEAEs in the 100-200 mg dose group (in which 42% of the patients were critically ill).

Other studies

The report on the non-pivotal study IND 32803 in patients with sepsis syndrome included a summary of the number of treatment-related TEAEs (16 ibuprofen, 13 placebo) but not the number of *patients* with treatment-related TEAEs. Treatment-related TEAEs were reported in 14/224 (6%) of the patients who received ibuprofen and 11/231 (4.8%) of those who received placebo.

The incidence of treatment-related TEAEs was a little higher in the placebo group. As previously discussed, the low incidence compared to the pivotal studies raises questions about the data collection. In addition to the potential causes mentioned in the previous section, it may also have been difficult for investigators to determine whether a particular TEAE represented an effect of study treatment or a complication of the underlying illness. However, for further clarification concerning this, please refer to the section below, '*Findings Relating to TEAE's Following Evaluation of Supplementary Clinical Data Provided',* which includes the evaluator's re-review and re-analysis of the data package.

Amongst the individual adverse event types, treatment-related hypotension appeared to be more common with ibuprofen, although the finding is based on only a small number of cases (4 ibuprofen and 1 placebo). As previously noted, GI bleeding (irrespective of cause) was more common in the placebo group but the incidence of treatment-related GI bleeding was slightly lower in the placebo group (2.2% versus 3.1%).

In the Phase I studies, treatment-related TEAEs were reported in 38% of Caldolor recipients, with most being injection site reactions. As previously noted, there were also several cases of decreased creatinine clearance and increased serum creatinine amongst subjects who received Caldolor 800 mg and oral ibuprofen and these were regarded by the investigator as treatment-related.

Findings relating to TEAE's following evaluation of supplementary clinical data provided

TEAEs

In the original submission, treatment-emergent adverse events (TEAEs) were presented for the overall study database and separately for the fever and pain studies. This information was summarised and discussed in the original clinical evaluation report. Additional material from the sponsor's response is covered here.

TEAEs - Combined indications

In the original evaluation, it was felt to be a shortcoming of the submitted studies that the incidence of infusion site reactions was determined only from open-ended questioning of subjects (regarding AEs in general), with no specific questioning or other predefined assessment regarding the presence, severity or nature of infusion site AEs. In response, the sponsor first stated that "adverse events and clinical laboratory assessments commonly associated with oral ibuprofen were specifically examined", which is not relevant to the issue of infusion site reactions. The sponsor then argued as follows: "Infusion pain, site pain and the tolerability of the infusion were investigated extensively in the Phase I Study CPI-CL-003, a randomised, placebo-controlled, cross-over study that enrolled 14 healthy subjects. No statistically significant differences were found between the placebo or IVIb treatments for assessment of infusion pain or site pain. No bruising or swelling was observed. Erythema was observed in two subjects but was considered

related to IV catheter insertion. If Caldolor was not found to cause significant injection site AE when compared [verbatim] to placebo it would appear unnecessary to specifically question patients on this TEAE during the pivotal clinical studies. Further, a number of additional variables would have potentially confounded the data including:

- the variety of catheter sites used for Caldolor infusions during the clinical efficacy studies
- some infusions of Caldolor were given while the patient was in surgery and unable to provide response
- other concomitant medication and IV fluids would have been administered via the same sites
- some critically ill patients were on respiratory support and unable to provide responses."

The statistical power of a study with only 14 subjects is far too low to exclude a clinically relevant increase compared to placebo in the incidence or severity of infusion site reactions. Given that Caldolor was irritant when given undiluted and that the pharmacokinetic studies prior to the pivotal trials had used weaker dilutions and longer infusion times than were used in the pivotal trials, it would have been preferable for the pivotal studies to specifically assess infusion site reactions. The potential confounders noted by the sponsor should not have prevented a valid assessment because they would have been evenly distributed between the Caldolor and placebo groups. Nevertheless, it is reasonable to assume that if any infusion site reactions were missed by the open-ended questioning, then they were probably minor and insufficient to prevent the registration of Caldolor.

TEAEs - Pivotal fever studies

The original clinical evaluation report noted that in the fever studies, the overall incidence of TEAEs, the incidence of TEAEs in some SOCs and the incidence of some individual TEAEs were higher in Caldolor recipients than in placebo recipients. The differences between Caldolor and placebo were not statistically significant but this offered little reassurance due to the low number of subjects involved and the resulting low power of the statistical analysis. Furthermore, a causal association between Caldolor and some of these TEAEs was plausible given the known pharmacological actions and/or adverse effects of nsNSAIDs.

The sponsor's response again drew attention to statistical comparisons, supplemented by a discussion of the circumstances of the individual AEs. The sponsor argued that the AEs should not be a cause for concern because the incidence was not significantly different between Caldolor and placebo and because the responsible investigator almost always considered that the AEs were not related to study treatment.

The lack of statistically significant differences between the treatment groups is essentially meaningless because of the low sample size and consequent low statistical power of the analyses. The fact that the investigators generally felt that the individual events were not related to study treatment offers some reassurance but ignores any patterns and trends in the data (the elucidation of which is, after all, one of the reasons for performing placebo-controlled trials). As noted in the original clinical evaluation unfavourable trends were seen for some TEAEs but the submitted studies for the fever indication are simply too small to either confirm or dismiss these potential safety signals, particularly for the critically ill population (in which there is little experience with oral ibuprofen) and when a direct or indirect causal relationship to ibuprofen is plausible on pharmacological grounds.

TEAEs - Pivotal pain studies

The original clinical evaluation noted that the overall incidence and pattern of TEAEs was similar in the Caldolor and placebo groups in the pivotal pain studies. However, a large proportion of the TEAEs were of types that were more likely to be related to concomitant opioid administration. These may have swamped small but potentially relevant differences between Caldolor and placebo. The evaluator also pointed out that the number of patients studied was only sufficient to have excluded a difference between Caldolor and placebo in respect of the most common AEs and that information relating to less frequent AEs would have to be extrapolated from experience with oral ibuprofen.

The sponsor responded that "ibuprofen is a well characterised medicine with extensive history of use and well known adverse effects including those considered to be rare".

This extensive history includes limited experience with pre-operative administration and does not take into account emerging evidence (as discussed in this supplementary evaluation) regarding risks associated with the short-term use of NSAIDs.

Treatment-related TEAEs

In the original submission, treatment-related TEAEs (TEAEs that were classified by the investigators as at least possibly related to study treatment or where the relationship to treatment was "unknown") were analysed only for the combined study database and not for the fever and pain indications separately.

Pivotal fever studies

Treatment-related TEAEs in the pivotal Fever studies are summarised according to SOC in Table 25, below.

Table 25. TEAEs related to study drug by SOC in pivotal fever studies.

SOC	Placebo (N=58)	IVIb		
		< 400 mg (N=61)	400 mg (N=61)	Overall (N=122)
Any event related to study drug	8 (14%)	6 (10%)	6 (10%)	12(10%)
		0.577	0.577	
Blood and lymphatic system disorders	3 (5%)	0	1 (2%)	1 (<1%)
Eye disorders	0	1 (2%)	(0 %)	1 (<1%)
Gastrointestinal disorders	4 (7%)	1 (2%)	4(7%)	5 (4%)
Injury, poisoning and procedural complications	0	1(2%)	1 (2%)	2 (2%)
Investigations	0	2 (3%)	0	2(2%)
Musculoskeletal and connective tissue disorders	1 (2%)	0	0	0
Skin and subcutaneous tissue disorders	0	0	1 (2%)	1 (<1%)
Vascular disorders	0	1 (2%)	0	1 (<1%)

IVIb = Caldolor.

The new analysis shows no concerning trends for treatment-related TEAEs in the Fever studies but no firm conclusions can be drawn due to the small number of patients studied.

Other fever studies

The original clinical evaluation questioned the low incidence of TEAEs reported in the non-pivotal study in critically ill patients, IND 32803. The sponsor has now stated that "This study was an NIH-sponsored (government grant) investigator initiated study, run by academic institutions - Cumberland, the US sponsor, simply obtained the rights to the data from this study. The low incidence of TEAEs is a characteristic of academic versus

sponsored trials and reflects their different aims. The academic sites only collected TEAEs that they felt could be related to the study drug in this seriously ill patient population. Therefore TEAEs should be viewed as treatment-related TEAEs."

This explanation is not entirely believable, given that (a) the report of IND 32803 included a separate section on treatment-related TEAEs (with a much lower incidence of events than the section on TEAEs) and (b) examination of the line listings shows that many TEAEs were classified by the investigators as not related to study treatment. However, given that the study was adequately blinded, it is reasonable to assume that each investigator used the same criteria for reporting TEAEs in all their patients, irrespective of whether they received IV ibuprofen or placebo. Thus, the absolute incidence of TEAEs in IND 32803 may be understated but the *relative* comparison between IV ibuprofen should remain valid. In relative terms, TEAEs were about 20% more common with ibuprofen than placebo, being reported in 52/224 (23%) of the patients who received ibuprofen, compared to 44/231 (19%) of those who received placebo (corresponding to a relative risk for TEAEs of 1.2).

Pivotal pain studies

Treatment-related TEAEs in the pivotal pain studies are summarised according to SOC in Table 26 below.

The incidence of treatment-related TEAEs was noticeably and statistically significantly higher in the Caldolor 400 mg dose group than in the placebo group but a corresponding increase was not seen in the Caldolor 800 mg dose group. This inverse relationship between Caldolor dose and the incidence of TEAEs within the one indication means that the finding is likely to have arisen by chance or is confounding.

The sponsor's response also included summary information regarding a case of hepatic failure in a Caldolor 800 mg recipient that was classified as treatment-related and noted in the original clinical evaluation. The information indicates that the hepatic failure and accompanying renal failure were preceded by and most likely due to severe hypotension, rather than having been caused by Caldolor.

Table 26. TEAEs related to study drug by SOC in pivotal pain studies.

SOC	Placebo (N=373)	IVIb		
		400 mg (N=134)	800 mg (N=403)	Overall (N=537)
Any event related to study drug	103(28%)	71 (53%)	107 (27%)	178 (33%)
		<0.001	0.747	
Blood and lymphatic system disorders	9 (2%)	4 (3%)	4 (<1%)	8 (1%)
Cardiac disorders	3 (<1%)	0	3 (<1%)	3 (<1%)
Gastrointestinal disorders	73 (20%)	51 (38%)	66(16%)	117 (22%)
General disorders and administration site conditions	24 (6%)	15 (11%)	20 (5%)	35 (7%)
Hepatobiliary disorders	0	0	2 (<1%)	2 (<1%)
Immune system disorders	1 (<1%)	2(1%)	0 (0%)	2 (<1%)
Infections and infestations	2 (<1%)	0	3(<1%)	3 (<1%)
Injury, poisoning and procedural complications	10 (3%)	4 (3%)	5 (1%)	9 (2%)
Investigations	19(5%)	17 (13%)	24 (6%)	41 (8%)
Metabolism and nutrition disorders	3(<1%)	1 (<1%)	4 (<1%)	5 (<1%)
Musculoskeletal and connective tissue disorders	4 (1%)	4 (3%)	5 (1%)	9 (2%)
Nervous system disorders	17 (5%)	17 (13%)	22 (5%)	39 (7%)
Psychiatric system disorders	3 (<1%)	2(1%)	6 (1%)	8 (1%)
Renal and urinary disorders	5 (1%)	2 (1%)	9 (2%)	11 (2%)
Reproductive and breast disorders	5 (1%)	3 (2%)	3 (<1%)	6 (1%)
Respiratory, thoracic and mediastinal disorders	5 (1%)	2(1%)	5 (1%)	7 (1%)
Skin and subcutaneous tissue disorders	20(5%)	8(6%)	17 (4%)	25 (5%)
Vascular disorders	11 (3%)	5(4%)	8 (2%)	13 (2%)

IVIb = Caldolor

Deaths and other serious adverse events (SAEs)

Pivotal studies

There were 6 deaths during the pivotal studies. There were 5 deaths amongst Caldolor recipients (0.8%) and 1 in a placebo recipient (0.2%). None were considered by the investigators to be related to study treatment. Of note, all of the deaths occurred in the critically ill subgroup of fever study CPI-CL-004. In this subgroup, 5/40 (13%) Caldolor recipients died, compared to 1/13 (8%) placebo recipients.

Overall, SAEs were reported in 7% of Caldolor recipients compared to 3% of placebo recipients. The incidence of SAEs was 5% and 7% in the Caldolor 400 mg and 800 mg dose groups, respectively. SAEs were much more frequent (18%) in the Caldolor 100-200 mg dose group.

The increased mortality associated with Caldolor use was confined to the critically ill subgroup. In that subgroup, mortality was increased 1.6 fold in the Caldolor group compared to placebo, or 5% in absolute terms. This finding is based on a small number of patients but is nevertheless a concern.

There were no SOCs or event types for which the incidence of SAEs was noticeably higher in Caldolor recipients compared to placebo. Many of the SAEs were potentially related to the underlying illness, surgical procedure or concomitant medication (such as morphine).

Nevertheless, the overall incidence of SAEs was approximately doubled in Caldolor recipients compared to placebo. The absolute increase in the incidence of SAEs was 4%.

Because SAE data were combined for the two indications, one cannot determine whether the risk of SAEs with Caldolor (compared to placebo) differed between the indications. The large (in percentage terms) excess of SAEs in the Caldolor 100-200 mg dose group is evidently an artefact due to a high proportion of critically ill fever patients in that relatively small subgroup. SAEs were more common in critically-ill fever patients than non-critically ill patients. Critically ill fever patients constituted 26 (42%) of the 61 patients in the Caldolor 100-200 mg dose group, and 9 of the 11 patients in that dose group who had SAEs. Nevertheless, the sponsor was asked to provide an analysis of SAEs within each of the two indications.

However, please refer to the section below '*Findings Relating to Deaths and Other Serious Adverse Events (SAEs) Following Evaluation of Supplementary Clinical Data Provided*', which provides a discussion of the available data by the clinical evaluator following the review of a re-analysis of the previously provided safety data.

Other studies

In the non-pivotal Study IND 32803, critically ill patients with sepsis syndrome received IV ibuprofen 10 mg/kg up a maximum of 800 mg or placebo q6h for 2 days. The primary outcome was the effect of IV ibuprofen on mortality. The study was stopped early, in accordance with the protocol, when a planned interim futility analysis showed that continuation of the trial would be very unlikely to reveal a significant difference between the two treatment groups. When the study was stopped, there had been 204 deaths which were evenly distributed between the IV ibuprofen 800 mg and placebo groups. Mortality at 14 days, 30 days and over the entire hospital admission was comparable in the IV ibuprofen and placebo groups (Table 21).

Table 21. IND 32803: Mortality.

	Placebo n=231	Ibuprofen n=224	Both n=455	Significance
Day 14	69 (29.87%)	62 (27.68%)	131 (28.79%)	Pearson Chi2 P=0.606 Fisher's Exact P=0.679
Day 30	92 (39.83%)	84 (37.50%)	176 (38.68%)	Pearson Chi2 P=0.610 Fisher's Exact P=0.631
This Admission*	102 (44.16%)	102 (45.54%)	204 (44.84%)	Pearson Chi2 P=0.767 Fisher's Exact P=0.778

* Includes all participants who died during this stay in the hospital, regardless of whether the death occurred during the 30 day study or after day 30.

Mortality in IND32803 was also examined within subgroups of patients with normal or elevated baseline values for creatinine, bilirubin or both. Within each of these subgroups, IV ibuprofen did not increase mortality compared to placebo.

The study report for IND 32803 included a summary of SAEs (16 ibuprofen, 19 placebo) but not the number of *patients* with SAEs. The evaluator was able to construct a summary table from the individual patient listings. SAEs (fatal or non-fatal) were reported in 11/224 (5%) of the patients who received ibuprofen and 17/231 (7%) of those who received placebo. Treatment-related SAEs were reported in 6 (2.7%) and 2 (0.9%) of the ibuprofen and placebo recipients, respectively.

There were no deaths or serious TEAEs during the Phase I studies.

In the pivotal Study CPI-CL-004, the use of Caldolor to treat fever in critically ill patients appeared to be associated with increased mortality but the finding was based on only a small number of patients. In the larger non-pivotal Study IND 32803, the short term use of IV ibuprofen in critically ill patients had no effect on mortality.

In IND 32803, the incidence of SAEs was similar in the IV ibuprofen and placebo groups. Treatment-related SAEs were three times as common with IV ibuprofen compared to placebo but the absolute incidence of treatment-related SAEs was low, as was the absolute difference between the two treatment groups (1.8%).

Findings relating to deaths and other Serious Adverse Events (SAEs) following evaluation of supplementary clinical data provided

Pivotal fever studies

As noted above, there were 6 deaths during the pivotal studies, none were considered by the investigators to be related to study treatment. All of the deaths occurred in the critically ill subgroup of fever study CPI-CL-004. In this subgroup, 5/40 (13%) Caldolor recipients died, compared to 1/13 (8%) placebo recipients (RR for death = 1.6). Although based on small numbers, this was a concern to the evaluator. In response, the sponsor reiterated that none of the deaths were ascribed to study medication by the investigators and argued that "The very small number of deaths in each treatment group makes it impossible to draw any conclusions from these results".

The circumstances of the deaths do not appear to be related to the known pharmacological actions of ibuprofen and the numbers are indeed too low to draw any meaningful conclusions. Reassuringly, IV ibuprofen did not increase mortality, compared to placebo, in the much larger non-pivotal study in critically ill patients, IND 32803.

SAEs in the pivotal fever studies are summarised in Table 27, below.

Table 27. SAEs by SOC in pivotal fever studies.

SOC	Placebo (N=58)	IVIb		
		< 400 mg (N=61)	400 mg (N=61)	Overall (N=122)
Any SAE	4 (7%)	11 (18%)	4 (7%)	15 (12%)
p-value vs. placebo		<0.001	0.379	
Cardiac disorders	0 (0%)	1 (2%)	1 (2%)	2 (2%)
Eye disorders	1 (2%)	1 (2%)	0 (0%)	1 (<1%)
Gastrointestinal disorders	3 (1%)	0 (0%)	2 (1%)	9 (1%)
General disorders and admin. site conditions	1 (2%)	3 (5%)	1 (2%)	4 (3%)
Infections and infestations	1(2%)	2 (3%)	1 (2%)	3 (2%)
Injury, poisoning and procedural complications	0	0	1(2%)	1 (<1%)
Musculoskeletal and connective tissue disorders	1 (2%)	0	0	0
Neoplasms benign, malignant and unspecified	1 (<1%)	0	0	0
Nervous system disorders	0	3 (5%)	0	3(2%)
Renal and urinary disorders	0	0	1 (2%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders	1 (2%)	3 (5%)	0	3 (2%)
Vascular disorders	0	2 (3%)	2 (3%)	4(3%)

IVIb = Caldolor.

