

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ellen Fields, MD, MPH
Subject	Deputy Division Director Summary Review
NDA/Supplement #	22348/005
Applicant Name	Cumberland Pharmaceuticals
Date of Submission	January 30, 2015
PDUFA Goal Date	November 30, 2015
Proprietary Name / Established (USAN) Name	Caldolor Injection/Ibuprofen intravenous injection
Dosage Forms / Strength	Injection/100 mg/mL
Proposed Indication(s)	In pediatric patients ages 6 months to 17 years of age 1. Reduction of fever 2. Management of mild-to-moderate pain 3. Management of mild-to-moderate pain as an adjunct to opioid analgesia
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	
OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Christina Fang, MD
Statistical Review	Katherine Meaker, MS; Freda Cooner, PhD
Pharmacology Toxicology Review	Carlic Huynh, PhD; Newton Woo, PhD; R. Daniel Mellon, PhD
CMC Review/OBP Review	N/A
Microbiology Review	N/A
Clinical Pharmacology Review	David Lee, PhD; Yun Xu, PhD
OPDP	
OSI	John Lee, MD; Janice Pohlman, MD, MPH; Kassa Ayalew, MD, MPH
CDTL Review	N/A
OSE/DMEPA	Millie Shah, PharmD, BCPS; Vicki Borders-Hemphill, PharmD
OSE/DDRE	N/A
OSE/DRISK	N/A
Pediatric and Maternal Health Staff	Miriam Dinatale, MD; Donna Snyder, MD; Hari Sachs, MD; Linda Lewis, MD

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Cumberland Pharmaceuticals, Inc. (the Applicant) submitted this 505(b)(2) Prior Approval Supplement to obtain the analgesic and antipyretic indications for Caldolor injection (ibuprofen intravenous injection) in pediatric patients ages 6 months to less than 17 years. They have submitted the results of one key efficacy, safety and pharmacokinetic study, along with two supportive studies to inform their proposed labeling changes. The key study fulfills two of the three studies required under the Pediatric Research and Equity Act (PREA) for Caldolor. This study will also respond in part to a pediatric Written Request (WR) issued on March 30, 2009, and amended on July 16, 2010. The WR is not the subject of this submission.

2. Background

Caldolor, an intravenous form of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, was approved on June 11, 2009, as the first intravenous ibuprofen product in the United States. It is indicated in adults for the reduction of fever, for the management of mild-to-moderate pain, and the management of moderate-to-severe pain as an adjunct to opioid analgesics. It was a 505(b)(2) submission relying in part on prior findings of efficacy and safety for the Listed Drugs, Children's Motrin oral suspension (NDA 20516), Advil Liqui-gels (NDA 20402), and Motrin tablets (NDA 17463). The current supplement is also a 505(b)(2) application relying on the same Listed Drugs. Advil Liqui-Gels (over-the-counter) is labeled for use in adults and children 12 years of age and older, Motrin tablets (prescription) are labeled for use in adults, and Children's Motrin oral suspension, is labeled for over-the-counter use in children ages 2 to 11 years of age.

At the time of initial approval, studies in pediatric patients birth to less than 17 years of age were deferred. The specific pediatric postmarketing requirements (PMRs) under the Pediatric Research Equity Act (PREA) at the time of approval are listed below:

- 205-1: A deferred study for the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics in pediatric patients 0 to 16 years
- 205-2: A deferred study for the treatment of reduction of fever in pediatric patients ages 0 to 16 years

On December 24, 2014, DAAAP released the above PREA PMR's. As Dr. Snyder states in her Pediatric and Maternal Health Staff (PMHS) review of this sNDA (dated October 19, 2015), "The Division determined that the efficacy study in fever along with existing efficacy information for oral ibuprofen could be used to support the efficacy of ibuprofen injection for pain in pediatric patients ages 6 months to 17 years of age and that the efficacy studies in pain were no longer needed. The sponsor's ongoing studies in fever were limited to ages 6 months to 17 years, therefore a third PMR to collect PK and safety data in pediatric patients from birth to 6 month of age was instituted to ensure that the entire pediatric age range was addressed. Completion of the program, if successful, would allow the product to be labeled down to birth for both indications."

