CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-348

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-348
Applicant Name	Cumberland Pharmaceuticals, Inc.
Date of Submission	December 11, 2008
PDUFA Goal Date	June 11, 2008
Proprietary Name / **Established (USAN) Name**	Caldolor/IV Ibuprofen
Dosage Forms / Strength	Solution for injection containing 100 mg/mL ibuprofen
Proposed Indication(s)	Management of fever Treatment of mild to moderate pain, moderate to severe pain as an adjunct to opioid analgesia
Action	Approval

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

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors and Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This is a 505(b)(2) application for an intravenous formulation of ibuprofen solution containing 100 mg/mL intended for the treatment of fever and pain.

2. Background

Ibuprofen was first approved in oral form as a prescription product in 1974 and as an over-the-counter product in 1984. In this application, reference is made to the Agency's prior findings of efficacy and safety for ibuprofen from three approved oral formulations, Motrin (NDA 17-463), Advil Liquid-gels (NDA 20-402) and Children's Motrin Drops (20-516).

There is an approved parenteral formulation of ibuprofen lysine (NDA 21-903), however, it is indicated to "close a clinically significant patent ductus arteriosus in premature infants weighing between 500 and 1500 g, who are no more than 32 weeks gestational age, when usual medical management (e.g., fluid restriction, diuretics, respiratory support) is ineffective". There are no parenteral formulations of ibuprofen approved for use in fever or pain.

This NDA was submitted under the Fast Track development program, granted on July 15, 2008. A priority review was granted as there are no approved parenteral therapies to treat fever.

The applicant originally did not seek an indication for the treatment of pain. However, the review division at the time, the Division of Analgesic, Arthritis and Ophthalmologic Drug Products, was concerned that this product would be used for pain and there would be no data to support this use. As a result, the applicant submitted studies in support of an indication for the treatment of mild to severe pain.

3. CMC/Device

The drug substance is described in DMF (b) (4) which has been reviewed and found acceptable. Testing of the drug substance by the drug product manufacturer is acceptable.

The drug product is a clear, sterile aqueous solution for injection containing ibuprofen 100 mg/mL as 4mL in a (b) vial and 8 mL in a (b) (4) vial. The drug product is intended for dilution prior to administration and was found to be compatible in normal saline, 5% dextrose or lactated ringers solution. The drug product uses arginine (b) (4) . There are no excipients other than arginine (b) (4) The vials are (b) (4) sterilized. There are no preservatives and the vials are intended for single use only. Specifications were found to be acceptable.

The drug product will be manufactured by (b) (4) contract manufacturers for Cumberland Pharmaceuticals: (b) (4) will manufacture both, 400 mg vial and 800 mg vial configurations, while (b) (4) will currently manufacture only a 400 mg vial configuration.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 48 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The nonclinical program for this application relies on reference to the Agency's prior findings of safety for Motrin (NDA 17-463), Advil Liquid-gels (NDA 20-402) and Children's Motrin Drops (20-516). Additional 28-day intravenous toxicology studies, blood compatibility studies and local tissue irritation studies were conducted and submitted as a bridge between this intravenous product and the orally administered reference products. There was evidence of local tissue irritation at the injection site, but this was not a problem during clinical studies. The blood compatibility study did demonstrate that dilution was necessary to avoid hemolysis.

The originally 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 gram, which were subsequently revised to NMT (b) (4) This still exceeds the ICHQ3A qualification threshold, however, as noted by Dr. Mellon, there are no structural alerts for these impurities and the specifications are apparently the most stringent for any ibuprofen product.

Similarly, the originally 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. These were revised during the review cycle to an acceptable level. As noted by Dr. Mellon, given the acceptable drug product specifications and the long history of the oral ibuprofen products containing the drug substance impurities, the drug substance specifications that exceed the ICHQ3A threshold is not a significant safety concern.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

One single-dose relative bioavailability study compared 200, 400 and 800 mg doses of Caldolor infused over 30 minutes to equivalent doses of Advil Liqui-Gel. Bioequivalence was demonstrated with the exception of a slightly lower Cmax for the 200 mg dose of Caldolor compared to the 200 mg dose of Advil Liqui-Gel. Comparison of Caldolor doses of 200, 400 and 800 mg produced a linear relationship for Cmax and AUC. Pharmacokinetic data was also

collected during clinical studies. In one study of patients with fever, when compared with non-critically ill subjects, critically ill subjects demonstrated values lower for the AUC_{0-4} and $Cmax_{0-4}$ by approximately 50%. Half-life was not notably different. The reason for the difference in AUC and Cmax is unclear, but may be due to differences in fluid balance in critically ill patients as a result of fluid resuscitation, given that the half-life was not shorter which would have suggested the lower levels were due to more rapid clearance. Review of the efficacy did not reveal any differences in the critically ill patients compared to the non-critically ill patients.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