The incidence of SAEs was noticeably and statistically significantly higher in the Caldolor <400 mg dose group (Caldolor doses of 100 or 200 mg) than in the placebo group but a corresponding increase was not seen in the Caldolor 400 mg dose group. This inverse relationship between Caldolor dose and the incidence of TEAEs within the one indication means that the finding is more likely to have arisen by chance or is confounding.

Pivotal pain studies

There were no deaths in the pivotal pain studies. SAEs in the pivotal pain studies are summarised in Table 28, below.

Table 28. SAEs by SOC in pivotal pain studies.

SOC	Placebo (N=373)	IVIb		
		400 mg (N=134)	800 mg (N=403)	Overall (N=537)
Any SAE	11 (3%)	6 (4%)	27 (7%)	33 (6%)
p-value vs. placebo		0.379	0.039	
Cardiac disorders	0	0	2 (<1%)	2(<1%)
Gastrointestinal disorders	3 (1%)	2 (1%)	7 (2%)	9 (2%)
General disorders and admin. site conditions	1 (<1%)	0	0	0
Hepatobiliary disorders	1 (<1%)	0	1 (<1%)	1 (<1%)
Infections and infestations	1(<1%)	0	6 (1%)	6(1%)
Injury, poisoning and procedural complications	0	1 (<1%)	3 (<1%)	4 (<1%)
Investigations	1 (<1%)	0	1 (<1%)	1 (<1%)
Musculoskeletal and connective tissue disorders	0	1 (<1%)	1 (<1%)	2 (<1%)
Nervous system disorders	0	0	1 (<1%)	1 (<1%)
Psychiatric Disorders	0	0	1 (<1%)	1 (<1%)
Renal and urinary disorders	0	0	2 (<1%)	2 (<1%)
Reproductive and breast disorders	0	0	2 (<1%)	2 (<1%)
Respiratory, thoracic and mediastinal disorders	3 (<1%)	2 (1%)	2 (<1%)	4 (<1%)
Surgical and medical procedures	0	0	1 (<1%)	1 (<1%)
Vascular disorders	2 (<1%)	0	2 (<1%)	2(<1%)

IVIb = Caldolor.

The incidence of SAEs was significantly higher in the Caldolor 800 mg dose group than in the placebo group. There was also an apparent relationship between Caldolor dose and the incidence of SAEs. The sponsor argued that most of the SAEs were classified by the investigators as not related to study drug and that when these were excluded there was no excess of treatment-related SAEs in the Caldor groups. There was also no excess of discontinuations due to SAEs in the Caldolor groups. These considerations are not sufficient, however, to completely discount the pattern that was seen in the all-cause SAE data. The pivotal studies show a small excess of SAEs when Caldolor 800 mg was used for the treatment of perioperative pain and this should be taken into account in the benefit-risk assessment.

Discontinuation due to adverse events

Pivotal studies

In the pivotal studies, TEAEs leading to discontinuation of study drug were reported in 32/659 (5%) of Caldolor recipients and 19/431 (4%) placebo recipients. The incidence of TEAEs leading to discontinuation was 3% for Caldolor 100-200 mg, 6% for Caldolor 400 mg and 4% for Caldolor 800 mg. The most common SOCs for TEAEs leading to discontinuation were Skin and Subcutaneous tissue disorders and Gastrointestinal disorders. Amongst the individual TEAEs leading to discontinuation, pruritus was the most common (in 1% of Caldolor and 2% of placebo recipients), followed by nausea, dizziness and headache (each in <1% of both Caldolor and placebo recipients).

In the pivotal studies, few patients discontinued due to TEAEs and there were no obvious differences between Caldolor and placebo. Because discontinuation data were combined for the two indications as part of the original submission, it was not possible to determine whether the risk of discontinuing Caldolor treatment (compared to placebo) differed between the indications, however, please refer to '*Findings Relating to Discontinuation Due to Adverse Events Following Evaluation of Supplementary Clinical Data Provided*' which provides additional clarification.

Other studies

In the non-pivotal Study IND 32803 in critically ill patients with sepsis syndrome, TEAEs led to discontinuation of treatment in 6/224 (3%) of the patients who received IV ibuprofen and 5/231 (2%) of those who received placebo.

One Phase I subject treated with 400 mg Caldolor was discontinued from the study due to the TEAE of "sensation of pressure" at the IV site, which was considered to be related to study drug.

Findings relating to discontinuation due to adverse events following evaluation of supplementary clinical data provided

In the original submission, discontinuations due to AEs were analysed only for the combined study database and not for the fever and pain indications separately. The sponsor's response included analyses for the separate indications.

Pivotal fever studies

Discontinuations due to AEs in the pivotal fever studies are summarised in Table 29, below. All occurred in the critically ill subgroup of Study CPI-CL-004.

Table 29. Discontinuations due to AEs by SOC in pivotal fever studies.

SOC	Placebo (N=58)	IVIb			
		100 mg (N=31)	200mg (N=30)	400 mg (N=61)	Overall (N=122)
Any TEAE: study/study drug discontinuation	1(2%)	2(6%)	0	0	2 (2%)
p-value					
Blood and lymphatic system disorders	1 (2%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (3%)	0	0	1 (<1%)
Eye disorders	0	1(3%)	0	0	1 (<1%)

IVIb = Caldolor.

The placebo patient was discontinued due to thrombocytopenia of moderate severity. One patient from the Caldolor 100 mg group was discontinued from study treatment due to multisystem organ failure and bilateral tension pneumothorax. The second discontinuation in the Caldor 100 mg treatment group was due to a dilated and fixed right pupil after one dose of study drug, the relationship to the study drug was unknown for this case.

No meaningful conclusions can be drawn from the limited data available.

Pivotal pain studies

Discontinuations due to AEs in the pivotal pain studies are summarised Table 30, below.

Table 30. Discontinuations due to AE

SOC	Placebo (N=373)	IVIb		
		400 mg (N=134)	800 mg (N=403)	Overall (N=537)
Any TEAE: study/study drug discontinuation	18 (5%)	12 (9%)	18 (4%)	30 (6%)
p-value		0.090	0.865	
Blood and lymphatic system disorders	0 (0%)	1 (<1%)	1 (<1%)	2 (<1%)
Gastrointestinal disorders	5 (1%)	3 (2%)	5 (1%)	8 (1%)
General disorders and admin. site conditions	2 (<1%)	3 (2%)	4 (<1%)	8 (1%)
Immune system disorders	1 (<1%)	2 (1%)	0 (0%)	2 (<1%)
Injury, poisoning and procedural complications	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Investigations	5 (1%)	0 (0%)	0 (0%)	0 (0%)
Nervous system disorders	0 (0%)	3 (2%)	4 (<1%)	7 (1%)
Psychiatric disorders	2 (<1%)	0 (0%)	1 (<1%)	1 (<1%)
Reproductive and breast disorders	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders	1 (<1%)	1 (<1%)	1 (<1%)	3 (<1%)
Skin and subcutaneous tissue disorders	7 (2%)	0 (0%)	6 (1%)	6 (<1%)

IVIb = Caldolor.

The incidence of discontinuations due to AEs was noticeably but not statistically significantly higher in the Caldolor 400 mg dose group than in the placebo group but a corresponding increase was not seen in the Caldolor 800 mg dose group. This inverse relationship between Caldolor dose and the incidence of TEAEs within the one indication means that the finding is likely to have arisen by chance or is confounding.

Laboratory tests

Pivotal studies

The pivotal studies were too small to reliably detect between-treatment differences in the laboratory safety profile of Caldolor and placebo *within* a particular study. Accordingly, the evaluation of laboratory safety relies on the aggregated data provided in the ISS. However there were a number of problems with ISS laboratory data that combined to prevent a satisfactory assessment of laboratory safety.

Importantly, the evaluator of the initial evaluation report felt that there were discrepancies between two sets of tables in regard to the number of patients with post

baseline laboratory abnormalities, however, for further information and clarification concerning this please see the following section, '*Findings Relating to Laboratory Tests Following Evaluation of Supplementary Clinical Data Provided'*.

Findings relating to laboratory tests following evaluation of supplementary clinical data provided

The sponsor has clarified that the source of the apparent discrepancies between different laboratory data tables in the original submission was the use of different definitions of "abnormal" for the summary tables of abnormalities and the shift tables. The former only included patients with post-baseline values that were abnormal in a clinically relevant direction (such as patients with a post-baseline urea above the upper limit of normal (ULN) were included but not those with a post-baseline urea below the lower limit of normal (LLN)). The denominator in these tables includes all patients with a post-baseline value for a particular test, including those who had no baseline value. In contrast, the shift tables included all patients with a post-baseline abnormality (either low or high), provided they also had a baseline value.

Regarding the tables of laboratory abnormalities, the original submission included tables showing the number of patients with a laboratory abnormality at any post-baseline time point and tables showing the number of patients with a laboratory abnormality at the final assessment. Since the final assessment was often well after study drug had been ceased, the former are regarded as being most relevant (and also correspond to the usual presentation of laboratory abnormalities in a submission).

As regards the shift tables, it was noted in the original evaluation that the tables combined the data for shifts to low and high abnormal values, even when only a shift in one direction would be clinically relevant. In their response, the sponsor declined to separate the two shift directions and stated that information relating to the shifts that were in a clinically relevant direction could be obtained from the tables of abnormal values and the tables of clinically significant abnormal values. This is not quite correct since the tables to which the sponsor referred include all patients with post-baseline abnormalities in a clinically relevant direction, *irrespective of the baseline value* but it is acknowledged that they provide the most relevant data.

The tables in the original submission were based on the combined indications so that any differences between the laboratory safety profiles of Caldolor in the two indications could not be assessed. For completeness, however, the main summary table of post-baseline laboratory abnormalities from the ISS is included as Table 31. Coagulation test results in the pivotal studies (combined fever and pain indications) are summarised in Table 32.

The sponsor has now provided separate analyses of the laboratory data for the two indications. This information is covered below, along with laboratory data from the non-pivotal study in critically ill patients.

Table 31. Pivotal studies: Patients with laboratory abnormalities at any post-baseline time point (Combined fever and pain studies). Table continued across 3 pages.

Abnormal Laboratory Values[1]	Placebo (N=431)	IVIb			
		< 400 mg* (N=61)	400 mg (N=195)	800 mg (N=403)	Overall (N=659)
Any Selected Abnormal Value	428/428 (100%)	60/60 (100%)	193/193 (100%)	391/391 (100%)	644/644 (100%)
Any Chemistry Abnormal Value:	400/421 (95%)	58/60 (97%)	189/192 (98%)	372/386 (96%)	619/638 (97%)
Albumin (g/dL): Any Abnormal Value	251/406 (62%)	50/58 (86%)	101/181 (56%)	245/372 (66%)	396/611 (65%)
≥ 3x ULN	0/406	0/58	0/181	0/372	0/611
≥ (1/3)x LLN	1/406(<1%)	4/58 (7%)	1/181 (<1%)	0/372	5/611 (<1%)
ALT (SGPT) (U/L): Any Abnormal Value	58/408 (14%)	29/59 (49%)	48/181 (27%)	31/371 (8%)	108/611 (18%)
≥ 3x ULN	9/408 (2%)	1/59 (2%)	11/181 (6%)	8/371 (2%)	20/611 (3%)
AST (SGOT) (U/L): Any Abnormal Value	63/408 (15%)	33/59 (56%)	58/181 (32%)	37/371 (10%)	128/611(21%)
≥ 3x ULN	12/408 (3%)	5/59 (8%)	12/181 (7%)	4/371 (1%)	21/611 (3%)
Bicarbonate (mmol/L) : Any Abnormal Value	50/417 (12%)	16/60 (27%)	40/192 (21%)	63/381 (17%)	119/633 (19%)
≥ 3x ULN	0/417	0/60	0/192	0/381	0/633
≥ (1/3) x LLN	0/417	0/60	0/192	0/381	0/633
BUN (mg/dL) : Any Abnormal Value	16/411 (4%)	14/60 (23%)	11/188 (6%)	9/379 (2%)	34/627 (5%)
≥ 3x ULN	1/411 (<1%)	0/60	2/188 (1%)	1/379 (<1%)	3/627 (<1%)
Chloride (mmol/L): Any Abnormal Value	76/417 (18%)	25/60 (42%)	59/192 (31%)	74/381 (19%)	158/633 (25%)
≥ 3x ULN	0/417	0/60	0/192	0/381	0/633
≥ (1/3)x LLN	0/417	0/60	0/192	0/381	0/633
Creatinine (mg/dL): Any Abnormal Value	23/414 (6%)	3/60 (5%)	8/188 (4%)	24/382 (6%)	35/630 (6%)
≥ 3x ULN	0/414	0/60	1/188 (<1%)	1/382 (<1%)	2/630 (<1%)
Glucose (mg/dL): Any Abnormal Value	269/410 (66%)	48/58 (83%)	132/188 (70%)	221/380 (58%)	401/626 (64%)
≥ 3x ULN	0/410	1/58 (2%)	1/188 (<1%)	3/380 (<1%)	5/626 (<1%)
≥ (1/3)x LLN	1/410 (<1%)	0/58	0/188	0/380	0/626
Lactate Dehydrogenase (U/L): Any Abnormal Value	134/410 (33%)	39/57 (68%)	82/186 (44%)	75/370 (20%)	196/613 (32%)
≥ 3x ULN	6/410 (1%)	1/57 (2%)	4/186 (2%)	2/370 (<1%)	7/613 (1%)

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Abnormal Laboratory Values[1]	Placebo (N=431)	IVIb			
		< 400 mg* (N=61)	400 mg (N=195)	800 mg (N=403)	Overall (N=659)
Potassium (mmol/L): Any Abnormal Value	90/417 (22%)	25/60 (42%)	47/192 (24%)	96/381 (25%)	168/633 (27%)
≥ 3x ULN	3/417	0/60	0/192	0/381	0/633
≥ (1/3)x LLN	0/417	0/60	0/192	0/381	0/633
Sodium (mmol/L): Any Abnormal Value	120/417 (29%)	25/60 (42%)	44/192 (23%)	72/381 (19%)	141/633 (22%)
≥ 3x ULN	0/417	0/60	0/192	0/381	0/633
≥ (1/3)x LLN	0/417	0/60	0/192	0/381	0/633
Total Bilirubin (mg/dL): Any Abnormal Value	56/406 (14%)	15/59 (25%)	34/181 (19%)	32/372 (9%)	81/612 (13%)
≥ 3xULN	2/406 (<1%)	1/59 (2%)	2/281 (1%)	2/372 (<1%)	5/612(<1%)
Total Protein (g/dL): Any Abnormal Value	293/406 (72%)	41/59 (69%)	142/180 (79%)	295/371 (80%)	478/610 (78%)
≥ 3x ULN	0/406	0/59	0/180	0/371	0/610
≥ (1/3)x LLN	0/406	0/59	0/180	0/371	0/610
Any Selected Abnormal Value	428/431 (99%)	60/61 (98%)	193/195 (99%)	391/403 (97%)	644/659 (98%)
Any Haematology Abnormal Value	424/428 (99%)	60/60 (100%)	192/193 (99%)	389/391 (99%)	641/644 (100%)
Basophils (%): Any Abnormal Value	34/407 (8%)	1/59 (2%)	34/187 (18%)	24/378 (6%)	59/624 (9%)
≥ 3x ULN	1/407 (<1%)	0/59	1/187 (<1%)	0/378	1/624 (<1%)
Eosinophils (%): Any Abnormal Value	56/408 (14%)	21/59 (36%)	58/187 (31%)	27/379 (7%)	106/625 (17%)
≥ 3xULN	27/408 (7%)	2/59 (3%)	22/187 (12%)	2/379 (<1%)	26/625 (4%)
Hematocrit (%): Any Abnormal Value	348/427 (81%)	56/60 (93%)	151/193 (78%)	345/391 (88%)	552/644 (86%)
≥ 3x ULN	0/427	0/60	0/193	0/391	0/644
≥ (1/3)x LLN	0/427	0/60	0/193	0/391	0/644
Haemoglobin (g/dL): Any Abnormal Value	348/428 (81%)	57/60 (95%)	155/192 (81%)	342/391 (87%)	554/643 (86%)
≥ 3x ULN	0/428	0/60	0/192	0/391	0/643
≥ (1/3)x LLN	0/428	0/60	0/192	0/391	0/643
Lymphocytes (%): Any Abnormal Value	366/413 (89%)	46/59 (78%)	168/188 (89%)	306/383 (80%)	520/630 (83%)
≥ 3x ULN	0/413	0/59	1/188 (<1%)	0/383	1/630 (<1%)
≥ (1/3)x LLN	55/413(13%)	19/59 (32%)	17/188 (9%)	26/383 (7%)	62/630 (10%)

*The <400 mg treatment group is comprised solely of patients enrolled in study CPI-CL-004. When comparing the <400 mg patients to the placebo patients from study CPI-CL-004, there were no clinically significant differences between treatment groups compared to placebo in the number of abnormal laboratory results coded as clinically significant. The placebo and 400 mg and 800 mg treatment groups above are comprised of patients enrolled in the additional studies CPI-CL-006, CPI-CL-008A (placebo and 400 mg), CPI-CL-008B (placebo), and CPI-CL-008C (placebo) and represent comparable integrated data.

IVIb = Caldolor. ULN = upper limit of normal. LLN = lower limit of normal. Note: References to "≥ (1/3)× LLN" are evidently incorrect and should actually read "≤ (1/3)× LLN".

Table 32. Pivotal studies: Summary of coagulation test results (Combined fever and pain studies).