The original PREA requirements were replaced them with the PMRs below:

- 205-3: A deferred pharmacokinetics (PK), safety, and efficacy study of Caldolor (ibuprofen) Injection for reduction in fever in pediatric patients aged 6 months to 16 years. [Final study report due: May 2015]
- 205-4: A deferred pharmacokinetic (PK) and safety study of Caldolor (ibuprofen) Injection for the management of mild-to-moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics in pediatric patients aged 6 months to 16 years. [Final study report due: May 2015]
- 205-5: A deferred pharmacokinetic (PK) and safety study of Caldolor (ibuprofen) Injection for reduction in fever, or management of mild-to-moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics, in pediatric patients aged birth to 6 months. [Final study report due: December 2018]

Based on reliance upon the Listed Drugs and their approval for fever and pain in pediatric patients two years of age and older, the similarity in the pharmacokinetic profile of ibuprofen in adults and pediatric patients, similar dosing for ibuprofen as an analgesic and antipyretic for the listed drugs in adults and children, and the extrapolation of efficacy for Caldolor for analgesia and fever from adults down to two years of age, the Division determined that PMR 205-4 could be fulfilled by the study described in PMR 205-3. The current submission addresses PMRs 205-3 and 205-4.

The Applicant submitted three clinical study reports to support the proposed pediatric indication; a small exploratory study in pediatric patients with fever (CPI-CL-005), a key efficacy study in pediatric patients with fever (CPI-CL-012), and a pain study in pediatric patients undergoing tonsillectomy who received pre-emptive treatment with Caldolor (CPI-CL-014). These will be discussed in more detail later in this memo.

3. CMC/Device

There were no changes to the Caldolor formulation in this supplement, therefore a CMC review was not conducted.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted with this supplement. However, included in the proposed label for this supplement is conversion of Section 8, Pregnancy, to comply with the Pregnancy and Lactation Labeling Rule (PLLR). Carlic Huynh, PhD, with secondary concurrence by Newton Woo, PhD and R. Daniel Mellon, PhD, wrote a memo that included a review of literature to further support changes to Sections 8.1 Pregnancy (teratogenic and nonteratogenic effects) and 13 Nonclinical Toxicology (animal studies including mutagenesis, carcinogenesis, and impairment of fertility). Refer to the final approved label for details of those sections.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by David Lee, PhD, with secondary concurrence by Yun Xu, PhD. They recommend approval of this application from the clinical pharmacology perspective for patients ages 6 months to less than 17 years.

The Applicant submitted pharmacokinetic (PK) results obtained from Study CPI-CL-012 (Study 012). This was a multi-center, randomized, open-label, parallel, active comparator, single or multiple-dose study to assess the efficacy, safety, and PK of ibuprofen administered IV to hospitalized febrile pediatric patients less than 17 years of age. Patients were randomized to intravenous ibuprofen 10 mg/kg or acetaminophen 10 mg/kg.

The patients were randomized to the following age groups: Birth to < 2 months, 2 months to < 6 months, 6 months to < 2 years, 2 years to < 6 years and 6 years to \leq 16 years. The following mean pharmacokinetic parameters by age group are shown in Table 1 from Dr. Lee's review.

Table 1 Mean Pharmacokinetic Parameters by Age Group

Age Category	Birth to < 2 months*	6 months to < 2 years	2 to < 6 years	6 to 16 years
N	1	5	12	25
AUC0-t ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	51.18	71.15	79.19	80.67
AUC0-4 ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	69.14	70.92	80.25	85.73
C _{max} ($\mu\text{g}/\text{mL}$)	49.83	59.24	64.18	61.89
T _{max} # (min)	10*	10 (10-30)	12 (10-46)	10 (10-40)
T _{1/2} (hr)	1.18	1.78	1.48	1.55
CL (mL/hr)	619.97	1172.5	1967.27	4878.47
V _z (mL)	1053.72	2805.73	3695.76	10314.21
CL/WT (mL/hr/kg)	129.16	133.66	130.064	109.22
V _z /WT (mL/kg)	219.53	311.2	227.23	226.824

AUC0-t: Area under the concentration-time curve from time zero to the last measurable concentration using linear-log trapezoidal rule.

