# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-348**

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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|---|---|
| **Date** | June 3, 2009 |
| **From** | Ellen Fields, M.D., M.P.H. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA #**<br>**Supplement#** | 22-348 |
| **Applicant** | Cumberland Pharmaceuticals, Inc. |
| **Date of Submission** | December 11, 2008 |
| **PDUFA Goal Date** | June 11, 2008 |
| | |
| **Proprietary Name / Established (USAN) names** | Caldolor/IV Ibuprofen |
| **Dosage forms / Strength** | Solution for injection containing 100 mg/mL ibuprofen |
| **Proposed Indication(s)** | 1. Management of fever<br>2. Treatment of mild to severe pain |
| **Recommended:** | 1. Reduction of fever in adults: **Approval**<br>2. Treatment of acute pain in adults: **Approval** |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | |
|---|---|
| Primary Medical Officer Review | **Christina Fang, M.D.** |
| Statistical Reviews | **Jonathan Norton, Ph.D., Dionne Price, Ph.D.** |
| Pharmacology Toxicology Reviews | **Asoke Mukherjee, Ph.D., Dan Mellon, Ph.D.** |
| Biopharmaceutics Reviews | **David Lee, Ph.D., Suresh Doddapaneni, Ph.D.** |
| CMC Reviews | **Martin Haber, Ph.D., Ali Al-Hakim, Ph.D.** |
| Product Quality Microbiology Review | **Vinayak Pawar, Ph.D.** |
| DDMAC | **Mathilda Fienkeng** |
| DSI | **Susan Leibenhaut** |
| OSE/DMEPA | **Richard Abate, RPh, MS, Melina Griffis, RPh, Denise Toyer, Pharm.D., Carol Holquist, RPh** |
| SEALD | **Iris Masucci** |

Cross Discipline Team Leader Review

# 1. Introduction

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) with a long history of use worldwide. Oral ibuprofen was first approved as a prescription drug in the United States in 1974, and was subsequently approved for non-prescription status in 1984. It was approved in the U.S. as a prescription antipyretic for children in 1989 and gained OTC status in the mid-1990s. There are multiple oral single-entity and combination approved ibuprofen products available both by prescription and OTC. Currently there are no approved IV formulations of ibuprofen in the United States or worldwide for the treatment of fever and management of pain. There are no IV medications of any type approved for the treatment of fever in children or adults.

The mechanism of action of ibuprofen appears to be associated with the inhibition of prostaglandin synthesis via cyclooxygenase inhibition. Although the exact mechanisms have not been established, ibuprofen and other NSAIDS appear to exert anti-inflammatory, analgesic, and antipyretic activity principally through the inhibition of the COX-2 isoenzyme; COX-1 inhibition is thought to be responsible for the unwanted effects on GI mucosa and platelet aggregation.

This intravenous ibuprofen injection (IVIb) formulation contains 100 mg/mL ibuprofen. The product has been developed by Cumberland Pharmaceuticals, Inc. under IND 62,605 for the proposed indications of the reduction of fever and management of mild-to-severe pain (b) (4)

This NDA was submitted as a 505(b)(2) application **referencing the Agency's prior findings of** efficacy and safety for three approved drugs; **Children's Motrin oral suspension (NDA 20-**516), Advil Liqui-Gels oral capsules (NDA 20-402), and Motrin oral tablets (NDA 17-463).

The application has been granted a Priority Review due to the unmet need of the intravenous treatment of fever in the inpatient setting.

# 2. Background

Presubmission regulatory activity for IND 62,605 began on February 10, 2000 during a Pre-IND meeting with the Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (DAAODP), when the Applicant was given guidance on the development of a **general investigational plan for IVIb. The Applicant's intention at that time was to** (b) (4)

At a June 1, 2001 meeting, the Applicant **was told that although their product's** pharmacokinetic profile was shown to be similar to oral ibuprofen, which would allow cross-reference to the existing data on the oral formulation, concerns regarding the use of IVIb in

critically ill hospitalized patients had not been addressed. Since IVIb is likely to be used in critically ill patients who cannot take or tolerate oral preparations and who are at increased risk for NSAID associated toxicity, IVIb must be studied in these patients. In addition, both the analgesia and antipyretic indications must be studied, since the product would probably be used off-label as an analgesic. The Applicant was also told that the safety and efficacy of IVIb must be established in adults prior to the initiation of pediatric studies.

Additional advice/comments conveyed by the Division during numerous meetings and teleconferences with the Applicant included:

- The inclusion of hemodynamically compromised patients and high risk groups in analgesic and pharmacokinetic studies in order to assess safety and provide dosing recommendations
- That the safety of IVIb with regard to renal and gastrointestinal toxicities, and bleeding potential in post-operative patients following major surgeries must be assessed
- That a clinical interpretation of the use of opioid sparing as the primary endpoint in the analgesic trials must be provided
- Statistical advice regarding the analyses of the clinical trials
- The size of the safety database

The Applicant submitted a s (b) (4) and comments were conveyed to the Applicant.

Fast track status was granted in a letter dated July 15, 2008.

A Pre-NDA meeting was held on May 29, 2008 at which time the content and format of the NDA submission were discussed. During this meeting the Applicant stated the intention to (b) (4) (b) (4) The Applicant was informed that they could request a Pediatric Written Request from the Agency.

No pediatric data has been submitted as part of this NDA. A PWR was issued on March 30, 2009.

Dr. Christina Fang, the primary clinical reviewer, noted in her review that in terms of quality, this NDA submission lacked the usual organization and consistency expected in a complete NDA submission. Consequently, numerous information requests to obtain clarifications and additional information were necessary in order for an adequate review to be completed. The Applicant supplied all requested information in a timely manner, enabling the completion of the clinical review. There did not appear to be major concerns regarding the quality of the data.

## 3. CMC/Device

The primary CMC review was performed by Martin Haber, Ph.D., with secondary concurrence from Ali Al-Hakim, Ph.D. The following contains **excerpts from Dr. Haber's review.**

Drug Product

The drug product, ibuprofen injection, is a clear sterile aqueous solution for injection containing 100 mg/mL of ibuprofen with 78 mg/mL of arginine (b) (4) [redacted]; [redacted] It is available in two strengths, 400 mg (4 mL in a (b) vial) and 800 mg (8 mL in a (b) (4) vial). The (b) (4) clear glass vials are closed with a (b) (4) [redacted] stopper and (b) (4) [redacted] flip-off seal.

The drug product formulation uses the amino acid base Arginine, USP as an excipient to (b) (4) [redacted] There are no other excipients. The drug product is manufactured at (b) (4) [redacted] had an acceptable cGMP status as of 4/30/09. EES for the drug product manufacturer in (b) (4) [redacted] is pending.

The drug product is manufactured using standard techniques for sterile injectable solutions. The vials are then (b) (4) [redacted] sterilized with a (b) (4) [redacted] There were no approvability issues noted in the product quality microbiology review for sterility assurance completed by Dr. V. Pawar.

In-process controls and drug product specifications were determined to be adequate by Dr. Haber. In a 3/11/09 Amendment, the related substance limits for any other individual impurity was tightened to NMT 0.15% as per ICH Q3B in response to a request from the Agency. A reflux extraction study with the drug formulation found no extractables released from the stopper components.

Drug Substance

The drug substance, ibuprofen, is a well characterized NSAID that is the subject of EP, JP, and USP monographs. It contains one chiral center but is produced as the racemate. It is a carboxylic acid with a molecular weight of 206.28. Ibuprofen is manufactured and tested at (b) (4) [redacted] as it has been for the last (b) years. (b) (4) [redacted] is the holder of DMF (b) (4) [redacted] for ibuprofen. The site was last found to have acceptable cGMP status on 12/18/08. DMF (b) (4) [redacted] was reviewed most recently on 6/2/08 and found to be adequate.

In response to an Information Request Letter sent by the Agency on 4/7/09, the Applicant agreed to tighten the limits for (b) (4) [redacted] impurities in the drug substance specifications since the drug product is intended for intravenous injection into very sick patients unable to take oral medications and the maximum daily dose is greater than 2 grams.

Description of Intended Use of the Drug Product

Ibuprofen injection vials are for single use only and do not contain any preservative. The intended dosage for adults is 400 or 800 mg every 4 to 6 hours as necessary for relief of pain or fever. In order to avoid any potential for local irritation due to administering undiluted drug, ibuprofen injection is intended to be added to commercially available 250 mL bags of

0.9% Sodium Chloride (normal saline, NS), 5% Dextrose (D5W) or Lactated Ringers Solution (LRS) prior to clinical use and infused over a 30 minute period. Testing demonstrated that the drug product was compatible with NS, D5W and LRS for at least 24 hours at room temperature. The drug product is stored at controlled room temperature 20° to 25°C with an expiry of (b) (4) . Submitted data for 48 months of drug product storage at 25°C demonstrated adequate drug product stability.

There are no outstanding CMC issues related to this NDA. An Approval action is recommended from the CMC perspective, pending a satisfactory cGMP inspection report (EES). No CMC related Phase 4 commitments or requirements have been recommended.

# 4. Nonclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology review was performed by Asoke Mukherjee, Ph.D., and the secondary review by Dan Mellon, Ph.D. The following is excerpted from Dr. Mellon's review verbatim. There are no outstanding Pharmacology/Toxicology issues, and an Approval action has been recommended.

The nonclinical development program for this 505(b)(2) NDA application relies on the Agency's previous findings of safety for three different approved drug products, as outlined in the table below:

| NDA# | Drug Name | Div | Strength (route) | Marketing Status | AP Date | Indication | Company |
|---|---|---|---|---|---|---|---|
| 17-463 | Motrin | DAARP (170) | 400, 600, 800 mg (oral tablet) | AP | 9/19/1974 | Signs and symptoms of rheumatoid arthritis and osteoarthritis, mild to moderate pain, primary dysmenorrhea | McNeil Consumer & Specialty Pharmaceuticals |
| 20-402 | Advil Liquid-gels | 560 | 200 mg (oral capsule) | AP | 4/20/1995 | Migraine | Wyeth Consumer Healthcare |
| 20-516 | Children's Motrin Drops | 560 | 50 mg (oral suspension) | AP | 6/16/1995 | Fever Reduction and pain relief | McNeil Consumer & Specialty Pharmaceuticals |

Appropriate patent certification has been provided. In addition, the application has included several literature references. It should be noted that the literature references were submitted for descriptive purposes only and are not necessary for approval of NDA 22-348.