APTT	**Placebo**	**Caldolor**			
		100-200mg	**400 mg**	**800 mg**	**Overall**
Baseline mean ± SD	30 ± 4.4	31 ± 5.4	30 ± 4.5	29 ± 3.7	29 ± 4.1
Mean ± SD change from baseline to most extreme value (seconds)	1 ± 6.7	3 ± 13.7 p=0.71 (NS)	3 ± 17.4 p=0.68 (NS)	2 ± 8.8 p<0.001	2 ± 12.5 p<0.001
n/N (%) with shift from normal at baseline to abnormal during the study	47/310 (15%)	12/43 (28%)	25/145 (17%)	42/287 (15%)	79/745 (17%)
PT	Placebo	Caldolor			
		100-200mg	400 mg	800mg	Overall
Baseline mean ± SD	12.0 ± 2.1	12.3 ± 1.8	12.0 ± 2.4	11.8 ± 2.1	11.9 ± 2.2
Mean ± SD change from baseline to most extreme value n(seconds)	1.3 ± 2.9	0.4 ± 3.6 p=0.002	0.9 ± 2.2 p=0.008	1.2 ± 1.4 p=0.97 (NS)	1.0 ± 2.0 p<0.001
n/N (%) with shift from normal at baseline to abnormal during the study	74/268 (27%)	4/42 (10%)	29/123 (24%)	72/223 (32%)	105/388 (27%)

Source: Data collated by the evaluator from ISS Tables 15.2.1.1 to 15.2.4.4 and 17.2.1. p-value for comparison to placebo using Wilcoxin rank sum test. Mean values for APTT were rounded by the sponsor to the nearest second.

Pivotal fever studies

Table 33 summarises the number and percentage of patients in the pivotal fever studies with clinical chemistry/haematology abnormalities at any post-baseline time point. Table 35 summarises the number and percentage of patients in CPI-CL-004 with laboratory abnormalities that were deemed by the investigators to be clinically significant (this assessment was not performed in CPI-CL-006).

Table 33. Pivotal fever studies: Patients with laboratory abnormalities at any post-baseline time point. Table continued across three pages.

Abnormal Laboratory Values[1]	Placebo (N=58)	IVIb		
		< 400 mg (N=61)	400 mg (N=61)	Overall (N=122)
Any Selected Abnormal Value	58/58 (100%)	60/60 (100%)	61/61 (100%)	121/121 (100%)
Any Chemistry Abnormal Value:	58/58 (100%)	58/60 (97%)	61/61 (100%)	119/121 (98%)
Albumin (g/dL): Any Abnormal Value	37/58 (64%)	50/58 (86%)*	44/60 (73%)	94/118 (80%)
≥ 3x ULN	0/58	0/58	0/60	0/118
≥ (1/3)x LLN	1/58(2%)	4/58 (7%)	1/60 (2%)	5/118 (4%)
ALT (SGPT) (U/L): Any Abnormal Value	34/58 (59%)	29/59 (49%)	31/60 (52%)	60/119 (50%)
≥ 3x ULN	6/58 (10%)	1/59 (2%)	10/60 (17%)	11/119 (9%)
AST (SGOT) (U/L): Any Abnormal Value	26/58 (45%)	33/59 (56%)	35/60 (58%)	68/119(57%)
≥ 3x ULN	7/58 (12%)	5/59 (8%)	9/60 (15%)	14/119 (12%)
Bicarbonate (mmol/L) : Any Abnormal Value	10/58 (17%)	16/60 (27%)	15/61 (25%)	31/121 (26%)
≥ 3x ULN	0/58	0/60	0/61	0/121
≥ (1/3) x LLN	0/58	0/60	0/61	0/121
BUN (mg/dL) : Any Abnormal Value	9/58 (16%)	14/60 (23%)	10/61 (16%)	24/121 (20%)
≥ 3x ULN	1/58 (2%)	0/60	2/61(3%)	2/121 (2%)
Chloride (mmol/L): Any Abnormal Value	16/58 (28%)	25/60 (42%)	26/61 (43%)	51/121 (42%)
≥ 3x ULN	0/58	0/60	0/61	0/121
≥ (1/3)x LLN	0/58	0/60	0/61	0/121
Creatinine (mg/dL): Any Abnormal Value	2/58 (3%)	3/60 (5%)	3/61 (5%)	6/121 (5%)
≥ 3x ULN	0/58	0/60	1/61(2%)	1/121 (<1%)
Glucose (mg/dL): Any Abnormal Value	37/58 (64%)	48/58 (83%)*	41/61 (67%)	89/119 (75%)
≥ 3x ULN	0/58	1/58 (2%)	1/61 (2%)	2/119 (2%)
≥ (1/3)x LLN	0/58	0/58	0/61	0/119
Lactate Dehydrogenase (U/L): Any Abnormal Value	48/58 (83%)	39/57 (68%)	52/60 (87%)	91/117 (78%)
≥ 3x ULN	4/58 (7%)	1/57 (2%)	2/60 (3%)	3/117 (3%)

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Abnormal Laboratory Values[1]	Placebo (N=58)	IVIb		
		< 400 mg (N=61)	400 mg (N=61)	Overall (N=122)
Potassium (mmol/L): Any Abnormal Value	21/58 (36%)	25/60 (42%)	23/61 (38%)	48/121 (40%)
≥ 3x ULN	0/58	0/60	0/61	0/121
≥ (1/3)x LLN	0/58	0/60	0/61	0/121
Sodium (mmol/L): Any Abnormal Value	13/58 (26%)	25/60 (42%)*	21/61 (34%)	46/121 (38%)
≥ 3x ULN	0/58	0/60	0/61	0/121
≥ (1/3)x LLN	0/58	0/60	0/61	0/121
Total Bilirubin (mg/dL): Any Abnormal Value	17/58 (29%)	15/59 (25%)	22/60 (37%)	37/119 (31%)
≥ 3xULN	1/58 (2%)	1/59 (2%)	2/60 (3%)	3/119 (3%)
Total Protein (g/dL): Any Abnormal Value	30/58 (52%)	41/59 (69%)	42/60 (70%)	83/119 (70%)
≥ 3x ULN	0/58	0/59	0/60	0/119
≥ (1/3)x LLN	0/58	0/59	0/60	0/119
Any Selected Abnormal Value	58/58 (100%)	60/61 (98%)	61/61 (100%)	121/122 (99%)
Any Haematology Abnormal Value	58/58 (100%)	60/60 (100%)	61/61 (100%)	121/121 (100%)
Basophils (%): Any Abnormal Value	5/58 (9%)	1/59 (2%)	7/60 (12%)	8/119 (7%)
≥ 3x ULN	1/58 (2%)	0/59	0/60	0/119
Eosinophils (%): Any Abnormal Value	41/58 (71%)	21/59 (36%)*	42/60 (70%)	63/119 (53%)
≥ 3xULN	27/58 (47%)	2/59 (3%)*	22/60 (37%)	24/119 (20%)
Hematocrit (%): Any Abnormal Value	53/58 (91%)	56/60 (93%)	56/61 (92%)	112/121 (93%)
≥ 3x ULN	0/58	0/60	0/61	0/121
≥ (1/3)x LLN	0/58	0/60	0/61	0/121
Haemoglobin (g/dL): Any Abnormal Value	57/58 (98%)	57/60 (95%)	59/61 (97%)	116/121 (96%)
≥ 3x ULN	0/58	0/60	0/61	0/121
≥ (1/3)x LLN	0/58	0/60	0/61	0/121
Lymphocytes (%): Any Abnormal Value	52/58 (90%)	46/59 (78%)	53/60 (88%)	99/119 (83%)
≥ 3x ULN	0/58	0/59	0/60	0/119
≥ (1/3)x LLN	7/58 (12%)	19/59 (32%)*	5/60 (8%)	24/119 (20%)

continued next page

Abnormal Laboratory Values[1]	Placebo (N=58)	IVIb		
		< 400 mg (N=61)	400 mg (N=61)	Overall (N=122)
Monocytes (%): Any Abnormal Value	41/58 (71%)	26/59 (44%)*	40/60 (67%)	66/119 (55%)
≥ 3x ULN	0/58	0/59	0/60	0/119
Neutrophils (%): Any Abnormal Value	54/58(93%)	43/59 (73%)*	54/60 (90%)	97/119(82%)
≥ 3x ULN	0/58	0/59	0/60	0/119
≥ (1/3)x LLN	2/58 (3%)	0/59	0/60	0/119
Platelets ($x10^9$/L): Any Abnormal Value	44/58 (76%)	47/60 (78%)	48/61 (79%)	95/121(79%)
≥ 3x ULN	0/58	1/60 (2%)	0/61	1/121(<1%)
≥ (1/3)x LLN	6/58 (10%)	11/60 (18%)	9/61 (15%)	20/121 (17%)
WBC ($x10^9$/L): Any Abnormal Value	41/58 (71%)	45/60 (75%)	43/61 (70%)	88/121 (73%)
≥ 3x ULN	2/58 (3%)	3/60 (5%)	0/61	3/121 (2%)
≥ (1/3)x LLN	0/58	0/60	0/61	0/121

1. Footnote omitted from original. It should presumably read the same as the footnote in the corresponding table of the original submission, namely "Patients numbers are reported as the number of patients with an abnormality as a percentage of the number of patients with a post-baseline value reported". IVIb = Caldolor. ULN = upper limit of normal. LLN = lower limit of normal. Note: References to "≥ (1/3)× LLN" are evidently incorrect and should actually read "≤ (1/3)× LLN".

Unsurprisingly, given patients who had malaria were critically ill or had some underlying medical condition (generally an infection) that was causing their fever, chemistry and haematology abnormalities were exceedingly common. The sponsor has flagged with an asterisk those cells where the percentage of patients with abnormalities in a Caldolor dose group was significantly different (either higher or lower) than the corresponding percentage in the placebo group. The analysis was not extended to include a comparison of the combined Caldolor dose groups (the "Overall" column in the table) with placebo. Given the multiplicity of tests and the small number of patients in each dose group, no firm conclusions can be drawn from the presence or absence of statistically significant differences. However, it is worth noting that there were no worrisome patterns in the laboratory results (such as an excess of abnormalities in the Caldolor groups combined with a positive dose-response relationship).

Pivotal pain studies

Table 34 summarises the number and percentage of patients in the pivotal pain studies with clinical chemistry/haematology abnormalities at any post-baseline time point. Table 35 summarises the number and percentage of patients with laboratory abnormalities that were deemed by the investigators to be clinically significant.

Table 34. Pivotal pain studies: Patients with laboratory abnormalities at any post-baseline time point. Table continued across three pages.

Abnormal Laboratory Values[1]	Placebo (N=373)	IVIb		
		400 mg (N=134)	800 mg (N=403)	Overall (N=537)
Any Selected Abnormal Value	370/370 (100%)	132/132 (100%)	391/391 (100%)	523/523 (100%)
Any Chemistry Abnormal Value:	342/363 (94%)	128/131 (98%)	372/386 (96%)	500/517 (97%)
Albumin (g/dL): Any Abnormal Value	214/348 (61%)	57/121 (47%)*	245/372 (66%)	302/493 (61%)
≥ 3x ULN	0/348	0/121	0/372	0/493
≥ (1/3)x LLN	0/348	0/121	0/372	0/493
ALT (SGPT) (U/L): Any Abnormal Value	24/350 (7%)	17/121 (14%)*	31/371 (8%)	48/492 (10%)
≥ 3x ULN	3/350 (<1%)	1/121 (<1%)	8/371 (2%)	9/929 (2%)
AST (SGOT) (U/L): Any Abnormal Value	37/350 (11%)	23/121 (19%)*	37/371 (10%)	60/492(12%)
≥ 3x ULN	5/350 (1%)	3/121 (2%)	4/371 (1%)	7/492 (1%)
Bicarbonate (mmol/L) : Any Abnormal Value	40/359 (11%)	25/131 (19%)*	63/381 (17%)*	88/512 (17%)
≥ 3x ULN	0/359	0/131	0/381	0/512
≥ (1/3) x LLN	0/359	0/131	0/381	0/512
BUN (mg/dL) : Any Abnormal Value	7/353 (2%)	1/127 (<1%)	9/379 (2%)	10/506 (2%)
≥ 3x ULN	0/353	0/127	1/379 (<1%)	1/506 (<1%)
Chloride (mmol/L): Any Abnormal Value	60/359 (17%)	33/131(25%)*	74/381 (19%)	107/512 (21%)
≥ 3x ULN	0/359	0/131	0/381	0/512
≥ (1/3)x LLN	0/359	0/131	0/381	0/512
Creatinine (mg/dL):	21/356 (6%)	5/127 (4%)	24/382 (6%)	29/509 (6%)
Any Abnormal Value				
≥ 3x ULN	0/356	0/127	1/382 (<1%)	1/509 (<1%)
Glucose (mg/dL): Any Abnormal Value	232/352 (66%)	91/127 (72%)	221/380 (58%)*	312/507 (62%)
≥ 3x ULN	0/352	0/127	3/380 (<1%)	3/507 (<1%)
≥ (1/3)x LLN	1/352 (<1%)	0/127	0/380	0/507
Abnormal Laboratory Values[1]	Placebo (N=373)	IVIb		
		400 mg (N=134)	800 mg (N=403)	Overall (N=537)

continued next page

Lactate Dehydrogenase (U/L): Any Abnormal Value	86/352 (24%)	30/126 (24%)	75/370 (20%)	105/496 (21%)
≥ 3x ULN	2/352 (<1%)	2/126 (2%)	2/370 (<1%)	4/496 (<1%)
Potassium (mmol/L): Any Abnormal Value	69/359 (19%)	24/131 (18%)	96/381 (25%)*	120/512 (23%)
≥ 3x ULN	3/359	0/131	0/381	0/512
≥ (1/3)x LLN	0/359	0/131	0/381	0/512
Sodium (mmol/L): Any Abnormal Value	107/359 (30%)	23/131 (18%)	72/381 (19%)*	95/512 (19%)
≥ 3x ULN	0/359	0/131	0/381	0/512
≥ (1/3)x LLN	1/359	0/131	0/381	0/512
Total Bilirubin (mg/dL): Any Abnormal Value	39/348 (11%)	12/121 (10%)	32/372 (9%)	44/493 (9%)
≥ 3xULN	1/348 (<1%)	0/121	2/372 (<1%)	2/493(<1%)
Total Protein (g/dL): Any Abnormal Value	263/348 (76%)	100/120 (83%)	295/371 (80%)	395/491 (80%)
≥ 3x ULN	0/348	0/120	0/371	0/491
≥ (1/3)x LLN	0/348	0/120	0/371	0/491
Any Selected Abnormal Value	370/373 (99%)	132/134 (99%)	391/403 (97%)	523/537 (97%)
Any Haematology Abnormal Value	366/370 (99%)	131/132 (99%)	389/391 (99%)	520/523 (99%)
Basophils (%): Any Abnormal Value	29/349 (8%)	27/127 (21%)*	24/378 (6%)	51/505 (10%)
≥ 3x ULN	0/349	1/127 (<1%)	0/378	1/505(<1%)
Eosinophils (%): Any Abnormal Value	15/350 (4%)	16/127 (13%)*	27/379 (7%)	43/506 (8%)
≥ 3xULN	0/350	0/127	2/379 (<1%)	2/506 (<1%)
Hematocrit (%): Any Abnormal Value	295/369 (80%)	95/132 (72%)	345/391 (88%)*	440/523 (84%)
≥ 3x ULN	0/369	0/132	0/391	0/523
≥ (1/3)x LLN	0/369	0/132	0/391	0/523

Abnormal Laboratory Values[1]	**Placebo (N=373)**	**IVIb**		
		400 mg (N=134)	**800 mg (N=403)**	**Overall (N=537)**

continued next page

Haemoglobin (g/dL): Any Abnormal Value	291/370 (79%)	96/131 (73%)	342/391 (87%)*	438/522 (84%)
≥ 3x ULN	0/370	0/131	0/391	0/522
≥ (1/3)x LLN	0/370	0/131	0/391	0/522
Lymphocytes (%): Any Abnormal Value	314/355 (88%)	115/128 (90%)	306/383 (80%)*	421/511 (82%)
≥ 3x ULN	0/355	1/128 (<1%)	0/383	1/511(<1%)
≥ (1/3)x LLN	48/355(14%)	12/128 (9%)	26/383 (7%)*	38/511 (7%)
Monocytes (%): Any Abnormal Value	77/355 (22%)	35/128 (27%)	92/383 (24%)	127/511 (25%)
≥ 3x ULN	0/355	0/128	0/383	0/511
Neutrophils (%): Any Abnormal Value	206/355(58%)	76/128 (59%)	195/383 (51%)	271/511 (53%)
≥ 3x ULN	0/355	0/128	0/383	0/511
≥ (1/3)x LLN	2/355 (<1%)	0/128	1/383 (<1%)	1/511 (<1%)
Platelets ($x10^9$/L): Any Abnormal Value	43/363 (12%)	18/130 (14%)	43/389(11%)	61/519 (12%)
≥ 3x ULN	0/363	0/130	0/389	0/519
≥ (1/3)x LLN	0/363	0/130	0/389	0/519
WBC ($x10^9$/L): Any Abnormal Value	185/362 (51%)	52/131 (40%)	146/388 (38%)*	198/519 (38%)
≥ 3x ULN	0/362	0/131	0/388	0/519
≥ (1/3)x LLN	0/362	0/131	0/388	0/519

1. Footnote omitted from original. It should presumably read the same as the footnote in the corresponding table of the original submission, namely "Patients numbers are reported as the number of patients with an abnormality as a percentage of the number of patients with a post-baseline value reported". IVIb = Caldolor. ULN = upper limit of normal. LLN = lower limit of normal. Note: References to "≥ (1/3)× LLN" are evidently incorrect and should actually read "≤ (1/3)× LLN".

Table 35. Pivotal pain studies: Patients with laboratory abnormalities at any post-baseline time point that were deemed by the investigators to be clinically significant.