AUC0-4: Area under the concentration-time curve from time zero to 4 hours.

C_{max}: Maximum observed concentration.

T_{max}#: Median (min-max)

*: Observed value (N=1).

T_{1/2} el: Elimination half-life, calculated as $\ln(2)/K_{el}$

Cl: Total body clearance, calculated as $\text{Dose}/\text{AUC0-inf}$.

V_z: Volume of distribution, calculated as $\text{Dose}/(K_{el} \times \text{AUC0-inf})$.

WT[^]: body weight (kg)

Study report CPI-CL-012

Dr. Lee provided the following assessment in his review:

The mean AUC0-4 increased slightly with age. The mean T_{1/2} values were similar among age categories. The body weight normalized clearance (CL) and volume of distribution (V_z) values appear to be similar in all age groups. The elimination half-life ranged from 0.79 to 2.87 hours with a mean of 1.55 hours.

Only one subject was recruited from age group birth to < 2 months, and no subject was recruited from 2 months to 6 months. Therefore, additional subjects in these age groups need to be recruited to characterize efficacy, safety, and pharmacokinetics of the product.

In order to better understand the PK in pediatric patients compared to adults, Dr. Lee performed a cross-study comparison of the data from pediatric Study 012 (10 mg/Kg, 10-minute infusion) with adult Study CPI-CL-004 from the original NDA submission (400 mg, 30 minute infusion). For comparison purposes, the first 4-hour ibuprofen concentrations from the 400 mg dose was used because the approved dose in adults is 400 mg administered over 30 minutes [the full range of doses approved in adults are 400 to 800 mg intravenous over 30 min Q6h as necessary (analgesia) and 400 mg intravenous over 30 min, followed by 400 mg Q4h to Q6h or 100-200 mg Q4h as necessary (fever)]. Dr. Lee’s overall observation is that, “the general shapes of ibuprofen plasma profiles from the pediatric febrile groups are very similar to that of the adult 400 mg febrile patients. In addition, the Cmax and AUC values are also comparable between the two groups.”

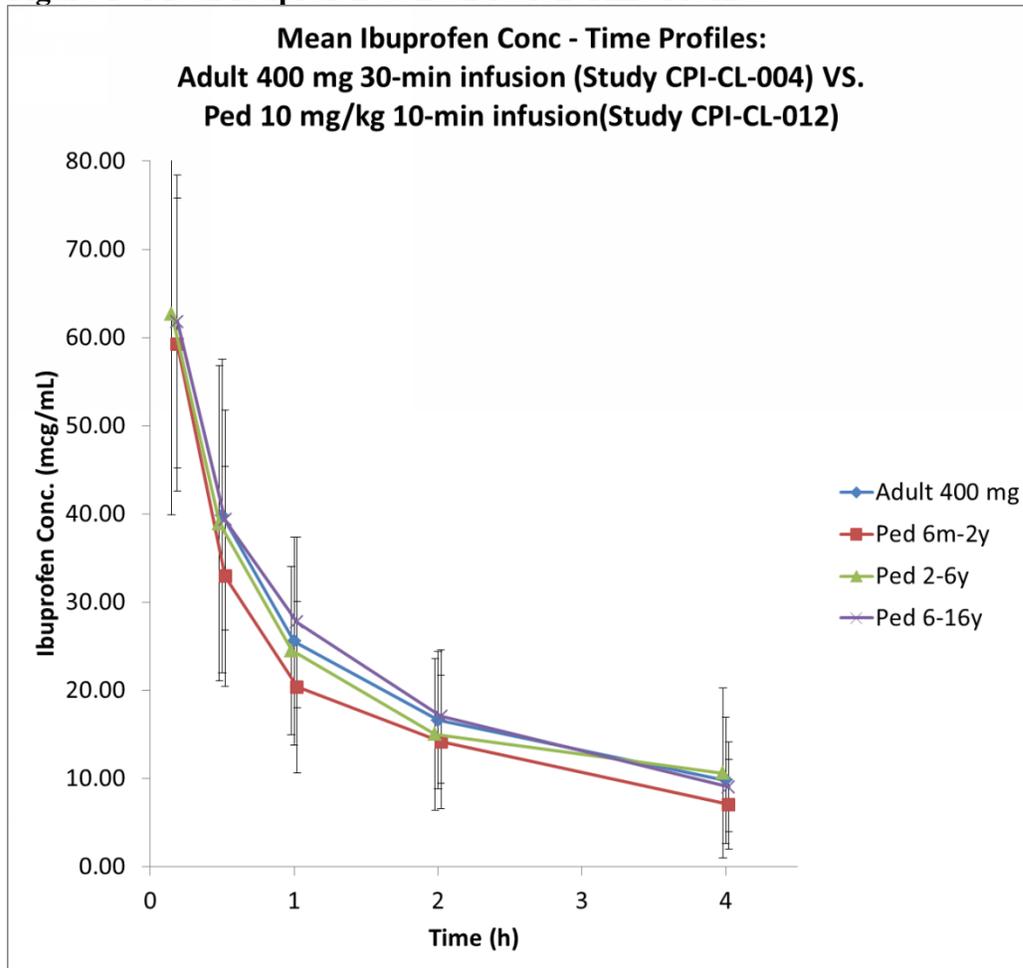
The following table and figure from Dr. Lee’s review show the similarity of the mean ibuprofen concentration (µg/mL) profiles from adult 400 mg 30-minute infusion and pediatric groups 10 mg/kg 10-minute infusion. Concentrations remain similar through the end of the four hour dosing period.