In contrast to the approved referenced products, the proposed drug product employs the intravenous route of administration. Therefore, the nonclinical development program was designed to bridge the existing data via additional 28-day intravenous toxicology studies, blood compatibility studies, and local tissue irritation studies. As noted in Dr. Mukherjee's review, intravenous infusion of ibuprofen resulted in the well known NSAID-related toxicities. Consistent with the known sensitivity of animals to NSAIDs, a clear NOAEL that provides coverage for the human exposure was not obtained. This is not unusual for this class of drugs and is consistent with the data previously obtained in the referenced drugs. The submitted nonclinical intravenous toxicity studies are adequate to support the NDA application. The results of the studies document that there is likely to be local tissue irritation at the injection

site, which was monitored during the clinical development program. In addition, it is clear from the submitted studies that the product must be diluted prior to injection, as labeled, in order to avoid hemolysis of the blood.

In addition to the local tissue reaction evaluation, there are two other review issues associated with this application: impurities in the drug substance and impurities/degradants in the drug product.

At the preNDA meeting in March 2008, the sponsor was informed of the following:

> For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification must include:
>
> a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies e.g. one Ames assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
>
> b. Repeat dose toxicology of appropriate duration to support the proposed indication.

The NDA was submitted with drug substance and drug product impurity specifications that exceeded the ICH qualification threshold. The Sponsor justified the safety of these impurities by stating that the drug substance meets USP and EP specifications and that ICH Q3A does not apply since that specifically only applies to new drug substances.

**Drug Substance Impurities:** When the NDA was submitted, the original proposed specifications for impurities in the drug substance exceeded the ICH Q3A qualification threshold of not more than (NMT) 0.05% for a drug product with a maximum daily dose of greater than 2 grams. The NDA did not contain any data to justify the safety of the proposed specifications (i.e., there were no genetic toxicity or repeat dose toxicity studies of the impurities). The original proposed drug substance specifications are listed in the table below.

| Original Proposed Drug Substance Specifications | USP32 | Revised Drug Substance Specifications | *Reviewer Comment* |
|---|---|---|---|
| (b) (4) | NMT 0.3% | (b) (4) | *Exceeds ICHQ3A(R)* |
| | NMT 0.1% | | *Exceeds ICHQ3A(R)* |
| | NMT 0.3% | | *Exceeds ICHQ3A(R)* |
| | NMT 0.3% | | *Exceeds ICHQ3A(R)* |
| | NMT 0.3% | | *Meets ICHQ3A(R)* |

NOTE: The USP32 monograph referenced is for ibuprofen drug substance.

Following discussions with the Sponsor during the review cycle, in conjunction with the drug substance manufacturer (b) (4) ), the Sponsor revised the drug substance specifications to NMT(b) (4) Although this specification still exceeds the ICHQ3A(R) qualification threshold, it is the most stringent specification for ibuprofen that either Cumberland (b) (4) is aware of. I (Dr. Mellon) am not aware of any genetic toxicology data on these impurities; however, there are no structural alerts for mutagenicity in any of the (b) (4) impurities. As noted by Dr. Mukherjee, the 28-day dog study was not able to test high enough doses of ibuprofen to provide coverage for the impurities.

**Drug Product Impurities:** The original proposed specifications for impurities in the drug product exceeded the ICH Q3B(R) qualification threshold of not more than (NMT) 0.15% for a drug product with a maximum daily dose of greater than 2 grams.

| Original Proposed Specifications | USP32* | Revised Specifications | *Reviewer Comment* |
|---|---|---|---|
| (b) (4) | None | (NMT (b)) | *now covered under any other impurity* |
| | NMT 0.25% | NMT (b) | *Meets ICHQ3B(R)* |
| | None | NMT(b) (4) | *Meets ICHQ3B(R)* |

*NOTE: the USP32 monograph referenced is for ibuprofen oral suspension. There is currently no USP monograph for an ibuprofen injectable product.

During the review cycle, the Sponsor reduced the impurity specifications to below the ICHQ3B(R) qualification thresholds. The revised drug product specifications are acceptable. Given the long clinical experience with ibuprofen containing these impurities via the oral route of administration, the lower specifications proposed for the drug product specifications, the fact that the drug substance specifications exceed the ICHQ3A qualification threshold does not raise significant safety concern.

Dr. Mukherjee has recommended that NDA 22-348 may be approved from the nonclinical pharmacology toxicology perspective. Although the revised drug substance specifications still exceed ICH Q3A(R) qualification thresholds, they have been tightened from NMT (b) (4) to NMT (b) (4) These revised specifications are more stringent than those in drug substance employed for other approved ibuprofen drug products, this drug product employs the intravenous route of administration, and therefore tighter specifications that those previously employed for oral drug products are appropriate. However, as the drug substance is not novel, and the revised drug product impurity specifications are below the ICH Q3B(R) qualification thresholds, the higher drug substance specifications are acceptable.

I (Dr. Mellon) concur with Dr. Mukherjee that from a nonclinical pharmacology toxicology perspective, NDA 22-348 may be approved pending agreement on final drug product labeling.

There are no recommended Phase 4 commitments or requirements from the Pharmacology/Toxicology perspective. Recommendations regarding labeling may be found in Dr. Mellon's review.

# 5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology/Biopharmaceutics review was completed by David Lee, Ph.D. with concurrence from Suresh Doddapaneni, Ph.D. The following paragraphs summarize Dr. Lee's review. There are no outstanding Clinical Pharmacology issues, and an Approval action has been recommended.

Pharmacokinetic data were obtained from two clinical studies, one single-dose relative bioavailability study (Study CPI-CL-001), and pharmacokinetic (PK) information from a Phase 3 study (Study CPI-CL-004 for fever indication).

In Study CPI-CL-001, 200, 400 and 800 mg of IVIb were compared to equivalent doses of Advil Liqui-Gel. The results indicated that the observed ibuprofen exposure was similar (90% Confidence Interval (CI) calculation) when equivalent single doses of ibuprofen were administered either as IVIb or Advil Liqui-Gel over the dose range 200 to 800 mg. One exception occurred following IVIb administration of a single 200 mg dose, which resulted in a slightly lower Cmax than that of Advil Liqui-Gel Cmax (90% CI: 70.0 – 87.4). The observed ibuprofen Cmax and AUC IVIb exhibited dose linearity from 200 to 800 mg. The observed T1/2 was approximately 2 – 2.5 h.

Table 1: Pharmacokinetic Profile of IVIb compared to Advil Liqui-Gel

| **Dose** | **200mg (CPI-CL-001)** | | **400mg (CPI-CL-001)** | | **800mg (CPI-CL-001)** | |
|---|---|---|---|---|---|---|
| **Formulation** | Advil Liqui-Gel | **IVIb** | Advil Liqui-Gel | **IVIb** | Advil Liqui-Gel | **IVIb** |
| No. of Patients | 12 | 12 | 12 | 12 | 12 | 12 |
| AUCinf (μg•h/mL) Mean (%CV) | 69.862 (25.7%) | 65.532 (21.5%) | 110.887 (24.2%) | 112.471 (29.2%) | 218.817 (25.1%) | 198.206 (20.0%) |
| Cmax (μg/mL) Mean (%CV) | 24.697 (17.1%) | 19.294 (16%) | 42.939 (11.4) | 39.217 (15.5%) | 81.046 (23.2%) | 72.640 (13.2%) |
| Tmax (h) Mean (%CV) | 0.65 (25.9%) | 1.13 (20.3%) | 0.55 (25.6%) | 1.05 (15.8%) | 0.85 (60.4%) | 1.00 (0) |
| T1/2 (h) Mean (%CV) | 2.33 (9.6) | 2.34 (12.4) | 2.23 (19.5) | 2.22 (20.1) | 2.48 (15.6) | 2.44 (12.9) |

Source: Dr. Lee's review, p.4

The 90% confidence intervals for the ratios of the geometric means are shown in the following table from Dr. Lee's review.

Table 2

| | 200 mg | 400 mg | 800 mg |
|---|---|---|---|
| Cmax | 78.2% **(70.0 – 87.4%)** | 94.5% (84.3 – 105.9%) | 91.1% (83.1 – 99.7%) |
| AUC 0-t | 94.3% (84.2 – 105.6%) | 100.3% (92.7 – 108.5%) | 91.3% (86.9 – 96.1%) |
| AUC 0-inf | 94.5% (84.3 – 105.9%) | 100.6% (93.0 – 108.8%) | 91.2% (86.5 – 96.2%) |

**Source: Dr. Lee's review**

Study CPI-CL-004 was a Phase 3 study for the antipyretic indication where 100, 200 and 400mg doses of IVIb were administered Q4h for 24 hours. In this study, blood samples were **obtained from 0 – 4 and 20 – 26 hours post IVIb** administration. However, pharmacokinetic **parameters were not presented for the 20 – 26** hour samples. The results indicated that the observed ibuprofen Cmax0-4 and AUC0 - 4 exhibited a linear relationship from 100 mg to 400 mg. No PK parameters were presented for time-points 20-26 hours; however no dramatic differences in the parameters are expected after multiple dosing. This was confirmed when the profiles from 0 - 4 hours were compared with 20 - 26 hours.

Table 3

| **Dose** | **AUC**0-4 (μg.h/mL) | **Cmax**0-4 (μg/mL) | **Tmax**0-4 (h) | **T1/2** (h) |
|---|---|---|---|---|
| 100 mg IVIb | 22.33 ± 12.75 | 12.17 ± 6.78 | 0.5 | 2.47 |
| 200 mg IVIb | 32.62 ± 17.39 | 18.94 ± 10.5 | 0.5 | 2.11 |
| 400 mg IVIb | 70.64 ± 31.93 | 39.76 ± 17.75 | 0.5 | 2.26 |

**Source: Dr. Lee's review**

A cross-study comparison of Cmax and T1/2 was used to assess ibuprofen exposure in healthy subjects compared to ill patients. The observed Cmax and T1/2 values were similar between healthy subjects and ill patients. The observed AUC values were not compared due to lack of AUC values in ill patients.