Patient group/subgroup Laboratory Values	Placebo	IVIb		
		400 mg	800 mg	Overall
Overall: N	373	134	403	537
Any Clinically Significant Value	42/370 (11%)	22/132 (17%)	48/391 (12%)	70/523 (13%)
p-value vs. Placebo[1]		0.131	0.823	
Chemistry	22/363 (6%)	14/131 (11%)	22/386 (6%)	36/517(7%)
Coagulation	2/360 (<1%)	1/131 (<1%)	1/380 (<1%)	2/511 (<1%)
Haematology	23/370 (6%)	12/132 (9%)	27/391 (7%)	39/523(7%)
Age 17-60 years: N	318	114	328	442
Any Clinically Significant Value	38/315 (12%)	18/112 (16%)	37/319 (12%)	55/431 (13%)
p-value vs. Placebo[1]		0.330	0.807	
Chemistry	19/309 (6%)	10/111 (9%)	15/315 (5%)	25/426 (6%)
Coagulation	2/305 (<1%)	1/111 (<1%)	1/311 (<1%)	2/422 (<1%)
Haematology	20/315 (6%)	12/112 (11%)	23/319 (7%)	35/431 (8%)
Age >60 years: N	55	20	75	95
Any Clinically Significant Value	4/55 (7%)	4/20 (20%)	11/72 (15%)	15/92 (16%)
p-value vs. Placebo[1]		0.198	0.269	
Chemistry	3/54 (6%)	4/20 (20%)	7/71 (10%)	11/91 (12%)
Coagulation	0/55	0/20	0/69	0/89
Haematology	3/55 (5%)	0/20	4/72 (6%)	4/92 (4%)
Male: N	56	35	61	96
Any Clinically Significant Value	7/56 (13%)	8/33 (24%)	9/58 (16%)	17/91 (19%)
p-value vs. Placebo[1]		0.249	0.792	
Chemistry	4/54 (7%)	4/33 (12%)	4/58 (7%)	8/91 (9%)
Coagulation	0/53	0/33	0/56	0/89
Haematology	3/56 (5%)	4/33 (12%)	6/58 (10%)	10/91 (11%)
Female: N	317	99	342	441
Any Clinically Significant Value	35/314 (11%)	14/99 (14%)	39/333 (12%)	53/432 (12%)
p-value vs. Placebo[1]		0.475	0.902	
Chemistry	18/309 (6%)	10/98 (10%)	18/328 (5%)	28/426 (7%)
Coagulation	2/307 (<1%)	1/98 (<1%)	1/324 (<1%)	1/422 (<1%)
Haematology	20/314 (6%)	8/99 (8%)	21/333 (6%)	29/432 (7%)

Patient group/subgroup Laboratory Values	Placebo	IVIb		
		400 mg	800 mg	Overall
White or Caucasian: N	230	112	265	377
Any Clinically Significant Value	28/228 (12%)	19/110 (17%)	35/255 (14%)	54/365 (15%)
p-value vs. Placebo[1]		0.244	0.788	
Chemistry	14/223(6%)	13/109 (12%)	16/252 (6%)	29/361 (8%)
Coagulation	2/221 (<1%)	1/109 (<1%)	1/246 (<1%)	2/355 (<1%)
Haematology	16/228 (7%)	10/110 (9%)	20/255 (8%)	30/365 (8%)
Black or African American: N	129	16	118	134
Any Clinically Significant Value	10/129 (8%)	2/16 (13%)	12/116 (10%)	14/132 (11%)
p-value vs. Placebo[1]		0.623	0.513	

Chemistry	4/127 (3%)	1/16 (6%)	5/114 (4%)	6/130 (5%)
Coagulation	0/126	0/16	0/114	0/130
Haematology	6/129 (5%)	1/16 (6%)	7/116 (6%)	8/132 (6%)
Other race: N	14	6	20	26
Any Clinically Significant Value	4/13 (31%)	1/6 (17%)	1/20 (5%)	2/26 (8%)
p-value vs. Placebo[1]		>0.999	0.135	
Chemistry	4/13 (31%)	0/6	1/20 (5%)	1/26 (4%)
Coagulation	0/13	0/6	0/20	0/26
Haematology	1/13 (8%)	1/6 (17%)	0/20	1/26 (4%)
[1] Based on Fisher's Exact Test				

IVIb = Caldolor.

The sponsor has flagged with an asterisk those cells where the percentage of patients with abnormalities in a Caldolor dose group was significantly different (either higher or lower) than the corresponding percentage in the placebo group. According to the sponsor, "Comparison to placebo for numbers of patients with increased or decreased laboratory values does not suggest a dose relationship with increasing doses of Caldolor for any laboratory values even where a significant difference to placebo exists".

It may be argued, however, that a relationship to Caldolor dose is apparent in Table 34 for abnormalities of haematocrit and haemoglobin. A more detailed breakdown of the data reveals that the statistically significant excess of haematocrit and haemoglobin abnormalities in the Caldolor 800 mg dose group consisted almost entirely of reductions to between the lower limit of normal and half the lower limit of normal (Table 36). A causal relationship to ibuprofen is plausible from a pharmacological perspective (possibilities include subclinical gastrointestinal bleeding or salt and water retention leading to haemodilution). The draft PI for Caldolor includes the following text under *Precautions - Haematological Effects:*

> "Anaemia may occur in patients receiving NSAIDs, including ibuprofen. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect on erythropoiesis. In patients on long-term treatment with NSAIDs, including ibuprofen, check haemoglobin or hematocrit if they exhibit any signs or symptoms of anaemia or blood loss. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effects on platelet function are less severe quantitatively, of shorter duration and reversible. Carefully monitor patients who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants."

Table 36. Pivotal pain studies: Patients with haematocrit or haemoglobin abnormalities at any post-baseline time point.

		IVIb		
Laboratory Panel Laboratory Parameter	**Placebo (N=373)**	**400 mg (N=134)**	**800 mg (N=403)**	**Overall (N=537)**
Hematocrit (%)				
Any Laboratory Value	369/370 (100%)	132/132 (100%)	391/391 (100%)	523/523 (100%)
Any Abnormality	295/369 (80%)	95/132 (72%)	345/391 (88%)	440/523 (84%)
> ULN - < 2xULN	0/369	1/132 (<1%)	1/391 (<1%)	2/523 (<1%)
2xULN - < 3xULN	0/369	0/132	0/391	0/523
≥3xULN	0/369	0/132	0/391	0/523
<LLN - > (1/2)xLLN	294/369 (80%)	94/132 (71%)	342/391 (87%)	436/523 (83%)
(1/2)xLLN - > (1/3)xLLN	1/369 (<1%)	1/132 (<1%)	2/391 (<1%)	3/523 (<1%)
≥(1/3)xLLN	0/369	0/132	0/391	0/523
Hemoglobin (g/dL)				
Any Laboratory Value	370/370 (100%)	131/132 (99%)	391/391 (100%)	522/523 (100%)
Any Abnormality	291/370 (79%)	96/131 (73%)	342/391 (87%)	438/522 (84%)
> ULN - < 2xULN	2/370 (<1%)	0/131	1/391 (<1%)	1/522 (<1%)
2xULN - < 3xULN	0/370	0/131	0/391	0/522
≥3xULN	0/370	0/131	0/391	0/522
<LLN - > (1/2)xLLN	289/370 (78%)	95/131 (73%)	339/391 (87%)	434/522 (83%)
(1/2)xLLN - > (1/3)xLLN	0/370	1/131 (<1%)	2/391 (<1%)	3/522 (<1%)
≥(1/3)xLLN	0/370	0/131	0/391	0/522

IVIb = Caldolor. ULN = upper limit of normal. LLN = lower limit of normal. Note: References to "≥ (1/3)× LLN" are evidently incorrect and should actually read "≤ (1/3)× LLN".

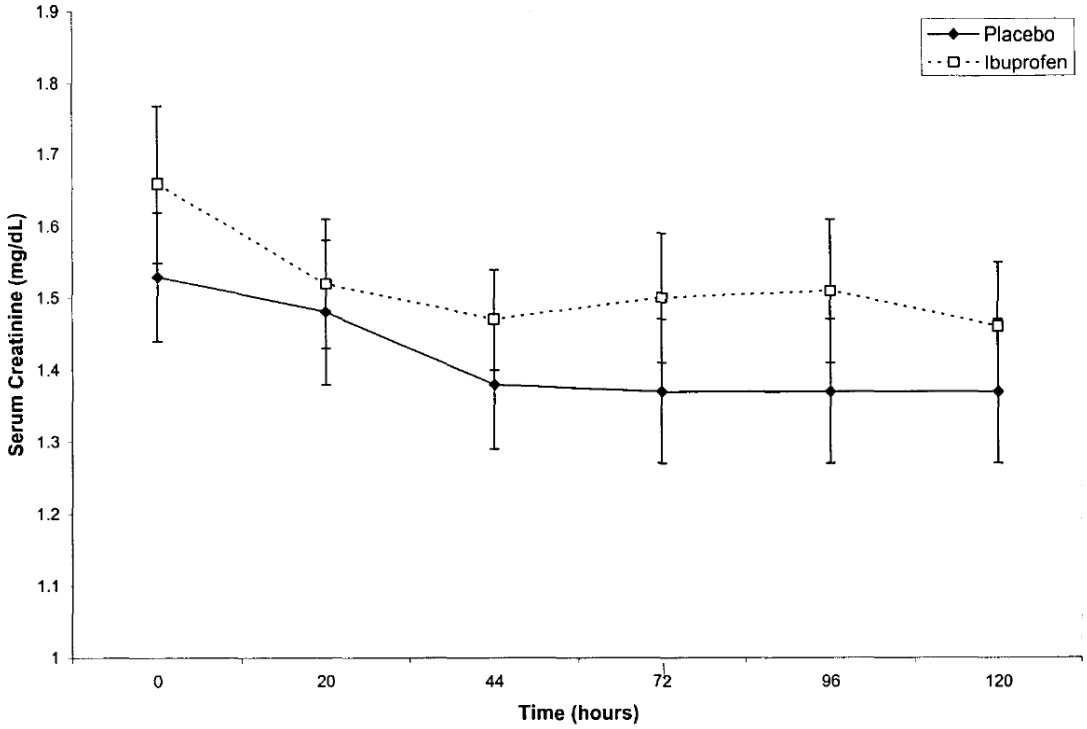
Non-pivotal study in critically ill patients

As noted in the original clinical evaluation, the report of the non-pivotal Study IND 32803 in critically ill patients with sepsis syndrome did not state the number and percentage of patients in each treatment group who had laboratory abnormalities at baseline, or treatment-emergent laboratory abnormalities, or treatment-emergent abnormalities at the final visit. The report did analyse mean and median laboratory changes from baseline in the two treatment groups but the clinical relevance of the changes could not be

determined in the absence of counts and percentages of patients with treatment-emergent laboratory abnormalities.

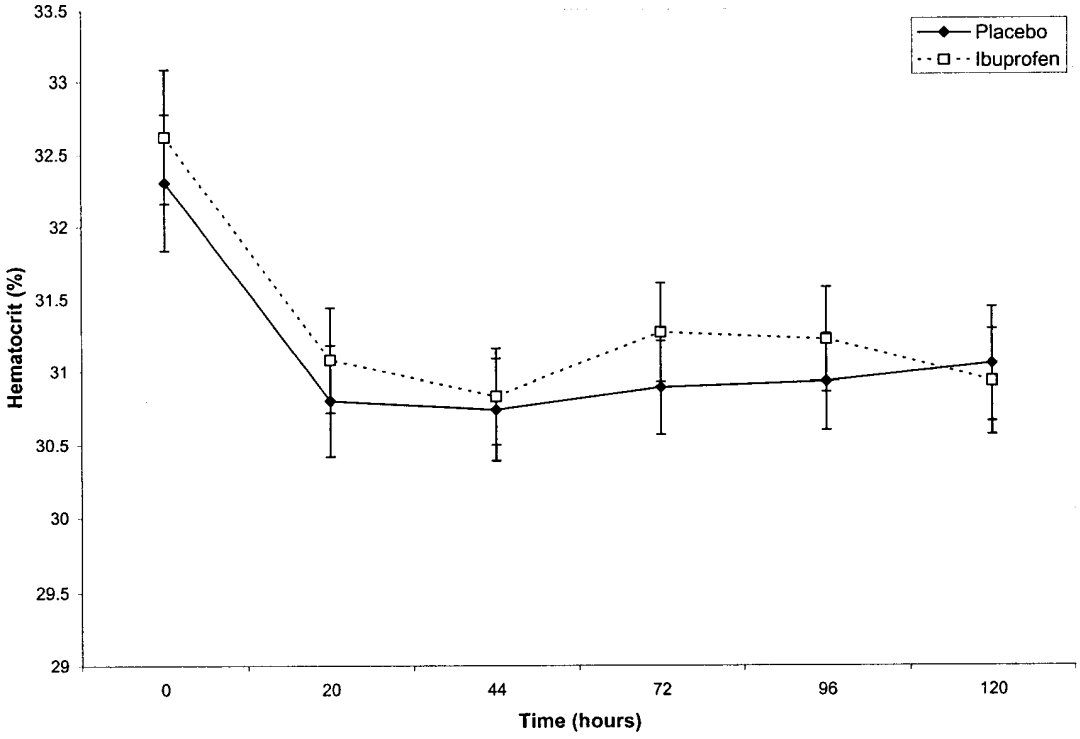
In response, the sponsor argued that no statistically significant differences were observed between placebo and IV ibuprofen in respect of mean and median laboratory changes from baseline (clinical chemistry/haematology results from IND 32803 are summarised, in Figures 7 to 9 below). The sponsor also argued that "Participants with sepsis frequently have abnormal laboratory measurements, however, if unexpected elevations or reductions in laboratory measurements were observed by the clinical centres they were reported as AEs. The laboratory measurements reported as AEs could be considered to be treatment-related adverse events." These were very few in number and are summarised in Table 37.

Figure 7. IND 32803 (Sepsis syndrome): Serum Creatinine over time (mg/dL, mean ± SE).



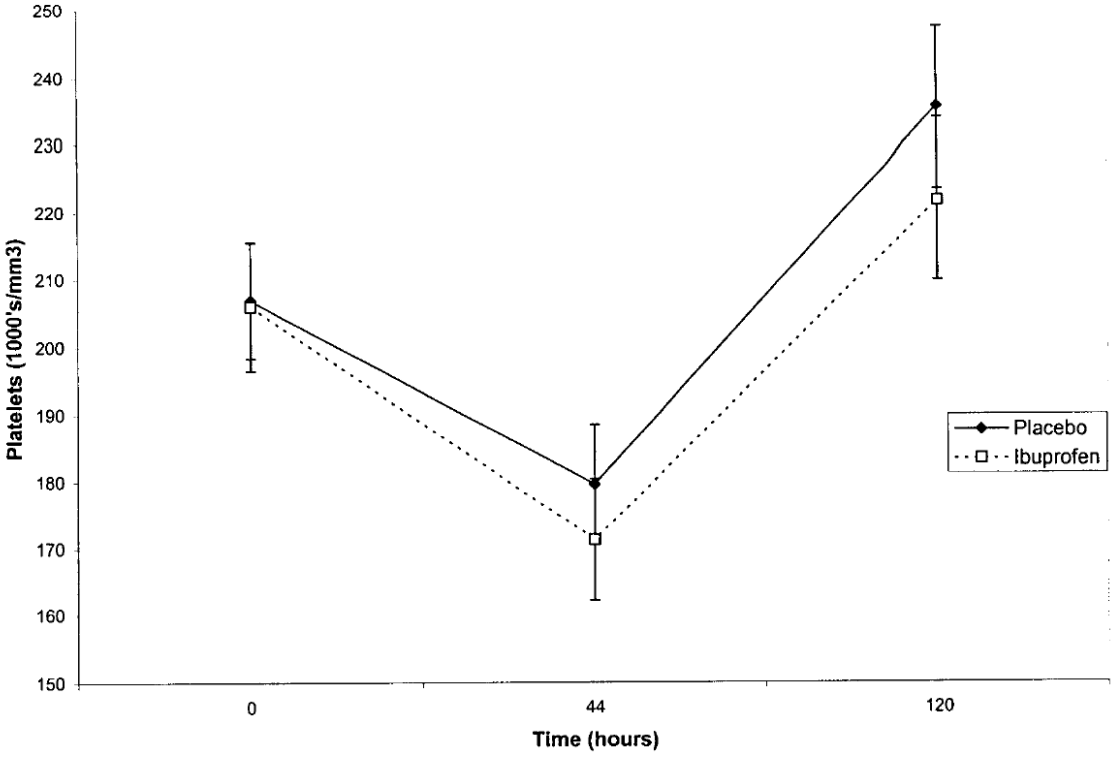
Note non-zero baseline on Y-axis.

Figure 8. IND 32803 (Sepsis syndrome): Haematocrit over time (%, mean ± SE).



Note non-zero baseline on Y-axis.

Figure 9. IND 32803 (Sepsis syndrome): Platelets over time (×103/mm3, mean ± SE).



Note non-zero baseline on Y-axis.

Table 37. IND 32803 (Sepsis syndrome): Number (%) patients with laboratory abnormalities reported as (treatment-related) AEs.

Laboratory abnormality	Placebo N=231	IV Ibuprofen N=224
Thrombocytopenia	2 (0.9)	2 (0.9)
Increased creatinine	3 (1.3)	3 (1.3)
Hyperbilirubinaemia	0	1 (0.4)

Percentages calculated by evaluator.

Although it was not a pivotal study, IND 32803 provides the main assessment of the safety of Caldolor in critically ill patients.

Aspartate aminotransferase (AST) was, on average, elevated at baseline. In the placebo group, AST dropped during treatment and then dropped further by the time of the post-treatment assessment. In the ibuprofen group, AST rose during treatment but then dropped to below baseline levels at the post-treatment assessment. Bilirubin showed a small rise in the placebo group and a small fall in the ibuprofen group. None of the between-treatment differences were statistically significant but the confidence intervals were wide. Hepatic adverse effects ranging from elevated liver function tests (LFTs) to fatal fulminant hepatitis are documented as potential adverse effects of ibuprofen in the US product literature[26].

Serum creatinine decreased somewhat in both treatment groups, with no meaningful difference between placebo and ibuprofen. Blood urea nitrogen decreased by a small amount in the placebo group and increased by a small amount in the ibuprofen group but the differences were not statistically or clinically significant.

Haemoglobin, haematocrit and white cell count fell slightly in both treatment groups over the course of the study, with no statistically or clinically significant difference between the ibuprofen and placebo groups.

Platelet count fell somewhat in both groups during treatment and then rose post-treatment, with no meaningful difference between the ibuprofen and placebo group results.

Overall, the pattern of laboratory abnormalities in critically ill patients given IV ibuprofen was consistent with the known effects of oral ibuprofen.

Coagulation tests

Prothrombin time (PT) and activated partial thromboplastin time (APTT) were measured in the submitted studies. Coagulation data separated by indication were not provided. Data from the original submission for the combined pivotal studies are summarised in Table 38.