Table 2 Mean Concentration by PK Sampling Time in Febrile Patients of Different Age

Time (h)	0.167	0.5	1	2	4
10-minute IV infusion, Pediatric	Concentration (µg/mL): mean (SD)				
6 months – 2 years, n=5	59.22 (20.61)	32.91 (14.31)	20.35 (7.91)	14.15 (5.88)	7.05 (3.66)
2 – 6 years, n=12	62.62 (22.73)	38.94 (17.90)	24.49 (9.54)	14.99 (8.64)	10.58 (9.63)
6 – 16 years, n=25	61.81 (16.59)	39.31 (12.45)	27.70 (9.71)	17.02 (7.55)	9.03 (5.12)
30-min IV infusion 400mg in adults		39.76 (17.75)	25.55 (11.77)	16.59 (7.77)	9.79 (7.16)

Source: Table 6 on page 20 of Dr. David Lee’s PK Review.

Figure 1 Mean Ibuprofen Concentration-Time Profiles



In addition to comparing the mean plasma concentrations, Dr. Lee looked at individual PK profiles for adults and pediatric patients in the same studies comparing the 400 mg dose in adults with the 10 mg/kg dose in pediatric patients and noted their similar shapes.

The following table from Dr. Lee's review compares the mean PK parameters from adult febrile patients who received Caldolor 400 mg over 30 minutes with pediatric febrile patients who received 10 mg/Kg over 10 minutes. Of note the C_{max} in adults appears lower than in all of the pediatric age groups.

Table 3 Adult and Pediatric Pharmacokinetic Data

Mean	CPI-CL-004 Adult febrile patients SD 400 mg 30-min infusion	CPI-CL-012 Pediatric febrile patients 10 mg/kg 10-min infusion		
	400 mg N=25	6 mo to < 2 y N=5	2 to < 6 y N=12	6 to 16 y N=25
C _{max} (µg/mL)	39.76	59.24	64.18	61.89
AUC ₀₋₄ (µg.h/mL)	70.64	70.92	80.25	85.73
T _{max} (h)	0.5	10 (range 10-30)	12 (range 10-46)	10 (range 10-40)
T _{1/2} (h)	2.26	1.78	1.48	1.55

Dr. Fang, the clinical reviewer, looked at the PK data from the label of the Listed Drug referenced by the Applicant, Children’s Motrin Oral Suspension, which shows a C_{max} of 55 µg/mL in febrile pediatric patients. The C_{max} of approximately 60 µg/mL for all pediatric age groups administered Caldolor is very close to that of the oral suspension, 55 µg/mL, in pediatric patients. Acknowledging that these are cross study comparisons and have limitations in terms of interpretability, it is reassuring that the C_{max} for oral ibuprofen in children is similar to that for Caldolor in children.