During the manufacture of Caldolor, the bulk solution is (b) (4) . In the production environment, all equipment and components required for manufacture of Caldolor are (b) (4) prior to use. The drug product is then sterilized (b) (4) . Testing methods for endotoxin and sterility met the requirements of USP <85> and USP <71>, respectively.

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Four clinical efficacy studies were submitted in support of the two proposed indications. For the treatment of fever, the two studies demonstrated efficacy. One study (CPI-CL-004) of hospitalized patients with fever due to infection explored three doses of Caldolor, 100, 200 and 400 mg, compared to placebo, administered over 30 minutes every four hours for a total of six doses. Rescue treatments with oral acetaminophen or cooling procedures were permitted. Subjects included critically ill patients, defined as requiring mechanical ventilation, vasopressors, or both. The primary efficacy endpoint, percentage of patients with a temperature below 101.0°F by Hour 4, was statistically significantly superior for the prespecified primary analysis, the 400 mg dose compared to placebo. Based on this outcome, the applicant recommended labeling the dose for treating fever as 400 mg every four to six hours. However, as noted in the following table modified from Dr. Fang's review, there was efficacy demonstrated for the 100 and 200 mg doses as well, with additional support from a number of secondary analyses. Dr. Fields points out that the results for the 100 mg dose were not as consistent as for the higher doses. While Drs. Fields and Fang concluded that there was no safety concern to preclude approval, ibuprofen is not without risk and, therefore, it is important to provide a range of options that include the lowest possible dose of Caldolor that can be effective. Based on this information, the option of using lower doses was discussed with the applicant and added to the package insert.

Table 5.3.1-13 Summary of Efficacy Finding, Fever Study CPI-CL-004

Study 004 Efficacy summary	Effect size of treatment differences from placebo		
	100 mg IVIb (n=31)	200 mg IVIb (n=30)	400 mg IVIb (n=31)
% with T<101.0°F by Hour 4, ITT	*33%***	*41%**	*45%**
% with T<101.0°F (38.3°C) by Hour 24	11%	7%	11%
% with T<100.0°F (37.8°C) by Hour 24	23%	19%	23%
% with T<99°F (37.2°C) by Hour 24	0	6%	16%
Mean temperature reduction in Hours 0-4 (°F)	1.27	1.48	2.05
Mean temperature reduction in Hours 0-24 (°F)	0.99	1.05	1.37

* Statistically significant difference.

** Statistically significant difference by the Applicant's analyses and borderline significant difference by Dr. Norton's analyses using T<38.3.0°C as a cut point.

Study CPI-CL-004 also examined efficacy in the critically ill patients as a subgroup. As described in detail in Dr. Fang's review, there appeared to be efficacy for this group

The second study, Study CPI-CL-006, randomized patients with fever due to malaria to Caldolor 400 mg every six hours for three days. Rescue was permitted as needed. This study also demonstrated the efficacy of the 400 mg dose of Caldolor dosed every six hours.

Taken together, these studies demonstrate efficacy for the treatment of fever. (b) (4)

Analgesic effects were evaluated in two randomized, double-blind, placebo-controlled studies in patients with postoperative pain. Study CPI-CL-008a enrolled patients who had undergone orthopedic, gynecologic or abdominal surgery. Patients were randomized to receive either 400 mg or 800 mg of Caldolor every six hours for up to 5 days. Morphine was available by patient controlled analgesia for rescue on an as needed basis. The prespecified primary efficacy endpoint was the total amount of morphine used in the first 24 hours following surgery. Secondary endpoints included pain intensity at rest and with movement. This is an unusual primary endpoint for an efficacy study in acute pain. There was concern on the part of the applicant that in the setting of postoperative pain, the concomitant use of rescue morphine by would result in an inability to distinguish treatment groups by pain intensity.