[26] US Prod Info MOTRIN ® oral tablets, 2007; US Prod Info CALDOLOR IV injection, 2009), cited in DRUGDEX ® EVALUATION, IBUPROFEN.

Table 38. Pivotal studies: Summary of coagulation test results.

APTT	Placebo	Caldolor			
		100-200 mg	400 mg	800 mg	Overall
Baseline mean ± SD	30 ± 4.4	31 ± 5.4	30 ± 4.5	29 ± 3.7	29 ± 4.1
Mean ± SD change from baseline to most extreme value (seconds)	1 ± 6.7	3 ± 13.7 p=0.71 (NS)	3 ± 17.4 p=0.68 (NS)	2 ± 8.8 p<0.001	2 ± 12.5 p<0.001
n/N (%) with shift from normal at baseline to abnormal during the study	47/310 (15%)	12/43 (28%)	25/145 (17%)	42/287 (15%)	79/745 (17%)
PT	**Placebo**	**Caldolor**			
		100-200 mg	**400 mg**	**800 mg**	**Overall**
Baseline mean ± SD	12.0 ± 2.1	12.3 ± 1.8	12.0 ± 2.4	11.8 ± 2.1	11.9 ± 2.2
Mean ± SD change from baseline to most extreme value n(seconds)	1.3 ± 2.9	0.4 ± 3.6 p=0.002	0.9 ± 2.2 p=0.008	1.2 ± 1.4 p=0.97 (NS)	1.0 ± 2.0 p<0.001
n/N (%) with shift from normal at baseline to abnormal during the study	74/268 (27%)	4/42 (10%)	29/123 (24%)	72/223 (32%)	105/388 (27%)

Source: Data collated by the evaluator from ISS Tables 15.2.1.1 to 15.2.4.4 and 17.2.1. p-value for comparison to placebo using Wilcoxin rank sum test. Mean values for APTT were rounded by the sponsor to the nearest second.

The summary data in Table 38 show some statistically significant differences between placebo and Caldolor in respect of mean changes from baseline but these did not translate into consistent changes in the percentage of patients with abnormal values. On pharmacological grounds, one would not expect ibuprofen to alter the PT or APTT and the findings are probably due to confounding and/or the play of chance.

Tests of platelet function were not performed but it is known that ibuprofen, in common with other nsNSAIDs, reversibly inhibits platelet aggregation.

Vital signs

Pivotal studies

As was the case for the laboratory data, the ISS combined vital signs data from all 5 pivotal studies and did not compare Caldolor with placebo within the two different indications.

There were small but statistically significant changes from baseline in mean systolic and diastolic blood pressure within each treatment group, consistent with expectations in patients recovering from surgery or an acute illness. There were no statistically significant differences between the Caldolor groups and placebo. Statistically significant differences in mean pulse rate were seen between each Caldolor dose group and placebo. The difference was not tested for the combined Caldolor dose groups but was numerically small. Body temperature was lower with Caldolor than placebo, consistent with the antipyretic action of Caldolor.

The percentage of patients with clinically significant vital sign abnormalities was similar in the placebo, Caldolor 800 and overall Caldolor groups, and higher in the Caldolor 100-200 and 400 mg dose groups. The between-group differences were not statistically significant but the statistical power of the comparisons would have been poor for the two lower dose groups. This pattern probably reflects the different patient mix in the various dose groups but this is only speculation without an analysis of the data within each indication. In relation to the use of Caldolor in critically patients, it is reassuring that in the small subset of critically ill patients in CPOI-CL-004, clinically significant vital sign abnormalities were less common in the Caldolor 100-200 mg and 400 mg dose groups (46% and 43%, respectively) than the placebo group (77%).

Other studies

In the non-pivotal Study IND 32803 in critically ill patients with sepsis syndrome, IV ibuprofen Patients were, on average, tachycardic at baseline (mean heart rate 113.3 in the IV ibuprofen group and 114.1 in the placebo group). Heart rate decreased in both groups over the course of the study but the reduction was significantly greater in the IV ibuprofen group. Compared to placebo, IV ibuprofen was associated with a small decrease of about 4 mmHg in systolic and diastolic blood pressure, 4 h after the first dose. This was not seen at other time points. IV ibuprofen had no significant effect on minute ventilation or pulmonary vascular resistance. Compared to placebo, IV ibuprofen significantly reduced body temperature in febrile patients (as discussed above) and also in "normothermic" patients (these paints were actually, on average, mildly febrile at baseline and IV ibuprofen reduced their mean temperature to normal).

Ibuprofen did not have any clinically important unfavourable effects on vital signs in critically ill patients with sepsis syndrome, most of whom were febrile.

In the Phase I studies, there were no subjects with clinically important abnormal vital signs, as determined by the investigators. Mean vital sign changes from baseline were similar in Caldolor and placebo recipients.

Specific safety issues

Based on its pharmacological properties, there are a number of specific safety issues associated with the proposed use of Caldolor.

Bleeding

An increased risk of bleeding is a particular concern when proposing the use of a non-selective NSAID such as Caldolor in surgical patients or in severely ill patients who have an increased background risk of bleeding (for example due to coagulation defects secondary to disseminated intravascular coagulation or hepatic impairment). Despite this:

The incidence of bleeding events was not a specific safety endpoint in any of the studies. Bleeding events were recorded as part of routine adverse event reporting and thus appear in the lists of TEAEs. However, they appear under various SOCs and event terms with no overall assessment of the number or percentage of patients in each treatment group who had a bleeding event. Individual study reports asserted that such events "were specifically examined" and that "there were no clinically significant differences…when compared to placebo" but quantitative analyses supporting these assertions were not provided.

The surgical studies did not systematically examine for example whether Caldolor increased the amount of postoperative blood loss via drains.

Please note that a summary of the sponsor's response and the evaluator's assessment of the Supplementary data provided can be found in the section below, '*Findings Relating to* Bleeding Events *Following Evaluation of Supplementary Clinical Data Provided'.*

Findings relating to bleeding events following evaluation of supplementary clinical data provided

As mentioned above, a particular concern of the original evaluation was that Caldolor administration might be accompanied by an unacceptable risk of perioperative bleeding. This could present as intraoperative bleeding (when the drug is administered at the start of surgery) or postoperative bleeding (when the drug is administered at either the start or end of surgery). Despite statements in the study reports and the sponsor's response to the effect that special attention was paid to the "possible impact [of Caldolor] on bleeding", this was not reflected in the case reports forms except in relation to transfusion requirements. Otherwise, the case report forms (CRFs) only provided for non-directed AE recording. Also, in the study reports and the ISS, TEAEs representing bleeding were listed under a range of terms with no analysis of the overall incidence of bleeding events. Finally, transfusion requirements were only analysed for the combined fever and pain indications.

In response:

The sponsor again asserted that "specific attention was paid to any adverse events and clinical laboratory assessments commonly associated with bleeding". While this may have occurred in the reporting, the reporting was evidently based on non-targeted data collection, as noted above.

The sponsor reiterated the relevant sections of the various study reports but these had already been considered during the first evaluation and had been regarded as having inadequately addressed the matter.

The sponsor provided a summary of transfusions, separated according to indication.

- In the fever studies, transfusion data were collected only in CPI-CL-004. The proportion of patients who received a transfusion was noticeably higher in the Caldolor 400 mg group than the placebo group (25% versus 14%). The difference did not reach statistical significance but the number of subjects and thus the statistical power of the analysis was low. On the other hand, the total volume transfused was lower in the Caldolor 400 mg group than the placebo group (mean 675 versus 975 mL).
- In the pivotal pain studies, there was no obvious difference between Caldolor and placebo in respect of transfusion rates or volumes. Indeed, transfusion requirements tended to be lower in Caldolor recipients.

The sponsor provided a summary table of treatment-emergent bleeding AEs in the pivotal studies by SOC, preferred term and severity (Table 39). The events in the table were stated to have been "searched under the MedDRA preferred terms[27]: post procedural haemorrhage, haematuria, urethral haemorrhage, vaginal haemorrhage, epistaxis, wound haemorrhage". This search, however, did not cover all of the treatment-emergent bleeding AEs that were listed for the pivotal studies in the original submission. Missing MedDRA preferred terms (representing treatment-emergent bleeding AEs from the pivotal studies that were listed in ISS Appendix Table 5.2 but not included in the sponsor's search) were: Peritoneal haematoma, Peritoneal Haemorrhage, Infusion site bruising, Incision site haematoma, Incision site haemorrhage, Subdural haematoma, Vaginal haematoma, Ecchymosis, Haematoma, and Wound complication (in cases where the original terms used by the investigator indicated a bleeding event, such as "wound bruising", "wound

[27] Medical Dictionary for Regulatory Activities is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products (such as medical devices and vaccines). Coding these data to a standard set of MedDRA terms allows health authorities and the biopharmaceutical industry to more readily exchange and analyse data related to the safe use of medical products.

bleed").[28] Furthermore, the table only presented data for the *combined* fever and pain indications, despite repeated statements in the original evaluation report that this was an unsatisfactory approach to the analysis of the safety data. The evaluator therefore searched through the relevant tables in the pivotal study reports and manually extracted the data relating to all treatment-emergent bleeding events. Salient features of the summarised data include:

- In each of the fever studies and in the combined fever studies, the incidence of bleeding events was low and similar in the Caldolor and placebo treatment groups.
- In the post-operative pain studies, the incidence of bleeding events was also similar in the Caldolor and placebo groups. In the individual studies, bleeding events were markedly more frequent in CPI-CL-008A than in any of the other studies (whether for fever or pain) but within that study the incidence was a little lower in Caldolor recipients than in placebo recipients.
- There is no evidence in the submitted studies that the risk of bleeding events is increased when Caldolor is started preoperatively (at the start of surgery) as compared to postoperatively (at the end of surgery). However, it should be remembered that this observation is based on cross-study comparisons; that the number of patients who received Caldolor at the start of surgery was relatively low (only 99); that intraoperative blood loss was not specifically assessed; and that the safety experience with oral ibuprofen for perioperative analgesia in adults relates to postoperative rather than preoperative administration.

Table 39. Pivotal studies (combined fever and pain indications): Sponsors summary of treatment-emergent bleeding adverse events.

		IVIb			
Adverse Event Group Greatest Severity	Placebo (N=431)	<400 mg (N=61)	400 mg (N=195)	800 mg (N=403)	Overall (N=659)
Any Treatment-Emergent Bleeding Event	20 (5%)	1 (2%)	15 (8%)	20 (5%)	36 (5%)
Mild	17 (4%)	1 (2%)	15 (8%)	18 (4%)	34 (5%)
Moderate	3 (<1%)	0	0	1 (<1%)	1 (<1%)
Severe	0	0	0	1 (<1%)	1 (<1%)
p-value[1]		0.496	0.135	0.872	

IVIb = Caldolor.

The sponsor also provided a summary table of "bleeding complications" in IND 32803 (Table 40). Such events were seen in 7% of ibuprofen recipients and 10% of placebo recipients. The sponsor stated that "gastrointestinal bleeding was considered prior to the beginning of the study to be [a] major area of concern regarding the relative safety of ibuprofen. Consequently haemoglobin and haematocrit were measured and the requirements for transfusion of blood products, including packed red blood cells, whole blood, fresh frozen plasma and platelets were tracked during the first five days of the study." This much was documented in the study report. However, the sponsor also asserted that "At the pre-study Investigators meeting, Investigators and coordinators were notified of these potential risks and were asked for diligence in reporting events related to

[28] ISS Appendix Table 5.2 also listed the MedDRA preferred term "Conjunctival haemorrhage". This event occurred in the fever study CPI-CL-004 but examination of the individual patient data revealed that it was not actually treatment-emergent but occurred 26 days before the first dose of study medication. In addition, a bleeding event coded as "Faeces discoloured", for which the investigator's original term was "bright red stool" and a bleeding event coded as "Abdominal injury" for which the original term was "punctate intraparenchymal haemorrhage" also occurred before the first dose of study drug in CPI-CL-004.

renal toxicity or bleeding, whether thought to be related to CTM or not". Mention of this could not be located in the study report and the statement contrasts with the sponsor's earlier assertion that adverse events in IND 32803 were generally recorded only if the investigators considered them to be related to study treatment. However, it would be reasonable to assume that the investigators' propensity to report AEs would be the same for both treatment groups in this blinded study, so although the data in Table 40 might underestimate the true frequency of bleeding events, the comparison between ibuprofen and placebo should remain valid.

Table 40. IND 32803 (Sepsis syndrome): Sponsor's Summary of "bleeding complications".

Preferred Term	Placebo (N=231)	Placebo not related	IVIb (N=224)	IVIb not related
Total bleeding events	25 (10%)	10	15(7%)	3
Cerebrovascular accident	2(<1%)	2	3 (1%)	1
Gastrointestinal bleed	19(8%)	6	9(4%)	2
Hematuria	1 (<1%)	0	0	
Pulmonary haemorrhage	0		1(<1%)	0
Thrombocytopenia	2(<1%)	1	2(<1%)	0
Rectal haemorrhage	1(<1%)	1	0	

IVIb = Caldolor.

As previously noted, there were small reductions in mean haemoglobin and haematocrit in both the placebo and ibuprofen groups in IND 32803. The percentage of patients who received packed red cells or whole blood in the past 24 h was similar at baseline in the two treatment groups. During treatment, the percentage was a little higher in the ibuprofen group than the placebo group, as was the average number of units transfused (when all patients were taken into account). However, amongst those who received transfusions, the average number of units administered during treatment was slightly lower in the ibuprofen group than the placebo group (3.34 versus 3.66 units per person). None of these differences were statistically significant.

Overall, the submitted studies combined with past experience with oral ibuprofen provide adequate reassurance that the administration of Caldolor to treat fever or *postoperatively* for the treatment of pain should not be accompanied by an unacceptable increase in the risk of bleeding. Data relating to the preoperative administration of Caldolor also do not show an increase in the risk of bleeding but are quite limited and preoperative administration in adults is not supported by experience with oral ibuprofen.

Adverse effects on renal function

NSAIDs are known to adversely affect renal function, particularly in patients who are not adequately hydrated or when used in combination with certain other drugs (such as diuretics and ACE inhibitors, aminoglycosides). These clinical circumstances are not unexpected amongst patients in whom the use of Caldolor will be considered if it is approved for the proposed indications. Dehydration is common in fever patients and particularly so in those who are so unwell that they cannot manage oral medication. Pre-operative dehydration is also common in surgical patients due to fasting and is not likely to have been fully corrected if Caldolor is administered at the start of surgery.

Furthermore, the entry criteria for the submitted studies mean that the patients who were most at risk of developing renal impairment due to the use of Caldolor were excluded from the studies. Finally, experience tells that Caldolor is likely to be used in such patients if approved for the proposed indications, despite the contraindications and precautions in the PI. Accordingly even a small increase in the risk of renal function abnormalities in Caldolor recipients in the clinical trials would be a potential concern because it is likely to be magnified in actual clinical practice.

Pivotal studies

The pivotal studies should have provided evaluable data on renal function before and after treatment with Caldolor. However, the analyses were affected by a failure to separate the two different indications and reporting discrepancies as described previously in this evaluation.[29]

Other studies

The ISS states that in the Phase I studies, increased creatinine clearance was reported as an adverse event in 3/60 (5%) of Caldolor recipients and 5/48 (10%) oral ibuprofen recipients, with no data presented for placebo. These figures are misleading because post-baseline creatinine clearance was only measured in one of the Phase I studies, CPI-CL-001 (the denominator has been spuriously increased and the percentage of affected subjects decreased by including subjects in whom the effect of Caldolor or oral ibuprofen on creatinine clearance was not actually measured). Amongst the Phase I study subjects in whom it was actually measured, the incidence of increased creatinine clearance reported as an adverse event was 3/36 (8%) for Caldolor and 5/36 (14%) for oral ibuprofen. Furthermore, the changes all occurred in the high dose (800 mg) cohort of the study, so as a proportion of subjects who received that dose the figures become 3/6 (50%) for Caldolor and 5/6 (83%) for oral ibuprofen. The reductions in creatinine clearance were temporary.

The effect of IV ibuprofen on a range of renal parameters was assessed in the non-pivotal Study IND 32803 in critically ill patients with sepsis syndrome. The proportion of subjects experiencing *new onset* low urine output (≤0.5 ml/kg/h or ≤30 ml/h) was significantly higher in the IV ibuprofen group (45%, versus 32% in the placebo group; p=0.005). There were no significant differences between IV ibuprofen and placebo in respect of mean urine output or serum creatinine at any time-point.

The ISS explains the difference in the percentage of patients with new onset low urine output as being due to ibuprofen's known effect of salt and water retention. The ISS also noted that the proportion of patients who *did not* develop low urine output over the course of the study was the same in the placebo and ibuprofen groups (20%). The ISS further noted that dialysis was instituted in 13 patients (5.6%) in the placebo group, compared to only 6 patients (2.7%) who received IV ibuprofen, although this difference was not statistically significant (p=0.126).

However, this does not present the full picture. The report of IND 32803 provided the following additional relevant information:

- A higher proportion of placebo patients already had a low urine output at baseline (67% versus 52% in the ibuprofen group). This reduced the opportunity for *new onset* low urine output in the placebo group and partly explains the excess of new onset reduced urine output in the ibuprofen group. Nevertheless, amongst those at risk (amongst those who did not already have reduced urine output at baseline), a significantly lower proportion of placebo compared to ibuprofen recipients subsequently developed a reduced urine output (29/74 [39%] placebo, 55/97 [57%] ibuprofen, p=0.0023). On the other hand, as noted in the ISS, the same proportion of patients in each treatment group (20%) had avoided a low urine output (either pre-existing or new onset) by the end of the study.
- As noted in the ISS, dialysis was newly instituted in fewer ibuprofen recipients. However, the ISS failed to point out that a higher proportion of ibuprofen recipients

[29] Sponsor comment: See also secondary clinical evaluator's comments with regards to renal adverse events under *Findings Relating to Adverse Effects on Renal Function Following Evaluation of Supplementary Clinical Data Provided* below.

were already on dialysis at baseline. Overall, 18 placebo recipients (7.8%) underwent dialysis due to renal failure during the study, compared to 16 (7.1%) in the ibuprofen group. An additional placebo recipient received dialysis for lithium toxicity. These figures favour ibuprofen slightly but not to the extent depicted in the ISS.