Table 4

| | 200 mg | | 400 mg | |
|---|---|---|---|---|
| | Ill patients | Healthy subjects | Ill patients | Healthy subjects |
| Cmax 0-4 | 18.9 | 19.3 | 39.8 | 42.9 |
| Tmax 0-4 | 0.5 | 1.13 | 0.5 | 0.55 |
| T1/2 | 2.11 | 2.34 | 2.26 | 2.22 |

**Source: Dr. Lee's review, p. 5**

Subpopulation comparison of PK data in Study 004 revealed that drug bioavailability was lower in critically ill patients in comparison to non-critically ill patients as shown in the following table.

Table 5

| **Treatment, Stratum** | **AUC**0-4 (μg.h/mL) | **Cmax**0-4 (μg/mL) |
|---|---|---|
| 100 mg IVIb<br>Critically Ill / Non-critically Ill % Difference | 61.2% | 56.6% |
| 200 mg IVIb<br>Critically Ill / Non-critically Ill % Difference | 49.6% | 50.0% |
| 400 mg IVIb<br>Critically Ill / Non-critically Ill % Difference | 52.7% | 52.3% |

**Source: Dr. Lee's review, p. 6**

The Applicant did not offer an explanation for the difference in the PK profiles in critically vs. non-critically ill patients. However, this may be due to a number of factors, including critically ill patients' changes in basal metabolic rate, fluid status and distribution, concomitant medications and underlying illnesses.

According to Dr Lee's review, there are no concerns regarding the approvability of IVIb from the Clinical Pharmacology perspective.

## 6. Clinical Microbiology

There as a microbiology consult by Dr. Pawar who found no problems with this preservative free parenteral formulation.

## 7. Clinical/Statistical- Efficacy

The primary clinical review was performed by Christina Fang, M.D, and the statistical review was completed by Jonathan Norton, Ph.D. A secondary statistical review was completed by Dionne Price, Ph.D. The discussion below includes aspects of these reviews where noted.

The two indications sought by the Applicant for IVIb are the reduction of fever and the treatment of mild-to-severe pain. In support of efficacy, the results of four Phase 3 efficacy trials were submitted, two for each indication.

Indication: Reduction of Fever

The results of two Phase 3 efficacy trials (004 and 006) were submitted in support of the antipyretic indication.

**Study 004** was a multi-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose, dose-ranging study of Ibuprofen IV Injection (IVIb) 100 mg, 200mg, and 400mg in hospitalized febrile patients. One hundred-twenty hospitalized patients with onset of fever of at least 101.0°F within seven days of enrollment were enrolled. Critically ill patients, defined as those on mechanical ventilation, receiving vasopressors, or both, accounted for 44% of the study population, and were approximately evenly distributed among the treatment groups. All subjects had infections as their underlying illness, the most common being blood and lung in origin. Almost 50% of the critically ill subjects had lung infections, while the same proportion of non-critically ill subjects had blood-borne infections.

The age range of the study population was 17 to 89 years with a mean of 38 years. Of the 120 patients, 48% were Caucasian, 11% were African American, 7% were Hispanic, 33% were Asian, and 27% were female. The treatment groups were balanced with regard to other demographic characteristics and baseline temperatures (102°-102.5°).

The patients were randomized in approximately equal groups to receive 30-minute infusions of IV ibuprofen 100mg, 200mg, 400mg, or placebo every four hours for a total of six doses. Rescue medication such as oral acetaminophen and cooling procedures were permitted post-treatment or during treatment in those designated as treatment failures ($T \geq 103.0^{\circ}$ F). Temperature was measured at baseline, every 0.5 hours during the first four hours post-treatment, and every two hours from Hour 4- Hour 24.

Over 90% of the 120 treated patients completed the study. The most common reasons for discontinuation were treatment failure and adverse events (each 2.5% of subjects). As would be expected, treatment failure was more common in those receiving placebo (7.1%), and adverse event more common in subject's receiving study drug (6.5%). Overall the number of discontinuations was small and those dropping out for any single reason ranged from zero to two per treatment group.

The rates of protocol deviations were similar among all treatment groups, and were largely due to deviations from the exclusion criteria. They were determined by Dr. Fang not to have had a major impact on study outcomes.

In terms of exposure, more than 80% of patients in each treatment group received all six doses of study treatment, and over 90% received five doses.

The primary efficacy parameter was the percentage of patients on IVIb 400mg with a temperature <101.0°F (38.3°C) at Hour 4 after the start of infusion compared to placebo.

The analysis as prespecified by the Applicant was the Cochran-Mantel-Haenszel (CMH) procedure adjusted for center using exact Chi-squared test statistic. The Intent-to-Treat (ITT) population consisted of all subjects who received at least one treatment, had a baseline assessment and at least one post-baseline evaluation. Missing data were imputed by the Last Observation Carried Forward (LOCF).

The Applicant's analysis of the primary endpoint is shown in the table below taken from Dr. Fang's review. Additional analyses included stratification of critically and non-critically ill subjects for each treatment group.

Table 6: Primary Efficacy Analysis-Study 004

| **Study 004<br>Fever reduced to <101.0°F at Hour 4** | **100 mg IVIb (n=31)** | **200 mg IVIb (n=30)** | **400 mg IVIb (n=31)** | **Placebo (n=28)** |
|---|---|---|---|---|
| **Number (%) reached T<101.0°F, ITT population** | 20 (65%) | 22 (73%) | **24 (77%)** | **9 (32%)** |
| **Comparison against placebo, p-value of CMH test** | p=0.0138 | p=0.0018 | **p=0.0005** | |
| Number (%) reached T<101.0°F, Critically ill | 10 (71%) | 6 (50%) | 8 (57%) | 1 (8%) |
| Comparison against placebo, p-value of CMH test | p=0.010 | p=0.0211 | p=0.0075 | |
| Number (%) reached T<101.0°F, Non critically ill | 10 (59%) | 16 (89%) | 16 (94%) | 8 (53%) |
| Comparison against placebo, p-value of CMH test | p=0.7585 | p=0.0245 | p=0.0089 | |

Source: Appendix Table 14.2.3 on pages 129-130 of the report for Study 004

The treatment differences in terms of percentage of subjects with fever reduced to a temperature <101.0°F (38.3°C) during the first 4 hours after the initial dose are summarized in the table above. Comparing 400mg IVIb to placebo, differences were 45% (77% verses 32%) in the ITT population, 49% (57% versus 8%) in the critically ill subpopulation, and 41% (94% versus 53%) in the non-critically ill subpopulation. All these treatment differences were statistically significant, however according to Dr. Norton's review, the Applicant did not employ correction for multiple endpoints. In addition, since all patients who received one

dose of study medication were included in the ITT population, the Division's standards were met in this regard.

It is of note that efficacy was demonstrated in the critically ill population (although a smaller proportion of patients achieved T <101.0°F during the first four hours) despite differences in the pharmacokinetic profile of IVIb in these patients. The values for AUC0-4 and Cmax0-4 for the critically ill patients were approximately 50% compared to the parameters for the non-critically ill patients. As stated previously in the Biopharmaceutics section of this review, the pharmacokinetic profile differences may be due to a number of factors, including critically ill patients' changes in basal metabolic rate, fluid status and distribution, concomitant medications and underlying illnesses. Despite the PK differences, efficacy was demonstrated in critically ill patients as well as non-critically ill, and dosing recommendations will be the same for both groups (start at lowest dose and increase as needed until maximum recommended dose reached).

Dr. Norton performed an analysis of the primary endpoint and confirmed the Applicant's findings. The following table is from Dr. Norton's review. (additional analyses in this table are explained in Dr. Norton's review)

Table 7: Statistical Reviewer Analysis of Primary Endpoint Study 004

| Treatment | N | Num. Afebrile (%) | Asymptotic p | Exact p | Applicant p |
|---|---|---|---|---|---|
| Placebo | 28 | 9 (32%) | N.A. | N.A. | N.A. |
| 100 mg | 31 | 19 (61%) | .0328 | .0581 | .0264 |
| 200 mg | 30 | 21 (70%) | .0079 | .0147 | .0043 |
| 400 mg | 31 | 24 (77%) | .0006 | .0011 | .0005 |

There were several secondary efficacy endpoints analyzed by the Applicant, and although these analyses were not adjusted for the multiplicity of endpoints, they are informative regarding the behavior of IVIb as an antipyretic in the study population. Dr. Fang's review contains a detailed discussion of the secondary endpoint analyses, a summary of which follows.

The percentage of patients receiving IVIb 200 mg or 100 mg whose temperature was less than 101.0°F (38.3°C) at Hour 4 compared to patients receiving placebo are illustrated in Table X above. When the total study population is assessed (critically ill plus non-critically ill), both dosages show statistical significance (not corrected for multiple endpoints) The only group that does not show statistical significance is the non-critically ill subgroup treated with the 100mg dose of IVIb.