Although there were trends favoring the active treatment groups, the amounts of morphine use across treatment arms were not statistically significantly different. The mean amount of morphine used during the first 24 hours was 46.3 mg for the 400 mg Caldolor arm, 43.8 mg for the 800 mg Caldolor arm and 48.9 mg for the placebo group. The applicant was able to demonstrate a statistical difference by transforming the data, however, as described by Dr. Price, there was not a statistically valid reason for doing so, as the deviation from normality was not extreme, nor was the sample size extremely small, conditions that could have justified transformation. As presented in Dr. Fang's review, there were differences in pain intensity across treatment groups as well.

Study CPI-CL-008b randomized patients who had undergone abdominal hysterectomy to Caldolor 800 mg or placebo. The protocol was otherwise comparable to Study CPI-CL-008a. The mean amount of morphine used during the first 24 hours was 47 mg for the 800 mg Caldolor

arm and 55 mg for the placebo group. This difference was statistically significant. The applicant also transformed this data and the difference remained statistically significant. In this study, the sample size was not small, and Dr. Price noted that she was not convinced that the departures from normality were extreme, and was concerned that the transformed data would not easily be clinically interpretable; therefore, an analysis of the untransformed data is preferable. The applicant sought to represent the (b) (4) in the package insert, but this was not permitted since the original, nontransformed results were the appropriate data to describe the study outcome. Pain intensity was statistically significantly different between the two treatment groups.

The use of morphine consumption as a primary endpoint is problematic, in that there is a challenge determining whether a difference of any number of milligrams of morphine is clinically relevant and able to provide enough efficacy data against which to weigh risk. For instance, in the setting of postoperative pain, the clinical significance of a difference in mean morphine use of 8 mg over 24 is unclear. Fortunately, there was also a difference in pain intensity between the active and placebo treatment group in this study, and also, we already understand that the drug substance has analgesic effects. However, for a 505(b)(1) application, and especially for a new molecular entity, reliance on the amount of opioid used as rescue can be very problematic in understanding the efficacy of a product. Additional information about opioid-related adverse events can be useful. A reduction in the amount of opioid use to a great enough extent to decrease associated adverse events would be one method to determine the clinical relevance of the morphine data, as well as provide an additional understanding of benefit. However, while the applicant did compare the adverse events across treatment groups here, the study was not powered for such an analysis, nor were specific opioid-related adverse events prespecified for analysis.

Although Study CPI-CL-008a did not meet its prespecified outcome, there were trends favoring efficacy, including support from the secondary analyses. Study CPI-CL-008b clearly demonstrated efficacy, although it is clear from the amounts of morphine used in both studies that Caldolor is not an adequate analgesic to treat postoperative pain at the doses studied. Unlike opioids, ibuprofen has a well defined maximum dose that cannot be exceeded safely. Therefore, while studies of opioid analgesics with similar study designs may also result in use of rescue, outside of the constraints of a clinical trial, the dose can be titrated as needed. Dr. Fang has suggested indicating Caldolor for the treatment of pain as an adjunct to opioids. However, as this is a 505(b)(2) application, we can rely on prior findings of efficacy as an analgesic for mild to moderate pain and do not need to restrict the indication to use only as adjunctive therapy. The package insert will describe the Study CPI-CL-008b, including the amount of concurrent morphine use. In this way clinicians can see the efficacy in the context of postoperative pain and along with their knowledge of ibuprofen, choose to use Caldolor for the treatment of pain where they see it providing benefit.

8. Safety

A thorough review of safety was conducted by Dr. Fang. The safety database of approximately 600 patients was adequate in size to evaluate safety. No deaths were attributable to study drug.

Most of the serious adverse events reported were also not attributable to study drug. The known safety profile of ibuprofen raises areas of concern for a hospitalized patient population, particularly for effects on renal function and, in the setting of surgery, hemostasis. Dr. Fang describes one case of acute renal failure in a young Asian male malaria patient with volume depletion as a result of persistent vomiting. He was found to have hypotension and rapid elevation in BUN and creatinine at the 24-hour assessment and was diagnosed with acute renal failure, but this resolved with appropriate treatment. This underscores the need for adequate volume replacement and monitoring of renal function in patients who are critically ill and treated with ibuprofen. The most commonly reported adverse events in fever studies with critically ill patients were abnormal laboratory results, diarrhea, infections, and blood pressure abnormalities in Study 004. In pain studies, the most common adverse events were nausea, flatulence, vomiting, constipation, pruritus and headache, although there were few adverse events that differed across treatment groups. This is likely a reflection of the considerable morphine use in both treatment arms. To avoid the appearance of no adverse events associated with the use of Caldolor in these patients, these adverse events were included in the package insert along with notation of the use of morphine in all treatment groups. The adoption of diluting the ibuprofen had addressed the problem of local irritation at the administration site seen during early PK studies.