- Serum creatinine values were not significantly different in the placebo and ibuprofen groups but this might just reflect a lack of statistical power as mean serum creatinine was a consistently a little higher in the ibuprofen group at each time point. More reassuring are the observations that this was also the case at baseline, that mean serum creatinine dropped in both groups over the course of the study and that it followed a fairly similar pattern in the ibuprofen and placebo groups (although perhaps with some divergence after the end of study treatment).

Overall, this study does not provide clear evidence regarding the effect of short-term IV ibuprofen treatment on renal function in critically ill patients with sepsis syndrome, due to baseline differences in the two treatment groups and the resulting difficulties of interpretation. However, further clarification was provided by the Sponsor as supplementary information which permitted the evaluation and conclusions provided in '*Findings Relating to Adverse Effects on Renal Function Following Evaluation of Supplementary Clinical Data Provided'.*

Findings relating to adverse effects on renal function following evaluation of supplementary clinical data provided

The sponsor submitted a reanalysis of renal adverse effects in the pivotal studies, in which data for the two indications were separated. This showed no differences between Caldolor and placebo within each indication. However, most of the events that were included in the reanalysis did not represent *renal* effects but rather were related to the lower urinary tract (dysuria, urinary retention, bladder discomfort, bladder spasm, pollakiuria and urethral haemorrhage) and are not relevant to the question of whether Caldolor has a significant adverse impact on renal function when used in critically ill patients or in the perioperative period.

In the pivotal fever studies, there were 2 cases of renal failure, both in patients who received Caldolor 400 mg. There were no cases of renal failure in placebo recipients. As shown in Table 41, treatment-emergent abnormalities of serum creatinine were slightly more common in Caldolor recipients than placebo recipients in the pivotal fever studies. The difference was small in absolute terms and not statistically significant (although the statistical power of the analysis was low due to the small sample size).

Table 41. Number (%) of patients with treatment-emergent abnormal serum creatinine in the pivotal fever studies.

	Placebo	Caldolor		
		<400 mg	400 mg	Overall
	(N=58)	(N=60)	(N=61)	(N=121)
Any abnormal value (> ULN)	2 (3%)	3 (5%)	3 (5%)	6 (5%)
Any value ≥3× ULN	0	0	1 (2%)	1 (<1%)

ULN = upper limit of normal.

In the pivotal pain studies, there was one case of acute renal failure in a patient who received Caldolor 800 mg and no cases in placebo recipients. As shown in Table 42, treatment-emergent abnormalities of serum creatinine occurred with equal frequency in

Caldolor and placebo recipients in the pivotal pain studies. The incidence of such abnormalities in the pain studies was similar to that seen in the fever studies.

Table 42. Number (%) of patients with treatment-emergent abnormal serum creatinine in the pivotal pain studies.

	Placebo	Caldolor		
		<400 mg	400 mg	Overall
	(N=356)	(N=127)	(N=382)	(N=509)
Any abnormal value (> ULN)	21 (6%)	5 (4%)	24 (6%)	29 (6%)
Any value ≥3× ULN	0	0	1 (<1%)	1 (<1%)

ULN = upper limit of normal.

In the non-pivotal study in patients with sepsis syndrome (IND 32803), serum creatinine decreased somewhat from baseline in both treatment groups, with no meaningful difference between placebo and ibuprofen. There was only a low incidence of creatinine elevations recorded as (treatment-related) AEs: 1.3% in both the ibuprofen and placebo groups. As noted in the original clinical evaluation, the proportion of subjects with new onset low urine output (≤0.5 mL/kg/h or ≤30 mL/h) in IND 32803 was significantly higher in the ibuprofen group (45% versus 32% in the placebo group; p=0.005) but this was probably a consequence of baseline differences between the two groups. There were no significant differences between ibuprofen and placebo in respect of mean urine output or serum creatinine at any time-point.

In summary, the use of Caldolor does not appear to be associated with a clinically significant increase in renal adverse effects, provided certain precautions are observed (as they were in the submitted studies). These relate to the adequate hydration of patients and caution in patients who may be predisposed to adverse renal effects (such as the elderly and patients with pre-existing renal impairment). These precautions have been documented in the draft PI.

Cardiovascular events

NSAIDs have been associated with an increase in the risk of cardiovascular events that is not confined to the COX-2 selective drugs. Most of the data are from long term usage and one would think that short-term usage should not lead to a significantly increased risk. However, the short term use of parecoxib and valdecoxib in patients undergoing coronary artery bypass graft (CABG) surgery was found to be associated with an increased risk of cardiovascular events[30]. Parecoxib and valdecoxib are COX-2 selective NSAIDs but it is not certain that the increased risk is related entirely to that selectivity and the FDA-approved labelling for all NSAIDs (including Caldolor) contraindicates them in patients undergoing CABG.

During the Caldolor study program cardiovascular adverse events were recorded as part of routine adverse event reporting and thus appear in the lists of TEAEs. However, they appear under various SOCs and event terms with no overall assessment of the number or percentage of patients in each treatment group who had a cardiovascular event. Subsequent to this the sponsor provided additional Supplementary information which have been evaluated below.

[30] Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352:1081-91.

Findings relating to cardiovascular adverse events following evaluation of supplementary clinical data provided

As noted above the long term use of nsNSAIDs has been found to increase the risk of cardiovascular (CV) adverse event, and recent observational data suggest that even the short term use of nsNSAIDs may carry an increased risk of such events. In the case of the postoperative use of a nsNSAID, major thrombotic events (myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism), arrhythmias and haemorrhagic stroke are of particular interest given that patients are likely to be in a pro-thrombotic state due to physiological responses to the recent surgery, at greater risk of arrhythmia due to electrolyte disturbances and given the antiplatelet effects of nsNSAIDs.

The original submission did not specifically examine the CV safety of Caldolor and this was noted in the original evaluation report. In response, the sponsor has submitted two analyses. The first analysis reiterated data from the ISS regarding TEAEs in the Cardiac disorders SOC. This information was noted at the time of the original evaluation but not regarded as useful because the Cardiac disorders SOC does not include all of the relevant event types (for example, it excludes events such as stroke and thromboembolic events occurring outside the heart). The second part of the sponsor's analysis examined the incidence of events from the following list of preferred terms: "arrhythmia, atrial fibrillation, atrioventricular block, atrioventricular block second degree first degree, bradycardia, cardiac failure congestive, cardio-respiratory arrest, extrasystoles, palpitations, sinus bradycardia, tachycardia, ventricular extrasystoles, cardiac murmur, electrocardiogram t-wave inversion, deep vein thrombosis, disseminated intravascular coagulation, extremity necrosis, flushing, haematoma, hot flush, hypertension, hypotension, orthostatic hypotension, phlebitis, phlebitis superficial, thrombophlebitis, thrombophlebitis superficial, wound haemorrhage". The problem with this second analysis is that it includes terms that are clearly not relevant to the matter under consideration, such as flushing, haematoma, hot flush, disseminated intravascular coagulation and wound haemorrhage, as well as terms such as phlebitis, phlebitis superficial, thrombophlebitis superficial that are much more likely to be related to local effects of the infusion rather than the systemic effects of ibuprofen.

Overall, the sponsor's new analyses do not provide useful information regarding the risk of CV events associated with the use of Caldolor. However, it is reasonable to assume on pharmacological grounds that the risk of CV events would be no different from that associated with oral ibuprofen.

Wound healing

By inhibiting inflammation and angiogenesis, NSAIDs could theoretically impair would healing after surgery. During the initial review the evaluator stated that this was not specifically addressed in the ISS. However, the sponsor provided Supplementary data relating to this by way of clarification, of which a review and subsequent conclusions are provided in the section, '*Findings Relating to Wound Healing Following Evaluation of Supplementary Clinical Data Provided*'.

Findings relating to wound healing following evaluation of supplementary clinical data provided

As outlined above the effect of Caldolor on would healing is of obvious relevance given the proposed use for postoperative analgesia but was not specifically examined in the original submission. The sponsor subsequently submitted analyses of "TEAEs relating to wound healing" in the pivotal fever and pain studies.

In the fever studies, such events were recorded in 5 (4%) Caldolor recipients compared to 0 placebo recipients. The TEAEs were "wound complication" (3 cases), "wound necrosis" and "wound infection" (1 case each). The difference between Caldolor and placebo did not

reach statistical significance (p=0.177) but the statistical power of the analysis was limited by the low number of subjects.

In the pain studies, the frequency of "TEAEs relating to wound healing" was similar in the placebo and combined Caldor groups (6% and 5%, respectively) with no evidence of a dose-response effect in the two Caldolor groups (6% and 4% in the 400 mg and 800 mg groups, respectively). However, the analysis included a number of event types that may not be related to wound healing themselves, such as incision site haematoma, incision site haemorrhage, procedural site reaction, would drainage and wound haemorrhage.

Overall, the new analyses are not particularly useful. However, it is reasonable to assume on pharmacological grounds that any effect of Caldolor on wound healing would be no different from that associated with oral ibuprofen.

Safety issues of general regulatory importance

Liver toxicity

One patient treated with Caldolor 800 mg is listed in the ISS summary tables as having severe acute hepatic failure. The data do not allow an assessment, however, of whether there were any "Hy's law" cases of hepatotoxicity because alkaline phosphatase, which is required to exclude cholestasis as the cause of a combined elevation of transaminase(s) and bilirubin, was not measured in the study subjects. Such cases would be relevant if Caldolor increases the incidence of hepatic abnormalities compared to placebo. See below for the secondary evaluator's conclusions following additional consideration and review of the Supplementary data and clarification provided.

Findings relating to liver toxicity following evaluation of supplementary clinical data provided

As noted above the data did not allow assessment of whether there were any "Hy's law" cases of heptotoxicity because alkaline phosphatase, which is required to exclude cholestasis as the cause of combined elevation of transaminase(s) and bilirubin, was not measured in the study subjects. In response the sponsor argued that there was "only one case of increased bilirubin and one case of aspartate aminotransferase increase in the 400 mg pain group from study CPI-CL-008A recorded as a TEAE. These conditions did not occur in the same patient". The implication is that there could not have been any Hy's law cases in the database (if one makes the assumption that a transaminase/bilirubin elevation large enough to qualify as a potential Hy's Law case would have been recorded as a TEAE). However, the sponsor's analysis is flawed because it is based on "possible *drug related* hepatic disorder treatment emergent adverse events" (emphasis added). The analysis should at least have been based on *all* hepatic disorder TEAEs, irrespective of the investigator's opinion of relationship to study treatment. Better still, the sponsor should have reanalysed the actual laboratory data to determine whether there were any subjects who had combined elevations of bilirubin and one or more transaminases that would have qualified them as a potential Hy's law case.

In summary, the new analyses are not useful. However, it is reasonable to assume on pharmacological grounds that any effect of Caldolor on the liver would be no different from that associated with oral ibuprofen.

Haematological toxicity

As noted in previously, the treatment of fever with Caldolor appeared to increase the risk of neutropenia (7% versus 3%). However no cases of agranulocytosis or severe neutropenia were reported in the submitted studies.

There were no cases of severe thrombocytopenia in the pivotal or Phase I studies. In IND 32803, 2 cases of thrombocytopenia were reported in each of the placebo and IV

ibuprofen groups. Those in the IV ibuprofen group were a case of severe thrombocytopenia classed as "not related" to study treatment and a case of idiopathic thrombocytopenic purpura classed as "probably not related" to study treatment. For additional information and clarification concerning this refer to *Findings Relating to Haematological Toxicity Following Evaluation of Supplementary Clinical Data Provided,* where the evaluator's discussion of the sponsor's response and their conclusions are provided.

Findings relating to haematological toxicity following evaluation of supplementary clinical data provided

As noted above, the treatment of fever with Caldolor appeared to be accompanied by an increase in the risk of neutropenia. The sponsor responded that all 10 cases of neutropenia in the pivotal fever studies occurred in Study CPI-CL-004: 2 from each of the placebo, 100 mg and 200 mg groups and 4 from the 400 mg group. No cases were observed in Study CPI-CL-006.

The sponsor also commented that the differences between placebo and Caldolor did not reach statistical significance but this is essentially meaningless given the low power of the statistical analysis resulting from the low number of subjects. The sponsor made no comment on the observation that the incidence of neutropenia in CPI-CL-004 was highest in the maximum Caldolor dose group (400 mg). More reassuring are the observations that all cases were from the non-critically ill subgroup, that all patients observed with neutropenia had malaria as an underlying disease, that all cases were classified as mild and that all resolved without further treatment with the exception of two cases, one in the 100 mg group and one in the 200 mg group, where both cases of neutropenia were considered chronic conditions. Finally, all cases of neutropenia were considered unrelated to study drug by the investigator.

Serious skin reactions

No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported in the submitted studies.

Cardiovascular safety

See *Cardiovascular events* above.

Unwanted immunological events

Hypersensitivity reactions were recorded in 1 placebo and 3 Caldolor recipients in the pivotal studies. There were no cases in the Phase studies or IND 32803.

Postmarketing experience

The submission contained 4 quarterly PSURs, covering the third quarter of 2009 (when distribution of Caldolor began in the USA) to the second quarter of 2010. All were short documents stating that no adverse events had been reported to the US Sponsor (Cumberland Pharmaceuticals) during the period.

The PSUR for fourth quarter of 2009 also included a literature review that located 3 published papers relating to the safety of IV ibuprofen. All 3 papers described the use of IV ibuprofen in premature infants with patent ductus arteriosus (PDA).

The studies are not directly relevant to the proposed usage of Caldolor in adults but they are indicative of and relevant to a potential off-label use of Caldolor. The design of the first study is such that one cannot determine whether the increased risk of bronchopulmonary dysplasia, intraventricular haemorrhage and acute renal failure was causally related to ibuprofen or instead related to the duration of persistent PDA, duration of mechanical ventilation, and/or other confounders. The other two observational studies are also

potentially subject to confounding but on pharmacological grounds a causal relationship between ibuprofen use and decreased renal function is plausible, as is a relationship between ibuprofen use and increased total bilirubin levels (via competition for hepatic glucuronidation).

Evaluator's overall conclusions on clinical safety following the initial review of the data

Following initial review of the safety data the clinical evaluator had a range of concerns which are summarised in the bullet points below:

Fever Studies:

- The duration of exposure to Caldolor in the submitted studies was quite short, being generally no more than 2 days and up to 5 days in a very small number of patients. This means that the safety of Caldolor has only been studied in short-term use and should be reflected in any approved indications.
- Infusion site reactions were not specifically examined in the pivotal studies but were merely recorded as part of routine adverse event reporting. Although Infusion site reactions recorded in this manner appeared to be only a minor problem when Caldolor doses of 200 to 800 mg were diluted in 200 to 250 mL normal saline and administered for no more than about 2 days.
- There was evidence that the safety profile of Caldolor differed between the fever and pain studies, so it is important to consider the two indications separately.[31] In the pivotal fever studies, TEAEs were more common amongst Caldolor recipients than placebo recipients (73% versus 64%). Several areas of potential concern were identified by the evaluator (Cardiovascular events, Abnormal Investigations and Infections).
- The number of patients in the pivotal fever studies was too small to adequately describe the adverse event profile of Caldolor in that indication. However, additional data were presented from a larger non-pivotal study, which did help to allay concerns arising from the pivotal studies regarding a higher mortality rate in Caldolor recipients. However, interpretation of safety data from both the pivotal and non pivotal fever studies was hindered by the enrolment of study populations that were not representative of the patients who are likely to receive the drug in Australia.

Pain studies:

- The use of Caldor as an adjunct to morphine for post-operative analgesia did not increase the overall risk of TEAEs compared to placebo (Caldolor 400 mg 88%, Caldolor 800 mg 87%, placebo 89%). There were also no obvious differences in respect of individual adverse event types that were consisted across the two Caldor dose levels (400 and 80 mg).
- The safety of Caldolor as monotherapy for the treatment of pain was not assessed. Because Caldolor was only studied as an adjunct to morphine for post-operative pain relief, small but potentially important differences between Caldolor and placebo in the risk of adverse events (such as cardiovascular and renal events) may have been obscured by the larger number of events arising as a consequence of the surgery itself and the use of morphine.

[31] Sponsor comment: As a consequence of this concern the sponsor provided an additional analysis of the safety data separating out the two indications and an assessment of this and the final conclusions of the evaluator are provided below.

- There was also no targeted assessment of bleeding complications associated with the perioperative use of Caldolor.
- Finally, while there is considerable experience with oral ibuprofen for the management of pain, oral ibuprofen is not specifically approved for use in the perioperative context (which would be the major use for Caldolor).

The evaluator therefore felt that these issues combined to prevent a satisfactory assessment of the safety of Caldolor for the treatment of fever and pain.

Clinical summary and conclusions

Assessment of benefits

Treatment of fever

As discussed above, the short term treatment of fever with Caldolor was shown to produce statistically significant reductions in body temperature compared to placebo but it is unclear whether the magnitude of this effect was clinically meaningful.

In CPI-CL-004:

- The primary outcome was reduction of body temperature below a threshold of 101°F, 4 h after the first dose of study medication, in the Caldolor 400 mg dose group compared to placebo. In the ITT population, 24/31 (77%) patients in the Caldolor 400 mg group, compared to 9/28 (32%) in the placebo group had such a reduction. The Caldolor - placebo difference was thus 45% and the number of patients who would need to be treated with Caldolor to produce each additional outcome of this type, compared to placebo (the NNT) is therefore 2.2. The 95% CI for the NNT could not be calculated because the sponsor did not determine a 95% CI for the Caldolor - placebo difference.
- However, the primary outcome used the same threshold to declare a treatment success as was used to declare a fever at enrolment, so achievement of the primary outcome did not necessarily equate to a clinically meaningful temperature reduction in an individual patient. An alternative outcome that is more intuitively relevant is the percentage of patients whose fever resolved with study treatment. In terms of the available outcomes, the closest to this is a *post hoc* analysis, requested by the FDA, of the time to temperature reduction below 99°F. That analysis showed trends in favour of Caldolor but the difference between Caldor and placebo was not statistically significant and calculation of the NNT is therefore not appropriate.

In CPI-CL-006:

- The primary efficacy outcome was the area above the temperature 37.0°C (98.6°F) versus time curve from 0 to 24 h after the start of treatment (AUC-T0-24). This was acceptable for demonstrating that the effect of Caldor on body temperature was statistically superior to that of placebo. However, neither it nor the other efficacy outcomes allowed an assessment of whether the statistically significant effects were clinically meaningful in terms of the magnitude of the effect in an individual patient. Consequently, the NNT for a clinically meaningful outcome could also not be determined.