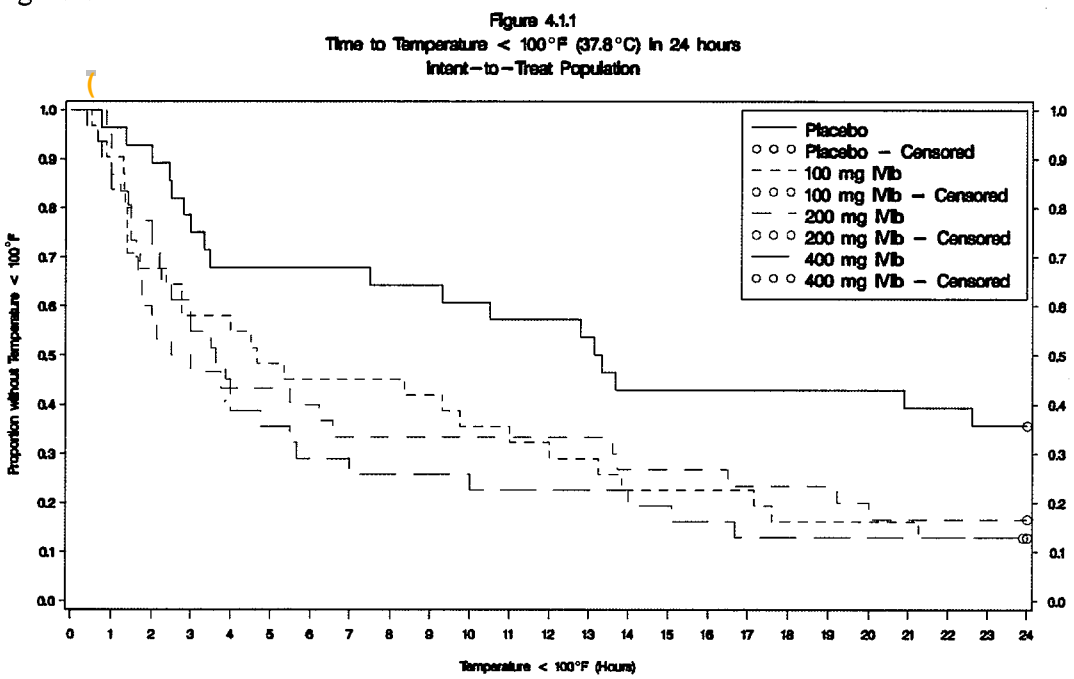
The time to a temperature of less than 101.0° F by Hour 24 was assessed for all treatment groups. The mean number of hours was 3.67 for the 100mg group, 4.4 hours for the 200mg group, and 3.61 hours for the 400mg group. All reached statistical significance compared to placebo, which was 8.47 hours. Given the small study population of less than 30 per treatment group, it is not possible to determine why the 200mg group performed worse than 100mg.

As would be expected, a larger proportion of subjects receiving placebo were treatment failures (temperature greater than 103.0° F at any time post dose), compared to any group

receiving IVIb. Approximately 30% of placebo subjects, compared to 13% of the subjects who received 400mg IVIb, 13% of 200mg IVIb, and 26% of 100mg IVIb, fell into this category.

The following figure from Dr. Fang's review illustrates the time to temperature of less than 101.0 ° F. There is a clear separation between the placebo curve and treatment curves.

Figure 1




The mean time to treatment failure was shortest for the placebo group (5.7 hrs), followed by 7.39 hours for the 100mg group, 10.29 hours for the 200mg group, and 10.75 hours for the 400mg group.

Over 80% of the subjects receiving any dose of IVIb had a temperature less than 100.0° F by 24 hours compared to 60% of subjects receiving placebo.

Please see Dr. Fang's review for discussion of additional secondary endpoints.

Dr. Fang concluded in her review that Ibuprofen injection at 400 mg, 200 mg, and 100 mg given every four hours is effective in treating fever in hospitalized patients, including critically ill patients, based on the demonstration of statistically significant and clinically meaningful

treatment differences in this study. Additionally, she noted that the end-of-dosing assessments of the initial dose and time-specific end-of-dosing assessments in 24 hours combined with overall multiple-dose efficacy results support a dosing interval of every 4 hours for fever indication.

Dr Norton concluded that the 200mg and 400mg doses of IVIb were superior to placebo, and that the 100mg dose was marginally superior at best.

I am in general agreement with these conclusions. The 400mg and 200mg doses of IVIb were clearly efficacious as antipyretics; however the findings related to the 100mg dose were not as clear cut. The treatment effects in subjects in the 100 IVIb group were numerically better than placebo although treatment differences were often small. Considering that some subjects did obtain clinical benefit from the 100mg dose, this dose may also be appropriate for the treatment of fever in the hospital setting.

The efficacy findings in the critically ill patients were comparable to the non-critically ill, despite the finding that the systemic exposure to ibuprofen in the critically ill patients is approximately half that of the non-critically ill. These results may be confounded by the lower mean baseline temperature in the critically ill patients (101.7-102.0°F) compared to non-critically ill (102.2-102.9°F).

**Study 006** was a single-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose, study of IVIb 400mg in adult febrile patients hospitalized for the treatment of uncomplicated malaria in Thailand.

Enrollment consisted of 60 hospitalized adult patients with a clinical diagnosis of uncomplicated malaria confirmed by laboratory testing, who experienced fever greater than 100.4°F by tympanic temperature measurement within 12 hours prior to receiving the study drug. The age range of the study population was 18 to 54 years with a mean of 30 years. All 60 patients were Asian and 20% were female. The two treatment groups were balanced with regard to demographic characteristics such as age, gender, and weight. Baseline temperature was 38.65°C (101.6°F) in the IVIb 400 mg group and 38.82°C (101.9°F) in the placebo group and was not considered clinically significantly different between the two groups.

Subjects were randomly assigned in a 1:1 ratio to receive either IVIb 400 mg or matching placebo 30-minute IV infusions every six hours for the first three days (12 doses) followed by q6-hour treatment as needed for temperature > 38.0°C (100.4°F) for two additional days.

Rescue treatments (cold packs, cooling blankets, alcohol baths) were allowed during the post treatment period and in cases of treatment failure where treatment failures were defined as temperature ≥106.0°F (41.1°C) ≥2 hours after the initial dose or ≥103.0°F (39.4°C) ≥2 hours after the subsequent doses in patients with uncomplicated malaria.

All 60 subjects completed the 3-day fixed dosing treatment period, and only one patient who received IVIb 400mg did not return for the 21-day follow-up assessment.

There were two major systematic protocol deviations. The first deviation, involving all 60 patients, was that the data were not double-entered as specified in the original protocol, but were single-entered and double-checked. The second deviation involved the first 38 patients enrolled. Laboratory tests that were to be collected daily during the first five treatment days were missing. This international study site was not inspected by the Division of Scientific Investigation due to the time constraints associated with this priority review. However, these protocol deviations were balanced between the treatment groups and would not be expected to have a differential impact on efficacy outcomes. Missing daily safety laboratory tests in more than 50% of the sample population does, however, shrink the size of the safety database in both treatment groups with regard to laboratory investigations.

Efficacy data collected included temperature by tympanic measurement recorded before the start of infusion, hourly during the first four hours after the start of the initial dose, and every four hours during the rest of the treatment period

The planned primary efficacy endpoint was fever reduction as measured by area above the temperature line of 37.0°C (98.6°F) versus the time curve within the first 24 hours of treatment (AUC-T°). The AUC-T° was calculated using the linear trapezoidal rule from all available data from each patient. Temperatures below 37.0°C (98.6°F) did not contribute to the AUC-T°. If a patient's last temperature measurement was missing, LOCF was used as the imputation method. For additional details regarding the calculation of the primary endpoint please refer to Dr. Norton's review.

Planned secondary endpoints included the following

- Area under temperature curve in Hours 0-4
- Area under temperature curve in Hours 24-72
- Area under temperature curve in Hours 0-72 (post hoc)
- Number and % of treatment failures (T≥106.0°F (41.1°C) ≥2 hours after initial dose or ≥103.0°F (39.4°C) ≥2 hours after any subsequent dose)
- Parasite clearance time (time from initial treatment to time of first negative result)

The planned intent-to-treat (ITT) population was to have included all treated patients with a baseline assessment and at least one post baseline evaluation of the primary endpoint. The planned efficacy-evaluable population (EEP) was a subset of the ITT population with no major protocol violations with regard to eligibility criteria or study conduct and no two (or more) consecutive temperature measurements missing within the first 24 hours of the treatment period. Only EEP was planned to have been used in the primary and secondary efficacy analyses. However, since all 60 subjects were included in the EEP, it was in fact the entire ITT population, and also met the definition for the Division's definition of ITT population (all subjects who received at least one dose of study medication regardless of post baseline measurement).

The results of the Applicant's analysis of the primary endpoint are shown in the table below from page 31 of Dr. Fang's review.

Table 8: Primary Efficacy Analysis

| **Study 006 Area under the temperature curve (above 37°C)** | **400 mg IVIb (n=30)** | | | **Placebo (n=30)** | | |
|---|---|---|---|---|---|---|
| | Mean (SD), °C·hr | Mean °F·hr | °F/hr | Mean (SD), °C·hr | Mean °F·hr | °F/hr |
| AUC-T° Hours 0-24, primary endpoint | 7.49 (7.94) | 13.48 | 0.56 | 16.44 (11.60) | 29.59 | 1.23 |
| AUC-T° Hours 0-4, secondary endpoint | 2.40 (1.54) | 4.32 | 1.08 | 5.18 (2.97) | 9.32 | 2.33 |
| AUC-T° Hours 24-72, secondary endpoint | 1.36 (4.00) | 2.45 | 0.051 | 0.50 (1.51) | 0.90 | 0.02 |
| AUC-T° Hours 0-72, endpoint not pre-defined | 8.85 (11.03) | 15.93 | 0.12 | 16.94 (12.23) | 30.49 | 0.42 |

The analysis of the primary endpoint demonstrated a statistically significant superiority as an antipyretic of 400mg IVIb over placebo at $p < 0.002$.

Dr. Fang states in her review that since 97% of both treatment groups return to T < 99.0°F in 24 hours, the efficacy endpoints defined by area under the temperature curve for an extended period are not informative. Treatment differences between IVIb 400 mg and placebo were shown mainly in terms of a temperature reduction of 1.3°F more in hourly average AUC-$T°_{0-4}$; a reduction by 1-2 more degrees (°F) in time-specific measurements from 1 to 8 hours; about 5 hours earlier on the average to reach T<100.0°F and 6 hours earlier to reach T<99.0°F. Her analyses of efficacy findings including secondary endpoints are illustrated in the table below from her review. Note that Dr. Fang converted temperatures from Celsius to Fahrenheit.

Table 9: Summary of Efficacy Findings-Study 006

| **Study 006 Efficacy summary** | **Effect size of treatment difference from placebo** |
|---|---|
| | **400 mg IVIb (n=30)** |
| **Primary efficacy endpoint** | |
| AUC-$T°_{0-24}$ (°F·hr) | 16.11 |
| Hourly average AUC-$T°_{0-24}$ (°F/hr) | 0.67 |
| **Secondary and additional efficacy endpoints** | |
| AUC-$T°_{0-4}$ (°F·hr) | *5.0* |
| Hourly average AUC-$T°_{0-4}$ (°F/hr) | *1.25* |
| Time-specific q4 hour temperature measurements (q6 hour dosing) in Hours 0-24 (°F)*, ITT | 1.0-2.1 (Hr 1-8)<br>0.2-0.8 (Hr 12-20) |
| Time to T<100.0°F (37.8°C) by Hour 24 (h) | 4.9* |
| Time to T<99°F (37.2°C) by Hour 24 (h) | 6.4* |

*Note: Statistically significant difference.