9. Advisory Committee Meeting

No advisory committee meeting was held for this application. The drug substance is not an NME and the indications are not novel.

10. Pediatrics

(b) (4)

In response to a proposed pediatric study request, a Written Request was issued to the Applicant under IND 62,605 for the study of fever in the pediatric population from birth to 16 years of age. The requested studies include single dose pharmacokinetic and safety data for all pediatric age groups, in addition to multiple-dose PK and efficacy assessments (randomized, double-blind, controlled, superiority study) for fever in children from birth to six months of age. The Applicant has chosen to fulfill the Pediatric Research Equity Act (PREA) requirements for this NDA with the studies outlined in the written request, as reflected in a Pediatric Plan was submitted on April 15, 2009 which contained a deferral request for all age groups because adult studies have been completed and are ready for approval. The Pediatric Plan was presented to and accepted by the Pediatric Research Committee on May 13, 2009.

11. Other Relevant Regulatory Issues

Reference is made to the Agency's prior findings of efficacy and safety for ibuprofen from three approved oral formulations, Motrin (NDA 17-463), Advil Liquid-gels (NDA 20-402) and Children's Motrin Drops (20-516). Adequate patent certification has been provided for the referenced products. As noted by Dr. Mellon, literature references submitted were for descriptive purposes only and were not considered necessary for approval of this NDA. The overdose language in the labeling for Motrin is outdated. The language was replaced with more relevant text that is consistent with general knowledge about the safety of ibuprofen in overdose.

Overall, the results of DSI inspections were acceptable with the exception of data from one study site, that of Dr. Lamar Snow (CPI-CPL-008a and 008b). The inspection of Dr. Snow's site revealed data integrity questions for both studies such that the data from this site were excluded in a reanalysis of the primary endpoint analysis for Study 008b by Dr. Norton. The exclusion of this data did not alter the outcome.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name, Caldolor, was reviewed by DDMAC and DMEPA and found to be acceptable. The labeling was amended as noted in the relevant sections above. As this product is parenteral and, therefore, not self-administered, there will be no NSAID class medication guide.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

There is an adequate demonstration of efficacy for the treatment of fever and pain based on the clinical studies submitted in support of this application and the Agency's prior findings of efficacy, and there are no new safety concerns that would preclude approval for these indications.

- Recommendation for Postmarketing Risk Management Activities

None.

- Recommendation for other Postmarketing Study Commitments

Pediatric studies will be conducted to fulfill the requirements of PREA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Hertz
6/11/2009 02:40:41 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

Memorandum

DATE: June 11, 2009

NDA#: 22-348 Caldolor (IV Ibuprofen)

RE: Analgesic Indication

FROM: Ellen Fields, M.D., M.P.H.
Clinical Team Leader
DAARP

THROUGH: Sharon Hertz, M.D.
Deputy Division Director
DAARP

The analgesic indication for Caldolor (IV Ibuprofen) originally proposed by the Applicant was "the treatment of mild-to-severe pain". Upon review of the clinical trials submitted in support of the pain indication, and the previously approved indications for oral ibuprofen upon which the Applicant was relying (mild-to-moderate pain), this was determined to be an inappropriate indication. Although patients in the clinical trials had moderate-to-severe pain, Caldolor was used as an adjunctive therapy to morphine in this setting, and did not treat severe pain as a primary, single treatment.

The CDTL memo for this NDA stated that the indication "treatment of acute pain" was appropriate for Caldolor. However discussions within the Division since that writing resulted in the conclusion that "treatment of acute pain" could be misleading and imply that Caldolor alone was effective for the treatment of mild-to-severe acute pain. As a result, the indication was amended to "treatment of mild-to moderate pain, and moderate-to-severe pain as an adjunct to opioid analgesia", as stated in Dr. Hertz's Summary Review for Regulatory Action.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ellen Fields
6/11/2009 04:39:07 PM
MEDICAL OFFICER

Sharon Hertz
6/11/2009 04:41:00 PM
MEDICAL OFFICER
I concur.