In any case, as noted previously in this evaluation, the benefit of temperature reduction in febrile patients has been historically accepted by clinicians and regulatory authorities but has not been convincingly demonstrated in terms of meaningful clinical outcomes (such as effects on morbidity or mortality). In relation to mortality in critically ill patients with

sepsis syndrome, the short term use of IV ibuprofen was not accompanied by an improvement in survival.

Treatment of pain

As discussed previously, short term treatment with Caldolor was shown to exert a statistically significant analgesic effect. However, the study designs meant that pain levels before the administration of study treatment could not be measured. This, in turn, means that the magnitude of the pain relief due to Caldolor in an individual patient could not be determined, nor could the proportion of patients with a clinically worthwhile pain reduction (which in acute pain studies is typically regarded as a 20 mm reduction in VAS pain score from baseline). Calculation of the number of patients who need to be treated with Caldolor to produce each additional patient with a clinically worthwhile pain reduction was therefore not possible.

In addition, the studies only examined the proposed use of Caldor as an adjunct to opioids for the treatment of moderate to severe pain. The proposed use of Caldolor as monotherapy for mild to moderate pain was not directly studied and although the effect of Caldolor monotherapy for that indication can be assumed to be clinically relevant on the basis of PK comparisons to oral ibuprofen, the magnitude of the effect in an individual patient has not been demonstrated and an NNT for Caldolor monotherapy also cannot be calculated.

Assessment of risks following review of the safety data package

As discussed previously, the risks of Caldor in the proposed indications were deemed by the original clinical evaluator not to have been adequately assessed following review of the initial data package. However, following review of the reanalysed safety data and the data provided as part of the original submission package the evaluator felt that the data demonstrated that the risks of Caldolor usage in the proposed indications are likely to be comparable to the risks that are associated with the use of oral ibuprofen for the same purposes. Although the proposed maximum dose of Caldolor for the treatment of pain is higher than currently approved in Australia for oral ibuprofen, the data from the pivotal pain studies provide sufficient reassurance that this higher dose is not likely to be accompanied by a clinically important increase in adverse events during short tern use. The safety of the 800 mg dose has not been assessed beyond 2 days or so, however, and cannot be assumed on the basis of previously evaluated data for oral ibuprofen (at least from the Australian regulatory perspective). It is also relevant to note that the extensive experience with oral ibuprofen does not extend to preoperative administration in adults and that data regarding the preoperative commencement of Caldolor itself, while not revealing any increased risk of bleeding events, are limited to only 99 patients.

Assessment of benefit-risk balance

Re-evaluation of the safety data package also caused the evaluator to revise the original opinion of the benefit-risk balance of Caldolor from 'undetermined' to the following:

As noted above, in the absence of an NNT, a quantitative benefit-risk balance was not possible. However, the existing Australian approval of oral ibuprofen, coupled with evidence that the benefits and risks of Caldolor are likely to be comparable to those of oral ibuprofen used under the same circumstances, lead to the conclusion that the benefit-risk balance of Caldolor should be favourable, provided that adequate precautions are observed in its use.

Recommendation regarding authorisation

As above, the initial evaluation of the safety data package deemed that approval of the product was not recommended, however, a re-analysis and corresponding re-evaluation of the safety data package the evaluator revised this opinion to one where the authorisation of Caldolor for the treatment of fever and acute nociceptive pain was recommended, subject to satisfactory revision of the PI. In particular, the PI should specify that when Caldolor is used for postoperative analgesia, Caldor should be commenced at the end of surgery (as there are currently insufficient data supporting the safety of preoperative commencement of the drug).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 43.

Table 43. Ongoing Safety Concerns

Important Identified Risks	None consistently identified at this time
Important Potential Risks	• Cardiovascular Thombotic Effects • Hypertension • Congestive Heart Failure and Oedema • GI effects – ulceration, bleeding perforation • Serious skin reactions • Hypersensitivity/Anaphylaxis reactions • Ophthalmological effects • Hepatic effects • Renal effects • Haematological effects
Important Missing Information	• Use in the paediatric population

OPR reviewer comment

The sponsor acknowledged that there is not extensive exposure of Caldolor in elderly patients. As a consequence of the limited quantity of information gathered in this population in the clinical studies conducted with IV ibuprofen an amendment to the PI was proposed by the sponsor.

Given the above use of routine risk minimisation[32] and the expected use of IV ibuprofen in this population, it is recommended that 'Use in the elderly' be included as Important missing information in the summary of the Ongoing Safety Concerns.

[32] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Pharmacovigilance plan

The sponsor stated that only routine pharmacovigilance activities[33], consistent with the activities outlined in the TGA adopted EU guideline[34] are warranted to monitor all the specified Ongoing Safety concerns at this time. This conclusion was based on the following:

- The well defined safety profile for ibuprofen in the clinical setting;
- The apparent safety of the current formulation when administered in the clinical trial and post marketing settings, even when administered at a higher MDD than is currently approved in Australia;
- The intended usage for the product; in a hospital environment where patient's physiological status is intensely monitored.

However, the sponsor advised that a paediatric development program is underway. A Phase II study, CPI-CL-005 Efficacy and Safety Study of Caldolor in Hospitalized Febrile Paediatric Patients, has been recently completed, although final clinical data are not yet available. Final study report on this and other ongoing paediatric studies (see below) in hospitalised patients are expected to be completed by January 2012 and will be filed with the TGA at the earliest possible opportunity in order to support the appropriate extension of indication to paediatric use:

- Cumberland Study CPI-CL-012. A Multicentre Randomized, Open-Label, Parallel, Active-Comparator, Multiple Dose Trial to Determine the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Paediatric Patients. The primary objective of the study is to determine the superiority of a single dose of IV ibuprofen compared to acetaminophen for the treatment of fever as measured by the area under the change in temperature versus time curve during the first 2 h of treatment.
- A Multicentre, Randomized, Open-Label, Parallel, Active-Comparator, Multiple Dose Trial to Determine the Efficacy, Safety, and Pharmacokinetics of Ibuprofen Injection in Paediatric Patients. Primary objective is to determine the safety and efficacy of Caldolor for the treatment of pain in paediatric patients.

OPR reviewer comment

There was no objection to the sponsor implementing only routine pharmacovigilance activities to monitor the Ongoing Safety Concerns at this time. However, the nonclinical and clinical aspects of the Safety Specifications (SS) remain subject to the evaluation by the Toxicology area of the Office of Scientific Evaluations (OSE) and by the Office of marketing Authorisation (OMA), respectively.

In addition to the Ongoing Safety Concerns as specified by the sponsor, it was recommended that 'Use in the elderly' be included as Important missing information and be monitored by routine pharmacovigilance activities. The PP of the RMP should be amended accordingly.

[33] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[34] 3.1.2 Routine pharmacovigilance practices In Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03) http://www.tga.gov.au/pdf/euguide/ich571603en.pdf

See also *Summary of Recommendations* below.

Risk minimisation activities

The sponsor has stated that routine risk minimisation activities are considered sufficient for all the specified Ongoing Safety Concerns and provided justification for such conclusion. Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for all the specified Ongoing Safety Concerns. No additional risk minimisation measures are planned.

OPR reviewer comment

The sponsor's justification for such conclusion appeared to be reasonable.

See also *Summary of Recommendations* below.

Summary of recommendations

The OPR provided these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted RMP is applicable without modification in Australia unless so qualified:

- The nonnclinical and clinical aspects of the SS remain subject to the evaluation by the OSE and by the OMA, respectively.
- It is recommended that 'Use in the elderly' be included as important missing information in the summary of the Ongoing Safety Concerns .
- There was no objection to the sponsor implementing only routine pharmacovigilance activities to monitor the ongoing safety concerns at this time. However, in regard to the paediatric development program, the specified ongoing studies are not considered to be part of the planned clinical studies in the PP, therefore the related study synopses have not been reviewed. Nevertheless, the US FDA has required final report submission for paediatric assessment (ages 0-16 years) for the treatment of reduction of fever by January 2011 and for pain management by January 2012. This would appear contrary to the sponsor's assurance that the related final study reports, which were expected to be completed by January 2012, will be filed with the TGA at the earliest possible opportunity in order to support the appropriate extension of indication to paediatric use. The sponsor was asked to clarify this situation.
- It was recommended that 'Use in the elderly', as Important missing information, be monitored by routine pharmacovigilance activities and that the PP of the RMP should be amended accordingly.
- The sponsor's proposed RiMP appeared to be reasonable. However, it was recommended that 'Use in the elderly' be included as Important missing information. It was acknowledged that routine risk minimisation has already been proposed for this Ongoing Safety Concern.
- In regard to the proposed routine risk minimisation activities, the draft product information document and the draft consumer medicine information document were considered satisfactory. However, the nonclinical and clinical aspects of these documents remain subject to the evaluation by the relevant TGA Offices.

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were no objections on chemistry, manufacturing and controls grounds to registration of this product, subject to a proposed amendment of the PI.

This submission was not referred to the Pharmaceutical Subcommittee of the ACPM as ibuprofen is a well established drug, presented in a conventional dosage form.

Nonclinical

The two major issues arising from the nonclinical evaluation are the reduced safety margins consequent to the increased MRHD, and potential local reactions at the administration site.

Reduced safety margins: Although IV studies with ibuprofen revealed no novel systemic toxicity due to the change in route of administration, the safety margins for GI and renal effects are not large (≤ 1), indicating potential risk of adverse effects on these organ systems with treatment at the maximum daily dose. As such, although there are no nonclinical objections to the proposed new dosage form and administration route, the nominated MRHD of 3200 mg/day may pose a risk of target organ toxicity and a reduction in the MRHD may be warranted. These concerns may be alleviated by adequate clinical safety data.

Local tolerance: Ibuprofen is a potential local irritant and haemolytic agent, and the proposed mandatory dilution instructions are endorsed.

The safety of Caldolor in patients with renal impairment or history of GI ulceration will need to be assessed from the clinical data.

Clinical

The clinical evaluator (CE) identified 3 studies with pharmacokinetic data, 6 studies (3 on fever and 3 on pain) with efficacy and safety data, 1 study with tolerability data, 1 integrated summary of efficacy on fever, 1 integrated summary of efficacy on pain and 1 integrated summary of safety.

Based on the pharmacokinetic (PK) data, the CE concluded that:

- It would have been preferable if the sponsor performed a direct bioavailability comparison of Caldolor with ibuprofen product registered in Australia. Nevertheless, pharmacokinetic reasoning indicates that the efficacy of Caldolor in the indications for which oral ibuprofen is approved in Australia (which includes the treatment of fever and various forms of pain) should be at least as good as the efficacy of the oral preparations.
- While insufficient to infer that Caldolor is safe for the proposed indications, the PK data in association with the tolerability Study CPI-CL-006 were considered sufficient to justify the choice of doses and the use of a 30 minute infusion in the pivotal studies. They also showed that Caldolor injection needs to be diluted prior to infusion to avoid an unacceptable incidence of infusion site pain.

- The PK data indicate that the proposed alternative of rapid infusion of Caldolor over 5 to 7 minutes is not acceptable, due to the resultant doubling of C_{max} with untested safety consequences. Rapid infusion was also associated with a high incidence of infusion site pain, albeit mild.
- The PK findings in CPI-CL-004 indicate that no change to the Caldolor dose *interval* is required in critically ill patients. Although the PK data also show that ibuprofen concentrations are approximately halved in critically ill patients for a given dose of Caldolor, the lack of a positive dose response in critically ill patients and potential safety concerns (most notably about adverse renal effects in patients with underlying fluid balance abnormalities and compromised renal perfusion) argue against routinely increasing the dose of Caldolor in patients who are critically ill.

Studies with tolerability data

On the basis of the findings it was concluded that Caldolor doses up to 400 mg could be safely diluted in 100 mL normal saline and infused over 30 minutes and this infusion protocol was used in the pivotal fever studies. The pivotal analgesia studies used doses of 400 or 800 mg Caldolor, diluted in 200 to 250 mL of normal saline (depending on the volume of the standard normal saline bags at each investigation site) and infused over 30 minutes.

The CE stated that:

The percentage of Caldolor infusions accompanied by infusion site pain was the same as in CPI-CL-003 but the assessment of tolerability was limited and insufficient to support approval of the rapid infusion. In addition, the rapid infusion led to doubling of ibuprofen C_{max} with untested safety consequences.

Studies with efficacy/safety data

Fever

CPI-CL-004

Efficacy outcome as per the CE:

At 4 h, in the ITT population, 24 of 31 (77%) patients in the Caldolor 400 mg group, compared to 9 of 28 (32%) in the Placebo group had a temperature <101.0°F (p=0.0005). The proportions were similar in the EEP (77% versus 30%, p=0.0003).

CPI-CL-006

Efficacy outcomes

Primary (ITT population)

The AUC-T_{0-24} was 7.49 ± 7.94 °C×h in the Caldolor 400 mg group and 16.44 ± 11.60 °C×h in the placebo group. The effect of baseline temperature on AUC-T_{0-24} was statistically significant, with AUC-T_{0-24} increasing by 6.75°C×h for every 1°C increase in baseline temperature. After adjustment for baseline temperature, the between-treatment difference in mean AUC-T_{0-24} was -8.14°C×h, which was statistically significant (p=0.0019). Mean temperature profiles over time for the Caldolor and placebo groups are shown in Figure 3 (see *Clinical Findings*).

Other (ITT Population)

See Table 44 below and summary under *Clinical Findings* above.

Table 44. Other efficacy outcomes.

Outcome*	**Placebo** *N=30*	**Caldolor 400 mg** *N=30*	**Effect due to treatment** (Between-treatment difference, Caldolor - placebo)	**Effect due to baseline temperature** (Change per 1°C increase)
AUC-T_{0-24}, °C×h *mean ± SD*	16.44 ± 11.60	7.49 ± 7.94	**(Primary)** **-8.14** **p=0.0019**	**6.75** **p=0.0240**
AUC-T_{0-4}, °C×h *mean ± SD*	5.18 ± 2.97	2.40 ± 1.54	**-2.49** **p<0.0001**	**2.32** **p=0.0008**
AUC-T_{0-72}, °C×h *mean ± SD*	16.94 ± 12.23	8.85 ± 11.03	**-7.18** **p=0.0176**	**7.60** **p=0.0303**
AUC-T_{24-72}, °C×h *mean ± SD*	0.50 ± 1.51	1.36 ± 4.00	**0.96** **p=0.2284**	**0.86** **p=0.3558**
Time to temp <100°F within first 24 hs, h median †	3.33	1.18	**p<0.0001**	-
Time to temp <99°F within first 24 hs, h median †	11.01	2.33	**p=0.0038**	-
Treatment failure, *n (%)*	3 (10%)	2 (6.7%)	p=0.6432	-
Malaria parasite clearance time, h *median [range]*	24.0 [13.5 - 50]	32.0 [14 - 50]	**8.0** **p=0.0025**	-

Results with p<0.05 are shown in bold. The primary efficacy outcome is shown in red.
* Technically, these secondary outcomes were analysed in the EEP but the EEP is identical to the ITT population in this study.
† Analysis requested during the FDA review.

Caldolor 400 mg significantly reduced AUC-T_{0-4} and AUC-T_{0-72} but had no effect on AUC-T_{24-72}. Caldolor significantly reduced the time to temperature <100°F and time to temperature <99°F (FDA-requested *post hoc* analyses).

Treatment failure was uncommon in both groups (2 patients (6.7%) in the Caldolor group and 3 (10%) in the placebo group) and the between-treatment difference was not statistically significant.

Malaria parasite clearance time was significantly increased in the Caldolor group (median 32.0 h compared to 24.0 h in the placebo group; median between-treatment difference 8.0 h; p=0.0025).

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Note**:** This study was *rejected outright* for the following reasons:

- Developmental formulation of IV ibuprofen was used.
- Hyper, hypo and normothermic patients were in the study.
- Use of confounders(paracetamol, cold packs) were permitted.

Analgesia

CPI-CL-008A, CPI-CL-008B and CPI-CL-008C

Primary efficacy outcome

Morphine usage

In Study CPI-CL-008A, only Caldolor 800 mg q6h and not Caldolor 400 mg q6h was significantly superior to placebo at the α=0.05 level in respect of this outcome (see Table 14 above).

Study CPI-CL-008B examined only Caldolor 800 mg q6h and found that regimen to be significantly superior to placebo. Caldolor 800 mg reduced mean morphine usage by about 10% in CPI-CL-008A and 15% in CPI-CL-008B (see Table 15).

Corresponding results were seen in the EEPs of both CPI-CL-008A and B and in the AH subpopulation of CPI-CL-008A.

In the AT and ITT populations and the EEP of Study CPI-CL-008C, Caldolor 800 mg q6h significantly reduced mean morphine usage by around 30 to 33% compared to placebo during the 28 h after the first dose of study medication (given pre-operatively at the induction of anaesthesia), although this was not the primary outcome in that study.

AUC-VAS with movement

In CPI-CL-008C, the primary outcome was the AUC-VAS with movement during the period from 6 to 28 h after the first dose of study medication (which was given pre-operatively at the induction of anaesthesia). Caldolor 800 mg q6h was significantly superior to placebo in respect of this outcome in the AT and ITT populations (see Table 16 above) and the EEP.

The results for corresponding (but non-primary) outcomes in the other studies were as follows:

- In both CPI-CL-008A and 008B, Caldolor 800 mg q6h significantly reduced AUC-VAS_{0-24}, AUC-VAS_{6-24} and AUC-VAS_{12-24} on movement, compared to placebo.
- In CPI-CL-008A, Caldolor 400 mg q6h significantly reduced AUC-VAS_{0-24}, AUC-VAS_{6-24} and AUC-VAS_{12-24} on movement compared to placebo but the effect was noticeably less than that of the 800 mg dose.