The following temperature curves (over 24 and 72 hours) taken from Dr. Fang's review further clarify the above findings.

Figure 2: Time-Specific Temperature Measurements in Hours 0-24, ITT population

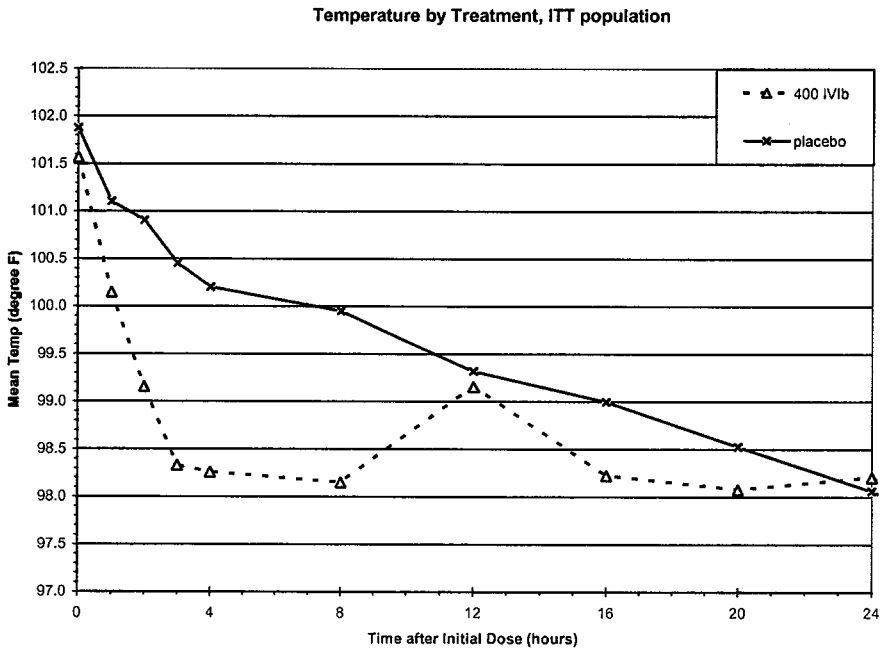
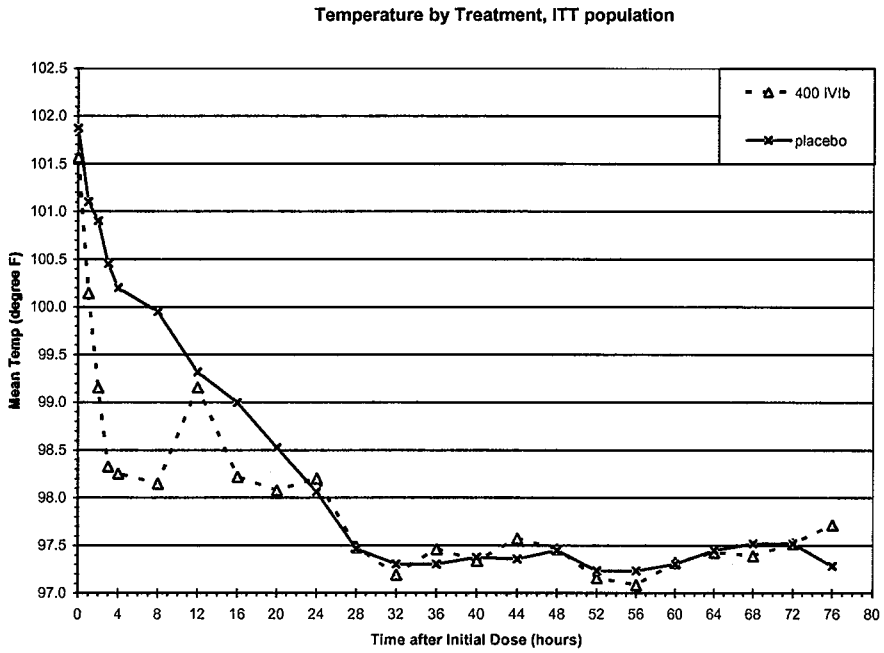



Figure 3: Time-Specific Temperature Measurements in Hours 0-72, ITT population




Dr. Norton utilized the SAS datasets in his calculation of the analysis of the primary endpoint and the results confirmed the Applicant's analysis. Details regarding minor discrepancies in the analysis presented in the CSR and the SAS datasets (that did not impact the analysis) are discussed in Dr. Norton's review.

Table 10: Primary Efficacy Analysis-Statistical Reviewer

| Endpoint | Statistic | Placebo (N=30) | Ibuprofen 400 mg (N=30) |
|---|---|---|---|
| AUC – 24 hours | Mean (SD) | 16.94 (11.69) | 7.99 (7.96) |
| | p-value vs. placebo | -- | .002 |
| AUC – 4 hours | Mean (SD) | 5.30 (2.94) | 2.56 (1.52) |
| | p-value vs. placebo | -- | < .0001 |
| Afebrile (< 38.3° C) at 4 Hours | Proportion (%) | 12/30 (40%) | 29/30 (97%) |
| | p-value vs. placebo | -- | .0006 |

Dosing interval was not adequately evaluated in this study because temperature was measured every four hours whereas study medication was administered every six hours. The overall results suggest a positive outcome of antipyretic multiple-dose effects with every six hour administration.

Two patients on IVIb 400 mg and three patients on placebo were identified as treatment failures. The range for the parasite clearance time was 14 to 50 hours in both treatment groups. Neither of these secondary endpoints was informative regarding the efficacy of IVIb 400mg.

In conclusion, the Applicant demonstrated that IVIb administered every six hours is efficacious as an antipyretic in this study population over 24 hours. This finding was confirmed by the statistical review team.

Indication: Management of mild to severe pain
The results of two Phase 3 efficacy trials (008a and 008b) were submitted in support of the analgesic indication. Both studies evaluated the use of IVIb as adjunctive analgesic therapy in patients receiving morphine for the treatment of postoperative pain.

The efficacy findings for both studies have been reviewed by Drs. Fang, Norton and Price. Dr. Norton found that the studies 008a and 008b were inadequate to draw any conclusions regarding findings of efficacy. Dr. Price has addressed these issues in her secondary statistical review. Aspects of all reviews will be reflected in this section where noted.

**Study 008a** was a multi-center, randomized, double-blind, placebo-controlled, parallel, multiple-dose, dose-ranging analgesic study of Ibuprofen IV Injection (IVIb) 400 mg and 800mg in hospitalized patients with postoperative pain requiring narcotic analgesia.

The study population consisted of 406 patients who received study medication, with an age range of 18 to 69 years and a mean of 45 years. Of the 406 patients, 86% were Caucasian, 11% were African American, 2% were Asian, and 79% were female. The treatment groups were approximately balanced with regard to demographic characteristics such as age, gender, race, height, and weight.

Subjects were randomized to strata based on age and weight to receive IVIb 400mg, IVIb 800mg, or matching placebo in approximately equal numbers. The initial dose of study medication was administered approximately at the initiation of skin closure, about 30 minutes prior to the end of surgery. Seven subsequent doses were administered every six hours for two days, followed by PRN dosing for three more days.

Concomitant narcotic use was limited to fentanyl given approximately 45 minutes prior to the end of surgery before the initiation of study medication. Morphine was administered every 5 minutes via PCA pump as required by the patient. The first dose of concurrent morphine was administered after the completion of the 30 minute infusion of ibuprofen. If other narcotics or NSAIDS were administered, the study medication was discontinued.

Pain intensity (PI) was measured at rest and with movement using an 11-point VAS scale at 1 and 3 hours and every 3 hours thereafter up to Hour 48, then daily through Day 5 if the study medication was continued on a PRN basis.

Close to 90% of the 406 patients completed the study. There were 49 dropouts, 11 from the 800 mg IVIb group and 19 from each of the 400 mg IVIb and placebo groups. The main reasons for dropouts were AEs (5% on IVIb 800 mg, 7% on IVIb 400 mg, and 5% on placebo) and treatment failure (1% IVIb 800 mg, 4% IVIb 400 mg, and 5% placebo).

Major protocol deviations were reported in 41% of patients, mainly as clinical trial material (CTM) or study medication administration error (24%), taking excluded medication (18%), meeting exclusion criteria (4%), and mistimed consent (3%). Minor protocol deviations were reported in 77% patients, mainly as missed assessment (76%), CTM administration error (18%), and Day 14 follow up error (6%). The specific types of protocol deviations were balanced between the treatment groups and would not be expected to have differential impact on study outcomes.

At least 90% of patients in each treatment group (90% on IVIb 400 mg, 93% on IVIb 800 mg, and 94% on placebo) received one day or four doses of treatment. Less than one third of the study population (28% on IVIb 400 mg, 30% on IVIb 800 mg, and 23% on placebo) received two days or eight doses of treatment. A total of 17 patients (less than 10%), including four subjects on IVIb 400 mg, 12 on IVIb 800 mg, and one on placebo, received more than eight doses.

The planned primary efficacy endpoint was the reduction in total morphine usage in the first 24 hours after surgery compared to placebo. Secondary endpoints included PI at rest and with movement at 48 hours, time to first subsequent narcotic analgesia for breakthrough pain (or time to treatment failure), and nocturnal awakenings due to pain. Reduction of opioid-related side effects was also planned as a secondary endpoint and was defined as time to gastrointestinal motility as measured by return of bowel sounds, resumption of ambulation, resumption of liquid intake and solid diet, length of hospital stay, and each individual and combined assessment of the following (each counted as a score of one): diffuse pruritus, overt respiratory depression, need for post-operative urinary indwelling catheter (after initial removal of surgical catheter), incidence of post-operative vomiting or need for anti-emetic medication.

Dr. Norton expressed concern in his statistical review regarding the primary endpoint analysis carried out by the Applicant. Dr. Price addressed these concerns in her review, and what follows is a brief summary. Please refer to both reviews for additional details.

As stated in Dr. Price's review:

> "In the clinical study report and statistical analysis plan, the Applicant stated that analysis of variance and covariance procedures would be used to analyze the primary endpoint and that the primary model would include terms for treatment and center. The Applicant allowed for the inclusion of additional terms in the model for "sensitivity analysis and robustness." In addition, the applicant evaluated the assumptions underlying the analysis of variance and covariance and stated that the data would be transformed if warranted based on a violation of the assumptions. Lastly, the Applicant's analysis plan allowed for the possibility that analog nonparametric procedures would be used to corroborate the results.
>
> Analyses were conducted on the intent-to-treat population including all randomized patients receiving one dose of treatment. The Applicant employed Dunnett's test to address multiplicity concerns. Missing data

was imputed using the mean of the assessments immediately prior to and after the missing value for patients having no more than two consecutive missing assessments. The mean morphine use in the placebo group (for the corresponding time point) was imputed for patients having more than two consecutive missing assessments. Missing data was replaced by the mean morphine use from the placebo group for each time point for patients dropping out of the study. As a sensitivity analysis, the Applicant also utilized the mean morphine use among the placebo group for all missing data. The strategies for handling missing data were consistent with the advice provided by the Agency."

The results of the analyses conducted on the original (i.e. untransformed) and transformed data are provided in the following Table from Dr. Price's review.

Table 11: Applicant's Results for Original and Rank Transformed Data

| | Placebo (n=134) | Caldolor 400 mg (n=134) | Caldolor 800 mg (n=138) |
|---|---|---|---|
| Total Morphine Use (mg) | | | |
| LS Mean (SE) | 49 (4) | 46 (4) | 44 (3) |
| LS Mean difference from placebo | | -3 | -5 |
| 95% CI of difference | | (-10,5) | (-12,3) |
| Pairwise p-value[1] | | 0.667 | 0.237 |
| Rank Transformed Morphine Use (mg) | | | |
| LS Mean (SE) | 223 (14) | 209 (14) | 191 (13) |
| LS Mean difference from placebo | | -14 | -32 |
| 95% CI of difference | | (-44,16) | (-62,-3) |
| Pairwise p-value[1] | | 0.458 | 0.030 |

Dr. Norton expressed concern that the Applicant's primary results were based on an ANOVA model of the rank-transformed data that included effects for age, weight, center, and treatment, although the study report and SAP stated that only center and treatment effects would be included in the primary analysis. Dr. Norton conducted an additional analysis using only center and treatment as covariates with and without data transformation, and again, a statistically significant difference between IVIb and placebo was evident only for the transformed data for the 800mg dose of IVIb. See Dr. Norton's review for details regarding this analysis.

Dr. Price reviewed advice given to the Applicant during drug development, and concluded that although the inclusion of age and weight in the model were of a "somewhat post hoc" nature, their inclusion did not appear to change the overall conclusions as evidenced by the comparison between the Applicant's and Dr. Norton's analyses.

According to the Applicant, the ANOVA model conducted on the original data, the log transformed data, and the Box-Cox transformed data violated the underlying assumption of normality. Thus, a nonparametric procedure was used and deemed most appropriate (by the Applicant).

The roles of transformation of data and nonparametric approaches are discussed in detail in Dr. Price's review. Her conclusion is that the nonparametric approach was not necessarily the most appropriate for this analysis. In addition, she "expected the results from the parametric analysis and the nonparametric analysis to yield consistent results", and consequently "based my conclusions on the pre-specified analysis defined as an analysis of variance on the original data".

Dr. Price's conclusion regarding the primary analysis for Study 008a was that the Applicant failed to demonstrate a statistically significant difference in total morphine use between arms.

Dr. Fang discussed the clinical significance of the efficacy findings. The mean difference in morphine use between the IVIb 800mg treated group and placebo was 10% (5mg), and between IVIb 400mg and placebo was 5% (3mg). Time-specific pain intensity measured at mid-dosing interval and end-of-dosing interval during the first 48 hours showed separations of the mean PI from placebo in a range of 0.5 to 1.0 units (on a 0-10 point scale) from 9 to 21 hours for the 400 mg dose, and 0.5 to 1.2 units from 9 to 33 hours for the 800 mg dose.

An important aspect of the clinical significance of the use of IVIb and potential decrease in morphine use is the incidence of opioid-related adverse events in those receiving IVIb compared to placebo-treated subjects. According to the Applicant's analysis, treatment differences in morphine-related AEs included an approximately 10% reduction in any morphine-related AE (pruritus, respiratory depression, vomiting, or need for antiemetic medication) 11-14% reduction in post-operative vomiting or need for anti-emetic medication, and 10-20% reduction in Combined Safety Assessment (all of the above listed AEs) of morphine-related AEs. It is of note that constipation is not included in this list, however return of GI motility is assessed as part of functional recovery.

In assessment of functional recovery (time to GI activity, ambulation, and hospital discharge) that might be affected by morphine treatments, the reduction in means from placebo included 12-18% reduction in time to GI motility, 16-22% reduction in time to resumption of liquid intake, 28-33% reduction in time to resumption of solid diet, and 10-15% reduction in time to ambulation. Treatment differences in means from placebo in functional recovery could also be summarized as 3-5 hours of reduction in time to GI motility and resumption of liquid intake and ambulation.

Although there does appear to be a some clinical benefit to the use of IVIb adjunctly with IV morphine in postoperative patients, given the statistical concerns and the relatively small treatment effect, I conclude that this study did not demonstrate efficacy for IVIb 400mg or 800mg for the treatment of pain in this setting.

**Study 008b** shared the same protocol and amendments as Study 008b, except for differences in the dosages of IVIb studied, the sample size, and the patient population. The study population consisted of 319 hospitalized patients scheduled for elective abdominal hysterectomy. The subjects were randomized 1:1 to receive either IVIb 800mg or placebo.

The demographic makeup of the population was as follows: age range of 22 to 65 years with a mean of 43 years. Of the 319 female patients, 39% were Caucasian, 55% were African American, and 6% were Hispanic. The treatment groups were approximately balanced with regard to demographic characteristics such as age, race, height, and weight.

Eighty-eight percent of the patients completed the study. There were 37 dropouts, 15 from the 800 mg IVIb group and 22 from the placebo group. The main reasons for dropout were treatment failure (5% in the IVIb 800 mg group and 8% in the placebo group) and AEs (3% in each of the two groups).

Protocol violations were not expected to impact the study outcomes, as they were balanced between the treatment groups and consisted mainly of patients taking excluded medications (20%) and missing or miss-timed assessments (62%).

In terms of exposure, more than 80% of patients in each treatment group (86% on IVIb 800 mg and 83% on placebo) received five doses of treatment. Only a few patients received six or more doses.

The primary efficacy endpoint was total morphine use in the first 24 hours following surgery. Although the analyses specified in the clinical study report (CSR) were similar to those specified for Study 008a, the primary analysis outlined in the SAP included a model selection procedure. Dr. Price explains in her review that such a strategy is used to determine the particular variables that should be in the final model.

Due to the discrepancy between the CSR and the SAP, an information request was sent by Dr. Price on May 13, 2009 for clarification. In response, the Applicant clarified that the language in the CSR was "not representative of the analyses performed and presented in the CSR." According to the Applicant, the SAP was followed and the model selection procedure was used to derive the final model. The Applicant's final model included factors for treatment, age, weight, and center.

The following table excerpted from page 7 of Dr. Price's review demonstrates the Applicant's analyses for the original and transformed data.

Table 12: Applicant's Results for Original and Box-Cox Transformed Data

| | Placebo (n=153) | Caldolor 800 mg (n=166) |
|---|---|---|
| Total Morphine Use | | |
| LS Mean (SE) | 57 (2) | 49 (2) |
| LS Mean difference from placebo | | -8 |
| 95% CI of difference | | (-13,-3) |
| Pairwise p-value[1] | | <0.001 |
| Box-Cox Transformed Morphine Use | | |
| LS Mean (SE) | 14 (.4) | 12 (.4) |
| LS Mean difference from placebo | | -2 |

| | |
|---|---|
| 95% CI of difference | (-2,-1) |
| Pairwise p-value[1] | <0.001 |

Source: Clinical Study Report Table 13 and Table 14.2.1.1.3
[1] Analysis based on ANOVA model with effects for age, weight, center, and treatment

Dr. Price stated in her review:

> **"When evaluating the evidence, I did** not focus on the results produced by transforming the data. As previously stated, the applicant deemed the data to be non-normal and consequently transformed the data. However, the normality assumption underlying an analysis of variance can be relaxed provided the sample size is large and/or the departure from normality is not extreme. In Study CPL-CI-008B, the sample size was not small, I was not convinced that the departures from normality were extreme, and I was concerned that the transformed data would not easily be clinically interpretable; therefore, an analysis of the untransformed data is preferable **in my opinion".**

In terms of the primary endpoint analysis using the untransformed data, Study 008b demonstrated statistically significant superiority of IVIb 800mg over placebo.

Dr. Fang discussed the clinical significance of the efficacy findings in her review. The mean reduction of morphine use in the first 24 hours post surgery was about 15% (9mg).

Time-specific PI measured at mid-dosing interval and end-of-dosing interval during the first 24 hours showed noticeable separations of mean PI from placebo in a range of 0.5 to 1.2 units (on a 0-10 point scale) from 9-24 hours and sizable separation of median PI from placebo in a range of 10-35% from 9-24 hours.

A comparison between treatment groups of morphine-related AEs included a 7% reduction in any morphine-related AE and 12.5% reduction in Combined Safety Assessment (CSA) of morphine-related AEs (defined above in 008a). In assessment of functional recovery (time to GI activity, ambulation, and hospital discharge) that might be affected by morphine treatments, noticeable reduction in means from placebo included 16% reduction in time to GI motility and 8% reduction in time to ambulation, representing a reduction in time to GI motility and ambulation of less than 2 hours.

The findings in Study 008b were similar to those of study 008a, however the statistical analysis of 008b was favorable in terms of the statistical superiority of IVIb over placebo. The statistical findings along with the additional clinically significant data support the conclusion that the addition of IVIb to morphine for postoperative analgesia may be therapeutically beneficial to some patients.