Other:

- In CPI-CL-008A, Caldolor 400 mg q6h and 800 mg q6h significantly reduced AUC-VAS at rest, consistent with their effect on AUC-VAS with movement. Similarly, Caldolor 800 mg q6h significantly reduced AUC-VAS at rest in CPI-CL-008B and C and AUC-VRS at rest in CPI-CL-008C.
- When Caldolor 800 mg was started preoperatively in CPI-CL-008C the VAS pain scores at rest and with movement were significantly reduced “immediately post-surgery” compared to placebo. This measurement was performed as soon as patients had recovered sufficiently from the anaesthetic to provide a pain assessment. When Caldolor 800 mg was started at the end of surgery in CPI-CL-008A, the mean VAS pain score was numerically reduced compared to placebo from the first post-surgical

observation (1 h after the first dose) but the difference did not become statistically significant until 9 h after the first dose (3 h after the second dose). In CPI-CL-008B, when Caldolor 800 mg was also started at the end of surgery, the mean VAS pain score was essentially the same as in the placebo group until 6 h after the first dose and did not become significantly lower until 15 h after the first dose. Overall, the data suggest that starting Caldolor preoperatively instead of at the end of surgery may provide earlier pain relief but this conclusion is based on a cross-study comparison and remains unproven.

- Short term persistence of efficacy was demonstrated according to the principal treatment periods in each study: 48 h in CPI-CL-008A, 24 h in 008B and 28 h in 008C. After these time points, the use of Caldolor was optional and the number of patients who remained on study treatment was too low to provide meaningful data.
- Neither Caldolor dose regimen had a significant effect on the number of treatment failures, time to return of GI motility, time to resumption of liquid or solid intake, or length of hospital stay. The time to ambulation was significantly reduced in the Caldolor 800 mg q6h group of CPI-CL-008B but not in CPI-CL-008C or in either Caldolor dose group of CPI-CL-008A.
- In respect of the "combined safety assessment" of opioid-related AEs, Caldolor 400 mg q6h was associated with a significantly reduced incidence of these AEs compared to placebo in the ITT population of CPI-CL-008A but this was not confirmed in the EEP. Caldolor 800 mg q6h did not significantly reduce the incidence of opioid-related AEs in any of the analysis populations across all three studies.

Safety findings (in accepted studies) as per CE:

Pivotal fever studies

See Table 19 in *Clinical Findings* above.

Pivotal pain studies

In the pivotal pain studies, the Caldolor dose was either 400 mg or 800 mg. TEAEs were reported in 88% of the Caldolor 400 mg group, 87% of the Caldolor 800 mg group and 89% of the placebo group.

See Table 20 under *Clinical Findings* above.

In the pivotal studies, TEAEs which were considered by the investigators to be at least possibly related to study treatment were reported in 29% of Caldolor recipients and 26% of placebo recipients. When broken down according to Caldolor dose, treatment-related TEAEs were significantly less common for Caldolor 100-200 mg than placebo, significantly more common for Caldolor 400 mg than placebo and there was no significant difference between Caldolor 800 mg and placebo. One case of acute hepatic failure was reported as a treatment-related TEAE in the Caldolor 800 mg group. There were no deaths considered to be study treatment related by the investigators.

Other studies:

In the Phase I studies, [no placebo controls] 28/60 (47%) subjects treated with Caldolor (200-800 mg) reported TEAEs. The maximum severity of TEAEs was mild in 17/28 (61%) and moderate in 11/28 (39%) of subjects. The majority of Phase I TEAEs were infusion site reactions, which were reported in 22/60 (37%) of the Phase I subjects. Infusion site reactions were most common when undiluted Caldolor was administered in Study CPI-CL-001, particularly in the 400 and 800 mg dose groups where they were reported by 7/12 (58%) and 6/12 (50%) of the subjects, respectively. When Caldolor 400 mg was diluted and infused over 1 h in CPI-CL-003, only 1/12 (8%) of the subjects reported an infusion site reaction, "pressure above IV insertion site". When Caldolor was diluted but infused

over 5-7 minutes in Study CPI-CL-011, 4/12 (33%) of the subjects reported infusion site reactions (all mild pain) during the Caldolor infusion. No subjects (0/12) reported infusion site reactions during the placebo infusions.

The next most common TEAE in Phase I Caldolor recipients was headache, which was reported in 8% of subjects after Caldolor infusion, compared to 6% after oral ibuprofen and 0% after infusion of placebo. There were no deaths or serious TEAEs during the Phase I studies.

Post marketing experience

No evaluated data in the clinical evaluation report (CER).

See also the clinical evaluator's *Benefit/Risk Assessment* above.

Recommendation regarding authorisation, the CE stated that:

Initially, as the benefit-risk balance of Caldolor in the proposed indications could not be determined, authorisation was not recommended.

NOTE: On reviewing the sponsor's Supplementary data, the CE stated that "Authorisation of Caldolor for the treatment of fever and acute nociceptive pain is recommended, subject to satisfactory revision of the PI. In particular, the PI should specify that when Caldolor is used for postoperative analgesia, Caldor should be commenced at the end of surgery (as there are currently insufficient data supporting the safety of preoperative commencement of the drug)".

On receiving the clinical evaluation report, the sponsor has modified the proposed indication to read:

> *"Caldolor injection is indicated in adults for the management of mild to moderate pain and the management of moderate to severe acute nociceptive pain as an adjunct to opioid analgesics, where an IV route of administration is considered clinically necessary".*
>
> *"Caldolor is indicated for the reduction of fever in adults where an IV route of administration is considered clinically necessary."*

Risk management plan

The sponsor provided an updated RMP taking the above OPR's recommendations into account. The updated RMP was considered acceptable by the OPR.

Delegate's comments

- Caldolor represents a parenteral form of ibuprofen, a previously approved active substance. Pharmacokinetic studies were carried out using Caldolor administered IV versus orally administered US-marketed ibuprofen capsules without any bridging data comparing the latter with an ibuprofen product registered in Australia. The pharmaceutical chemistry evaluator has not raised a concern on the issue stating that the submission was not referred to the Pharmaceutical Subcommittee of the ACPM as ibuprofen is a well established drug, presented in a conventional dosage form. The clinical evaluator stated that there is anecdotal regulatory experience that different immediate release oral ibuprofen preparations proposed for registrations do not differ in relation to AUC.
- Caldolor infused over 30 minutes produced a C_{max} that was close to that of the same oral dose of US marketed ibuprofen, with a t_{max} shorter than the same dose of Caldolor infused over 1 h in healthy, non-critical patients. Diluted Caldolor was better tolerated than the undiluted Caldolor.

- In the management of fever Caldolor 400 mg was superior to placebo at lowering temperature <100°F or 38.3°C 4 or 6 h after administration. Similar tendency was shown for the 100 mg and 200 mg Caldolor strengths, especially in the critically ill patients with genuine fever of any cause. Approach towards normal temperature (<99°F or 37°C) was quicker for Caldolor 400 mg than any other treatment. Fever studies' treatment outcomes were provided for 1 and 3 days. The fever studies did not extend to children and adolescents <18 years.
- There were no studies submitted on the use of Caldolor as monotherapy in the management of mild to moderate pain nor any other opioid except morphine used in the pain studies. There were three studies on the efficacy and safety of Caldolor (supposedly) as adjunct to morphine for the treatment of post operative pain in adults. The word "supposedly" has been inserted so as to illustrate the Delegate's understanding rather that the design of the studies is aimed towards investigating the use of Caldolor in post operative pain with or without morphine contrary to the proposed "Caldolor as adjunct to morphine" indication. In the management of pain, all three studies showed that Caldolor 800 mg administered 6 h was superior to placebo in reducing total morphine usage in the 24 h to 28 h following the first dose of Caldolor. Furthermore, Study CPI-CL-008C showed that the area under the pain intensity (AUC-AS) with movement during the period between 6 and 28 h after the first dose of Caldolor 800 mg given every 6 h was significantly superior to placebo. Caldolor 800 mg at q6h demonstrated efficacy in acute post operative (nociceptive) pain situation when commenced either pre or postoperatively. The treatment outcomes of the Pain studies were persistent and available for 24 to 48 h. After those time periods, the use of Caldolor became optional and the number of patients who remained on study treatment was too low to yield any evaluable data. The pain studies did not cover children and adolescents <18 years. Given the observed role of Caldolor 800 mg at q6h in controlling and reducing morphine usage in what appears to be moderate to severe acute post operative pain, it may be assumed that formal study on the use of Caldolor as monotherapy in the management of mild to moderate pain is not mandatory after all.
- For the management of fever, the total initial daily dose of Caldolor ranged from 1600 mg to 2400 mg (400 mg at q6h or q4h). For pain management, the total daily dose was 4000 mg (800 mg start dose either pre or immediately post operative followed by 800 mg at q6h for 24 hs). It is noteworthy in this regard, that the maximum daily dose of oral ibuprofen theoretically could be 3200 mg as earlier stated in this Delegate's overview.
- The most common Caldolor treatment emergent adverse events (TEAE's) with incidence >3% by SOC and by study treatment in both Fever and Pain study trials, are as previously tabulated. Most of the TEAE's are also listed for ibuprofen oral preparations and while the safety issues of particular interest relating to Cardiovascular events, Renal abnormalities, Bleeding events may have been derived from routine adverse event reporting rather than targeted data collection, the latter have been mentioned in the draft PI. The precautionary statements on those special safety matters for Caldolor should be matched to those for parecoxib (a registered injectable COX-2 inhibitor) regarding the same safety matters.
- There is ample evidence in the evaluated data to support the significant superiority of Caldolor over placebo in reducing temperature and pain in the febrile and acute post-operative patients often encountered in contemporary medical and surgical practice. The safety issues associated with such use of Caldolor are not unique to it and are rather typical of all NSAIDs, be it oral or injectable. Given that parecoxib (similar to Caldolor) and ketorolac (a potent NSAID) injectables with similar safety profiles have been approved, Caldolor can be rated as having a satisfactory benefit-risk assessment

for the proposed indications. There were however some outstanding RMP issues raised by the CE. These issues would need to be addressed by the sponsor.

- The quality evaluator recommended an amendment to the proposed PI and had no objection to the registration of Caldolor.
- The nonclinical evaluator drew the attention of the Delegate to the following issue:
- "Possible toxicity risk to target organ at the maximum recommended human dose (MRHD) of 3200 mg/day**"**. Although the maximum dose given over 24 h in the clinical trial studies was 4000 mg, the Delegate agreed with the nonclinical evaluator that a reduction in the MRHD is warranted to minimise risks.
- The NE also suggested amendments to the PI.
- The available clinical data showed that the duration of scheduled Caldolor use was 1 to 3 days in the fever study trials and 2 days in the pain study trials, followed by duration of Caldolor use on an as needed basis for up to 2 days in the fever study trials and up to 5 days in the pain study trials. In practice, after those periods, most patients will be expected to take either oral antipyretics for fever or oral analgesics for pain post operatively for the conditions treated. It is therefore recommended that the *duration* of scheduled Caldolor use be limited to *2 days***.**
- Available pharmacokinetic data indicate that Caldolor infusion over a period of 30 to 60 minutes (infusion period was for 30 minutes in the efficacy/safety clinical trials) yielded peak ibuprofen concentrations approximating those seen with same dose of oral ibuprofen. The 60 min infusion was delayed (t_{max}) compared to the oral dosing. The 5 to 7 minute infusion led to a shorter t_{max} compared to that of oral dosing, with a doubling of peak ibuprofen concentration [C_{max}] and therefore potential adverse implications.
- As there are no clinical trial studies submitted on the use of Caldolor in either spinal or epidural analgesia, any reference to the latter in the draft Pl cannot be supported at present. lngesting oral ibuprofen in spinal injury is not the same as Infiltrating Caldolor in spinal and epidural analgesia and there could be consequences.

Proposed action

The Delegate proposed that consideration be given to the approval of the application to register a new dose form of a previously approved active substance (ibuprofen) as Caldolor (ibuprofen injection). Given the design of the study trials for pain, it was proposed that the approved indications be modified to read:

"Caldolor injection is indicated in adults for the management of acute (a) mild to moderate post-operative (nociceptive) pain and (b) moderate to severe post-operative (nociceptive) pain with or without morphine, where an IV route of administration is considered clinically necessary".

"Caldolor is indicated for the reduction of fever in adults where an IV route of administration is considered clinically necessary."

The recommendation was subject to resolving issues arising from the ACPM deliberations and to the finalisation of matters pertaining to the PI and RMP to the satisfaction of the TGA.

The submission was submitted to the ACPM for advice.

Response from Sponsor

Caldolor is an IV formulation of ibuprofen (100 mg/mL) developed by Cumberland Pharmaceuticals Inc. (Cumberland) in the USA for the reduction of fever and management of pain in adult and paediatric patients. IV preparations of drugs to treat mild to moderate pain, and fever, are considered beneficial for those patients unable to take such medication orally. Examples already approved for use in Australia include paracetamol and parecoxib.

The sponsor was in agreement with the indication proposed by the Delegate:

> *Caldolor injection is indicated in adults for the management of acute (a) mild to moderate post-operative (nociceptive) pain and (b) moderate to severe post-operative (nociceptive) pain with or without morphine, where an IV route of administration is considered clinically necessary.*
>
> *Caldolor is indicated for the reduction of fever in adults where an IV route of administration is considered clinically necessary.*

This was a modification of the indication proposed in the original application:

> *Caldolor injection is indicated in adults for the management of mild to moderate pain and the management of moderate to severe pain as an adjunct to opioid analgesics.*
>
> *Caldolor is indicated for the reduction of fever in adults.*

Caldolor is an IV formulation of ibuprofen (100 mg/mL) developed by Cumberland Pharmaceuticals Inc. (Cumberland) in the USA for the reduction of fever and management of pain in adult and paediatric patients. IV preparations of drugs to treat mild to moderate pain, and fever, are considered beneficial for those patients unable to take such medication orally. Examples already approved for use in Australia include paracetamol and parecoxib.

Efficacy

The sponsor was in agreement with the Delegate's statement that:

> *there is ample evidence provided in this submission to support the significant superiority of Caldolor over placebo in reducing temperature and pain in the febrile and acute post-operative patients encountered in contemporary medical and surgical practice.*

The Delegate also commented that;

> "*Caldolor 800 mg at q6h demonstrated efficacy in acute post-operative (nociceptive) pain situations when commenced either pre- or postoperatively."*

Of the three clinical trials submitted to support the safety and efficacy of Caldolor, the study drug was administered in two of the studies (CPI-CL-008A and CPI-CL-008B) near the end of surgery, after haemostasis, at the start of skin closure (perioperatively). The protocol for Study CPI-CL-008C required that the study drug be administered at approximately the initiation of anaesthesia, prior to the surgical procedure (pre-operatively).

Quality

The sponsor was in agreement with the quality evaluator's statement:

> *There are no objections on Chemistry, Manufacturing and Control grounds to the registration of this product, subject to the amendment of the PI.*

The draft PI has been amended at the recommendation of the evaluator with the removal of Lactated Ringer's solution from the list of acceptable diluents.

Nonclinical safety

The nonclinical evaluator (NE) indicated there were no nonclinical objections to the proposed new dosage form and administration route.

The two issues arising from the nonclinical evaluation were that ibuprofen is a potential local irritant and that the nominated MRHD of 3200 mg/day for Caldolor may pose a risk of target organ toxicity. The nonclinical evaluator was concerned that the IV formulation may be expected to have greater bioavailability then the PO formulation. However, the clinical pharmacokinetic studies submitted indicate that this is not the case and that the PO formulations tested have similar bioavailability to the IV formulation. The NE has agreed with the dilution instructions included in the draft PI and the product labels. All recommendations from the nonclinical evaluator for amendments to the PI have been included in the updated proposed PI.

Clinical safety

The sponsor was in broad agreement with the conclusions of the clinical evaluator following evaluation of Supplementary data and has modified the indication as requested by the clinical evaluator (CE). Note that the Supplementary data provided was not additional data but reanalysis of the safety data from the submitted clinical trials separated for the fever and pain indications. This data was available in the appendices and tables of the ISS or clinical study appendices in the original application but in a form difficult to analyse.

The CE stated that the PI should specify that when Caldolor is used for post-operative analgesia, it should be commenced at the end of surgery (as there are currently insufficient data supporting the safety of pre-operative commencement of the medicine). This concern was only brought to the attention of the sponsor after the evaluation of the Supplementary data for Caldolor. It was not mentioned in the original evaluation of clinical data. There was no indication, after the initial evaluation of the clinical data, that the CE considered Study CPI-CL-008C was inadequately powered to support the safety of Caldolor for pre-operative use.

RMP

The Delegate commented on outstanding RMP issues raised by the CE that needed to be addressed by the sponsor. The outstanding issues were not specified by the Delegate. The sponsor stressed that there was every intention, on their part, to make the recommended changes to the RMP once the appropriateness of these proposed amendments was confirmed by the Delegate.

Conclusion

In conclusion, the Delegate recommended approval of Caldolor and agreed that efficacy has been demonstrated for both the pain and fever indications. The sponsor was in agreement with the changes to the indications requested by the Delegate and also the majority of the modifications to the PI requested by the Delegate.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The application seeks to register a new route of administration (solution for IV injection) and two new dosage forms.

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality considered this product to have a positive benefit-risk profile for the proposed indications.

> *Caldolor injection is indicated in adults for the management of acute mild to moderate post operative pain and moderate to severe post-operative pain with adjunctive reduced morphine dosage, where an IV route of administration is considered clinically necessary*

Caldolor is indicated for the reduction of fever in adults where an IV route of administration is considered clinically necessary.

The ACPM noted that the evidence submitted supports duration of treatment of up to two days. The ACPM strongly recommended that the sponsor conducts studies to support use in the paediatric population.

The ACPM supported the amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI) and advised of the need to also include:

- a statement in the *Dosage and Administration section* and *Precautions* section to strengthen the reference to use of the lowest possible dosage, with consideration to the following additional words "use of the recommended maximum dose of Caldolor 800 mg every 6 h has only been studied for a period of up to 2 days"; and deletion of reference to 5 - 7 minute infusion duration.
- A statement in the *Precaution / Contraindication* section regarding use for spinal and epidural anaesthesia / analgesia.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided; would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Caldolor (ibuprofen) 400 mg/4mL and 800 mg/mL concentrated solutions for injection vial, indicated for:

Caldolor injection is indicated in adults for the management of acute mild to moderate post operative pain and moderate to severe post-operative pain with adjunctive reduced morphine dosage, where an IV route of administration is considered clinically necessary.

Caldolor is indicated for the reduction of fever in adults where an IV route of administration is considered clinically necessary.

Specific conditions applying to these therapeutic goods:

1. The implementation in Australia of the ibuprofen 400 mg/4 mL and 800 mg/8 mL concentrated solution for injection via Risk Management Plan (RMP), version 02 dated 25 January 2011, included with this submission, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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Reference/Publication #