## Efficacy Conclusions

Fever indication

Studies 004 and 006 successfully demonstrated that IVIb at 100mg, 200mg and 400mg given every four hours, and 400mg administered every six hours is efficacious for the treatment of

fever in hospitalized patients. The analysis of the primary endpoint in both studies showed statistical significance at $p < 0.05$ level, and additional support of the clinical utility of IVIb in this setting was provided by the secondary endpoint findings.

Study 004 demonstrated efficacy of IVIb as an antipyretic in both critically ill and non-critically ill patients. In this study, the systemic exposure to ibuprofen in critically ill patients was found to be approximately 50% that of non-critically ill patients, and the proportion of critically-ill patients who achieved T <101.0°F was smaller than the non critically-ill patients for all doses of IVIb. The contributions of the lower mean baseline temperature (~0.5°F) in the critically ill group to these findings is unknown. Dosing adjustment for critically ill patients is not recommended based on the findings from this study. However, the lowest effective dose should be recommended for all patients.

Pain indication

Only Study 008b demonstrated statistically significant results for the treatment of pain in postoperative patients for IVIb 800mg every six hours in patients receiving morphine concurrently for analgesia. The primary endpoint was morphine usage over the first 24 hours **postoperatively. Although the Applicant's analysis** of Study 008a demonstrated efficacy for **IVIb 800mg (not 400mg), this was based on "transformation of data" that** the statistical team found unacceptable. The rank transformation would have been more credible had it been the pre-specified analysis. According to the **Applicant a non-parametric procedure "may" have** been performed to corroborate results, but in actuality, it produced varying results from other methods. Secondary endpoints in both studies supported the clinical utility of IVIb as an adjunct analgesic in this setting, although observed treatment effects were relatively small.

The study population, hospitalized postoperative patients receiving morphine analgesia, may not be the ideal inpatient population in which to asses the efficacy of IVIb. These patients experience moderate-to-severe pain requiring opioid analgesia. A large treatment effect (decrease in morphine use) resulting from the addition of IVIb to an opioid would not be expected, given that the oral formulation of ibuprofen has been shown effective in the treatment of mild-to-moderate pain. While the results of both studies (008a and 008b) showed a decrease, albeit small, in morphine use (approximately 10-15%), one could anticipate that a larger treatment effect would occur in a more suitable population of hospitalized patients suffering mild-to-moderate pain who are NPO or unable to tolerate oral medication.

# 8. Safety

The safety database contains safety data from six clinical studies including two Phase 1 studies in healthy volunteers and four Phase 3 studies in hospitalized patients with fever (Studies 004 and 006) and pain (Studies 008a and 008b).

The Applicant was originally advised on October 30, 2003 that at least 300 subjects must be exposed to the 800mg dose (3200mg/day) for 7-10 days. However, in meeting minutes dated October 4, 2004, the Division agreed that the database proposed by the Sponsor (225 post - operative patients and 299 additional patients) would be acceptable.

Six-hundred-eight subjects were exposed to IVIb, including about 200 hospitalized patients exposed to either 400 mg every 4-hour dosing for up to one day or every 6-hour dosing for up to three days, and 316 hospitalized patients exposed to 800 mg every 6-hour dosing for up to four days. Most patients had 1-2 days of exposure to IV ibuprofen. The longest duration of exposure to IVIb was three days in fever patients in Study 006. Given the most recent advice provided by the Division, the size of the safety database is acceptable.

The Phase 3 study population consisted of 95% non-elderly subjects, approximately 75% female, and 60% Caucasian.

Since the IV formulation of ibuprofen is bioequivalent to the oral formulation and its duration of use is limited in the hospital setting, an important aspect of the safety review is the adverse events occurring in inpatients who are seriously ill. For that reason, data on SAEs and common AEs has been pooled by study population; patients with serious infections/critically ill (004), malaria (006), and post-operative patients (008a and 008b). Data on laboratory tests and vital signs were pooled across all Phase 3 studies.

Safety monitoring consisted of AE reporting, vital signs, transfusion monitoring, and routine laboratory tests, and is considered adequate in studying short term use of IV ibuprofen in a hospitalized population.

There were six reports of deaths. All deaths occurred in Study 004 in critically ill patients during the one-month post-treatment observation period. All were due to complications of underlying disease and none was considered study drug-related.

There were 48 reports of nonfatal serious adverse events (SAEs), 13 in patients (mostly critically ill) in Study 004 and 35 in post-operative patients in Study 008a and 008b. Twelve of the 13 SAEs in Study 004 were appeared to be caused by complications of underlying disease. One case of acute renal failure occurred in a young Asian male patient with malaria who had volume depletion associated with fever, persistent vomiting and frequent blood sampling. He received six doses of IVIb 400 mg during the first day of the study. The patient was found to have hypotension and a rapid elevation in BUN and creatinine at the 24-hour assessment and was diagnosed with acute renal failure. The SAE resolved with treatment with no sequelae. Although the event was rated by the Investigator as unrelated to the IVIb treatment, ibuprofen with its known renal toxicity is suspected as having played an important role in the development of ARF in a patient who was at a higher risk for drug associated renal toxicity due to volume depletion by fever, vomiting, and blood sampling and complication by potential renal damage with malarial infection.

The majority of the 35 cases of SAEs reported in the pain studies were complications of surgeries and not considered study drug-related based on the nature of the events, the time of occurrence with respect to study drug administration, and Dr. Fang's review of the individual Case Report Forms.

The most commonly reported AEs were abnormal laboratory results, diarrhea, infections, and blood pressure abnormalities in Study 004, where close to half of the population was critically

ill. The most commonly reported AEs in the pain studies were GI symptoms such as nausea, flatulence, vomiting, constipation, pruritis and headache with similar rates of occurrence between the IVIb 800 mg group and the placebo group. There were numerous reports of local irritation associated with the administration of undiluted IVIb solutions in PK Study 001. In the tolerability Study 003 infusion pain was reported in more subjects receiving IVIb 400 mg than placebo. After switching to diluted preparations in subsequent studies reports of local reactions decreased and occurred at similar rates in both placebo and IVIb treatment groups.

AEs reported in patients with malaria in fever Study 006 were minor symptoms and most (7 of the 9 AEs listed for the IVIb group) had only one occurrence in the IVIb treatment group. The AEs reported in more than one patient in the IVIb group included nasal congestion in two patients on IVIb (versus none in the placebo group) and abdominal pain in five patients on IVIb (versus three in the placebo group).

For Study 004 involving critically ill patients, AEs reported by three or more patients (≥10%) in any IVIb treatment group are summarized in the table below from Dr. Fang's review. There are more AEs of anemia, neutropenia, blood urea increased, and hypertension in the IVIb 400 mg than the other three treatment groups. However due to the small size of the study groups and the underlying illnesses of the patients, it is difficult to assess causality. AEs listed in the table are consistent with those generally seen in the sick populations with severe infections, multiple organ failure, and other end-stage medical conditions.

**Table 13: Treatment Emergent AEs in ≥3 (≥ 10%) Patients in Any IVIb Treatment Group in Study 004**

| SOC | Preferred Term | Placebo (n=28) | IVIb 100 mg (n=31) | IVIb 200 mg (n=30) | IVIb 400 mg (n=31) |
|---|---|---|---|---|---|
| | | Number (%) of patients with any AE | | | |
| | Any Treatment-Emergent AEs | 25 (89%) | 27 (87%) | 25 (81%) | 23 (74%) |
| Blood & lymphatic system disorder | **Anemia** | **4 (14%)** | **5 (16%)** | **6 (19%)** | **11 (35%)** |
| | Eosinophilia | 7 (25%) | 7 (23%) | 7 (23%) | 8 (26%) |
| | **Neutropenia** | **2 (7%)** | **2 (6%)** | **2 (6%)** | **4 (13%)** |
| | Thrombocythemia | 0 | 3 (10%) | 2 (6%) | 1 (3%) |
| GI disorder | Diarrhea | 2 (7%) | 3 (10%) | 3 (10%) | 2 (6%) |
| Infections & infestations | Pneumonia bacterial | 0 | 3 (10%) | 1 (3%) | 2 (6%) |
| | Bacteremia | 0 | 4 (13%) | 1 (3%) | 0 |
| Investigations | Blood lactate dehydrogenase increased | 1 (4%) | 3 (10%) | 2 (6%) | 1 (3%) |
| | **Blood urea increased** | **0** | **0** | **0** | **3 (10%)** |
| Metabolism & nutrition disorders | Hypokalemia | 5 (18%) | 4 (13%) | 4 (13%) | 6 (19%) |
| | Hypoproteinemia | 2 (7%) | 3 (10%) | 0 | 4 (13%) |
| | Hypoalbuminemia | 1 (4%) | 3 (10%) | 1 (3%) | 3 (10%) |
| | Hyponatremia | 0 | 2 (6%) | 0 | 3 (10%) |
| Vascular disorders | Hypotension | 1 (4%) | 0 | 2 (6%) | 3 (10%) |
| | **Hypertension** | **0** | **0** | **0** | **3 (10%)** |

Source: Dr. Fang's review, p 83

The common AEs reported in ≥3% post-operative patients in the two pain studies are summarized in the table below. The most common (>10%) AEs had similar rates of

occurrence between the IVIb 800 mg group and the placebo group, although the 400mg group often had a higher rate. They included nausea (53% of patients on IVIb 800 mg versus 62% on placebo), flatulence (16% versus 15%), vomiting (15% versus 17%), constipation (13% versus 17%), pruritis (15% versus 16%), and headache (12% versus 11%). There were no common AEs that occurred at a markedly higher rate in the 800mg group than in placebo patients.

**Table 14: Treatment Emergent AEs in ≥3% Patients on Any IVIb Treatment in Pain Studies**

| System Organ Class | Preferred Term | Placebo (N=287) | 400 mg (N=134) | 800 mg (N=304) |
|---|---|---|---|---|
| | Any Treatment-Emergent AEs | 258 (90%) | 118 (88%) | 260 (86%) |
| Blood & lymphatic system disorders | Anemia | 6 (2%) | 5 (4%) | 7 (2%) |
| Gastrointestinal disorders | **Nausea** | **179 (62%)** | 77 (57%) | **161 (53%)** |
| | **Flatulence** | **44 (15%)** | 10 (7%) | **49 (16%)** |
| | **Vomiting** | **50 (17%)** | 30 (22%) | **46 (15%)** |
| | **Constipation** | **49 (17%)** | 23 (17%) | **38 (13%)** |
| | Abdominal distension | 10 (3%) | 1 (<1%) | 7 (2%) |
| | Dyspepsia | 2 (<1%) | 6 (4%) | 4 (1%) |
| | Abdominal discomfort | 0 | 4 (3%) | 2 (<1%) |
| General disorders & administration site conditions | Pyrexia | 32 (11%) | 9 (7%) | 16 (5%) |
| | edema peripheral | 4 (1%) | 1 (<1%) | 9 (3%) |
| Investigations | Body temperature increased | 8 (3%) | 0 | 7 (2%) |
| | Hemoglobin decreased | 3 (1%) | 4 (3%) | 6 (2%) |
| Metabolism & nutrition disorders | Hypokalemia | 8 (3%) | 5 (4%) | 3 (<1%) |
| Nervous system disorders | **Headache** | **31 (11%)** | 12 (9%) | **35 (12%)** |
| | Dizziness | 5 (2%) | 8 (6%) | 13 (4%) |
| Psychiatric disorders | Insomnia | 13 (5%) | 4 (3%) | 6 (2%) |
| Renal & urinary disorders | Urinary retention | 10 (3%) | 7 (5%) | 10 (3%) |
| Reproductive system disorders | Vaginal hemorrhage | 16 (6%) | 13 (10%) | 13 (4%) |
| Respiratory disorders | Cough | 1 (<1%) | 4 (3%) | 2 (<1%) |
| Skin & subcutaneous tissue disorders | **Pruritus** | **47 (16%)** | 10 (7%) | **46 (15%)** |
| Vascular disorders | Wound hemorrhage | 4 (1%) | 4 (3%) | 4 (1%) |
| | Hypertension | 8 (3%) | 1 (<1%) | 4 (1%) |

Source: Dr. Fang's review, p. 83

Changes in laboratory test values and changes in vital signs were reported in all treatment groups with intra-group and inter-group variations. These changes could be associated with complications of medical conditions (such as post surgical complications or multi-organ failure in patients with severe sepsis), concurrent illness, concomitant medication, and ibuprofen treatment. There were no clear patterns to suggest a dose dependent association of the changes with the use of IV ibuprofen.

Due to the limited sizes of subpopulations including age, gender and race, safety analysis for drug-demographic interactions was not possible. However, there did not appear to be any additional safety signals noted.

I am in agreement with Dr. Fang that based on the review of safety data there are no new safety signals or major issues identified. Short-term use of IV ibuprofen at a dosage of up to

400 mg four to six times a day and 800 mg four times a day for up to a few days, is considered relatively safe. Patients should be well hydrated before receiving IV ibuprofen to minimize the risk of acute renal toxicity. Undiluted IVIb solution should not be administered due to local irritation and infusion pain, and the minimum effective dosage should be targeted based on the individual response for better tolerance and safety.

## 9. Advisory Committee Meeting

An Advisory Committee Meeting was not deemed necessary for this application.

## 10. Pediatrics

No pediatric studies were submitted with this NDA. At the Pre-NDA meeting held on May 29, 2008 the Applicant stated their intention (b) (4) The Applicant was informed that they could request a Pediatric Written Request from the Agency.

(b) (4)

# 11. Other Relevant Regulatory Issues

DSI inspections

The Division of Scientific Investigation (DSI) performed inspections of four study sites, two for each indication. There are no outstanding issues based on the inspection of two sites for the fever indication (Study 004). The final results and conclusions regarding the two sites for the pain indication (Studies 008a and 008b) are pending at this writing.

An audit of Dr. Peter Morris's subject records for fever study 004 showed that the study appeared to have been conducted adequately and the data from his site may be used in support of the studied indication.

A Voluntary Action Indicated (VAI) letter was sent by DSI to Dr. John Promes who also participated in fever study 004. The audit revealed that one subject with the diagnosis of closed head injury (out of 21 patients enrolled at this site) was enrolled in violation of the protocol exclusion criteria "have a history of severe head trauma". Additionally, the DSMB associated with this site and the Sponsor advised against enrolling patients with long bone fractures due to literature suggesting that NSAIDs inhibit osteoblast proliferation and bone healing. The Division was not informed of this change in protocol. Neither of these violations would be expected to impact the efficacy findings associated with this study. DSI stated that the study appears to have been conducted adequately and the data generated by this site may be used in support of the studied indication.

A report received from DSI on May 19, 2009, presented the results of inspections of Dr. Henry Frazer (008a) and Dr. Lamar Snow (008a and 008b). According to the report, the data generated by Dr. Frazer appears acceptable in support of the application. However, the inspection of Dr. Snow's site revealed concerns regarding data integrity in study 008b related morphine use for three subjects whose data could not be verified by source documents. There were also two subjects who received morphine at incorrect times in relation to study drug. For Study 008a, morphine use for one subject was not verifiable from source documents, and two of the 32 enrolled subjects were unblinded to study staff so that the medication administration records of these subjects indicated the treatment assignment.

Due to these issues, the primary endpoint analysis for Study 008b was redone by Dr. Norton excluding Dr. Snow's results. This analysis revealed similar results with statistical significance in favor of the IVIb group for the primary endpoint. Study 008a was not reanalyzed since the initial analysis did not show statistical significance for the primary endpoint.

Financial disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangement with the any clinical investigator had been made whereby study outcomes affects compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such

interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

505(b)(2) Issues
There are no outstanding 505(b)(2) issues related to this application.

## 12. Labeling

**The Applicant's initial proposed proprietary name** for ibuprofen injection was Amelior. The name was reviewed by the Division of Drug Marketing, Advertising, and Communications (DDMAC) and was not recommended **because it "overstates and guarantees the efficacy of the drug". The second proposed proprietary** name was Caldolor, which the Division of Medication Error Prevention and Analysis (DMEPA) and DDMAC found acceptable.

**Draft labeling was submitted in PLR (Physician's Labeling Rule) format. The labeling is** currently under review by the Division and SEALD. In addition to product specific information, the contents of this label will follow the NSAID template that was instituted in 2005, and required the inclusion of warnings (including a Box Warning) regarding serious cardiovascular and gastrointestinal adverse events associated with NSAID use. The template also required that a Medication Guide be included as part of all prescription NSAID labels, however since this product is intended for use in hospitals, a Medication Guide is considered unnecessary.

The label will not contain dosing recommendations for pediatric patients. Studies in this population must be completed prior to the inclusion of the pediatric indication in the product label.

The proposed product labeling including the PI and carton/container was reviewed by DDMAC. Their comments consisted mainly of recommendations regarding the removal of promotional language from the label. Details of their recommendations are found in their review dated May 15, 2009.

The label was also reviewed by the Office of Surveillance and Epidemiology (OSE), DMEPA. Recommendations consisted of revision of the presentation of the strength of the vials to be expressed in terms of net quantity (i.e., 400mg/4ml and 800mg/8ml) followed by concentration (100mg/ml). They also provided recommendations regarding the package insert and carton/container. Appropriate comments were sent to the Applicant.

## 13. Recommendations/Risk Benefit Assessment

**Recommended Regulatory Action**

I recommend the Approval of Caldolor (Ibuprofen) Injection for the reduction of fever and the treatment of acute pain in adults.

**Risk Benefit Assessment**

The basis for the approval of the fever indication is the results of two adequate and well-controlled Phase 3 efficacy trials, where Caldolor was found effective for the reduction of fever in hospitalized patients with a variety of underlying causes for fever. Caldolor at 100mg, 200mg, and 400mg doses given every four hours, and 400mg every six hours was shown to be an effective antipyretic in both critically ill and non-critically ill patients with fever.

The basis for the approval of the analgesic indication is the result of one well-controlled Phase 3 efficacy trial in which the efficacy of Caldelor was measured in terms of opioid sparing in postoperative patients receiving morphine for the treatment of pain. The study showed an approximately 10% reduction in morphine use in the patients receiving Caldolor 800mg compared to placebo in addition to morphine. A second similar trial was performed however statistical superiority of Caldolor 400mg and 800mg compared to placebo was not demonstrated. Secondary endpoints in both studies showed small treatment effects in favor of treatment with Caldolor in terms of pain intensity and decreases in opioid associated adverse events.

My rationale for the approval of Caldolor for analgesia in the face of only one successful trial relies on the following:

- Caldolor is a new formulation of a known analgesic.
- The pharmacokinetic profile of Caldolor is almost identical to oral ibuprofen (Advil Liqui-gels) being referenced in this 505(b)(2) application.
- Regulatory requirements in this setting typically consist of one successful adequate and well-controlled Phase 3 efficacy trial along with sufficient safety data that indicates the risk/benefit ratio is maintained for the new formulation.

The Applicant has proposed an indication for the treatment of mild-to-severe pain. In the Phase 3 trial 008b, patients with moderate-to-severe pain were assessed in terms of morphine use, and those who received Caldolor as adjunctive therapy had statistically significantly less morphine usage. Given that oral ibuprofen is approved for the treatment of mild-to-moderate pain, and Caldolor demonstrated efficacy as an analgesic in patients with moderate-to-severe pain, it is appropriate to grant Caldolor the broad indication for **"treatment of acute pain".**

No new or unexpected safety signals were detected upon review of the safety database. The **Applicant fulfilled the Division's requirement that the safety of Caldolor be demonstrated in** severely-ill patients.

In order to maximize the safe use of Caldolor, patients must be adequately hydrated and the lowest effective dose should be used for the treatment of fever and pain. The product label will include all information from the NSAID template including a Box Warning regarding serious NSAID associated cardiovascular and gastrointestinal adverse events.

**Recommendation for Postmarketing Risk Management Activity**

Appropriate product labeling appears adequate to mitigate the risks of this product.

**Recommendation for other Postmarketing Study Commitments**

Pediatric trials to fulfill PREA are the only recommended postmarketing study requirements.

**Recommended Comments to Applicant**

None

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/s/

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Ellen Fields
6/3/2009 02:33:04 PM
MEDICAL OFFICER