The difference in mean T_{max} for adults (30 minutes) and pediatric patients (10-12 minutes) may be due to differences in infusion time or differences in plasma sampling time, but nonetheless is unlikely to be associated with adverse clinical consequences. This is also true for the slight differences in T_{1/2} and AUC between the two populations.

Dr. Lee concluded that the pharmacokinetic data from pediatric patients ages 6 months to 16 years is adequate to inform the dosing of Caldolor in this age range. Because only one patient less than 6 months old provided data, an additional study must be conducted to describe the PK of Caldolor in that age group.

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

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

Christina Fang, MD conducted the efficacy review, and Katherine Meaker, MS, with secondary concurrence by Freda Cooner, PhD, conducted the statistical review. Both review teams have recommended approval from their perspectives.

The Applicant submitted complete study reports for three studies:

- CPI-CL-005: A randomized, parallel, open-label, active-controlled efficacy and safety study of ibuprofen injection in 30 hospitalized febrile pediatric patients 6 months to 17 years of age (“pilot fever study”)
- CPI-CL-012: A randomized, parallel, open-label, active-comparator, multiple dose study to determine the pharmacokinetics, safety and efficacy of IV ibuprofen in 118 pediatric patients treated with fever from birth to 16 years of age (“fever efficacy study”)
- CPI-CL-014: A randomized, double-blind, placebo-controlled, single-dose study of the safety and efficacy of IV ibuprofen for treatment of pain in 161 pediatric patients 6 years to 16 years of age undergoing tonsillectomy (“pain study”)

Dr. Fang reviewed Study 012 in detail as the key study to determine the effectiveness of Caldolor for the treatment of fever in pediatric patients ages 6 months to <17 years. She also reviewed Study 005, a small, exploratory, single-dose study of febrile pediatric patients provides preliminary information on the efficacy of IV ibuprofen compared to acetaminophen. Study 014, a study of the effect of pre-emptive administration of Caldolor on post-tonsillectomy pain provides only safety data for this sNDA, as the study design does not support the use of Caldolor for the proposed indications nor does it address the PMRs. For details regarding Studies 005 and 014 refer to Dr. Fang’s review.

Study 012 was a multi-center, randomized, open-label, parallel, active-comparator, multiple-dose trial to determine the efficacy, safety, and pharmacokinetics of IV ibuprofen in pediatric patients ages birth to and including 16 years of age, conducted at 14 sites in the United States. The objectives of the study were to assess study single-dose PK and multiple-dose efficacy and safety of IV ibuprofen in the included age groups, with the primary objective to determine superiority of a single dose of IV ibuprofen compared to acetaminophen for fever reduction during the first two hours of treatment.

The randomized population consisted of 103 pediatric patients hospitalized or scheduled to be hospitalized between birth (28 weeks to < 40 weeks gestational age) and ≤ 16 years with onset of fever within seven days of enrollment, documented by temperature (tympanic measurement) ≥101.0°F (38.3°C). The enrolled patients ranged from one month to 15 years of age, with a mean age of 6 years, were 55% male, and 85% Caucasian.

The patients in the study population were generally very ill, and hospitalized for serious medical conditions such as sepsis, bowel perforation, appendicitis with abscess formation, different types of pneumonia, meningitis, cellulitis, urinary tract infection, severe burn, trauma with bone fracture, toxic shock syndrome, sickle cell anemia, and febrile seizure.

Patients were randomized 1:1 to receive either ibuprofen 10.0 mg/kg IV infusion over 10 minutes (not to exceed 400 mg per dose or 2400 mg per day for up to 30 doses) or

acetaminophen 10.0 mg/kg oral solution or suppository (not to exceed 650 mg per dose or 3900 mg per day) q4 hours for the first 24 hours and then q4 hours as needed during the 120-hour treatment period. The two treatment groups were approximately evenly distributed with regard to age, gender, race, and weight. There were three patients less than 6 months of age and they were not included in the efficacy analysis due to the small number. The age distribution by treatment group is shown below:

Table 4 Exposure Data

Treatment/Age	< 6 months*	6 months-<2 years	2-<6 years	6-<12 years	12-<17 years	Total
IV ibuprofen	1	6	13	15	13	48
APAP	2	14	14	19	6	55
Total	3	20	27	34	19	103

*Not included in efficacy analysis due to small number

Only 25% of the patients completed the study per protocol. The most common reasons for discontinuation (46%) were fever no longer required treatment and discharge from the hospital. More subjects treated with APAP discontinued because of hospital discharge (45%) compared to 17% who received IV ibuprofen. It is unlikely that this finding reflects any actions of the study drugs, as these discontinuations probably reflect the underlying reasons for fever and course of illness.

The proportion of patients with protocol deviations was about 70% and was similar in the two treatment groups. The most frequently reported deviations were related to safety data collection (missing, incomplete, mistimed), which were unlikely to have a major impact on efficacy outcomes.

Forty-eight patients received at least one dose of IV ibuprofen and 55 received at least one dose of acetaminophen. A total of 51% of patients had a cumulative exposure to at least four doses or at least two days in the IV ibuprofen group. In the acetaminophen group 47% had a cumulative exposure to at least two doses and 43% had at least two days of exposure.

The planned primary efficacy parameter, AUC_{0-2} (the area under the curve of temperature change from baseline over the first two hours post-dose), was to have been analyzed using an ANCOVA model or the non-parametric method of Wilcoxon rank-sum test if endpoint is not normally distributed. The study demonstrated the superiority of IV ibuprofen over APAP based on the primary endpoint. The results are summarized in the table below from Dr. Fang's review. Mean AUC_{0-2} was 1.5 over 2 hours for the IV ibuprofen group and 0.9 for the acetaminophen group. The treatment difference of 0.6 in AUC_{0-2} was statistically significant based on the Applicant's analysis.

Table 7 Temperature Reduction AUC₀₋₂ by Treatment Group, ITT

Study 012 Primary endpoint	IV Ibu^a (N=47)	APAP^b (N=53)
N	46	50
AUC ₀₋₂ for T↓		
Mean (SD)	-1.5 (1.11)	-0.9 (0.89)
LS Means (SE)1	-1.5 (0.15)	-0.9 (0.14)
Median	-1.4	-0.9
Min, Max	-4.4, 0.1	-3.0, 0.7
Ibu>APAP	-0.6	
p-value2	0.012	

Source: Table 14.2.1.1.1 on page 140 and Table 14.2.1.1.2 on pages 143, 146, and 149 of the report for Study 012 in submission dated March 20, 2015.

Kate Meaker, the statistical reviewer, was able to duplicate the Applicant’s analysis of the primary endpoint.

Both the Applicant and Dr. Fang conducted a number of secondary analyses to further understand the efficacy of IV ibuprofen for fever in this study. These include the summed temperature reduction over the full dosing interval of four hours and over 24 hours (AUC₀₋₄ and AUC₀₋₂₄), the proportion of patients becoming afebrile and the time to reach afebrile status, and time to remedication.

Treatment differences in addition to the primary endpoint analysis in favor of the IV ibuprofen group included 0.2 to 0.6°C more temperature reduction in the first dosing interval of 4 hours, 0.4 hours shorter median time to reach a temperature reduction to <37.5°C, and 17% more becoming afebrile by the end of the first dosing interval. Treatment differences in favor of the lower dose acetaminophen group included 23% more in need of repeated doses and 1.4 hour shorter single-dose duration for the IV ibuprofen treatment than acetaminophen. In the subpopulation actually receiving repeated doses the median and mean time to the second dose were similar between the two treatment groups.

Temperature data were mostly collected during the first six hours after the initial dose. After hour 6 only one or two patients had temperature measurements reported at the scheduled time points. Dr. Fang stated in her review that, “multiple-dose efficacy was not evaluable due to lack of data.”

The study protocol was amended such that the dosing regimen was changed from a fixed dosing interval of every 4 hours for the first 24 hours, to “as needed not more frequently than every 4 hours. Twenty-two of 47 (47%) in the IV ibuprofen group and 20 of 53 (38%) in the acetaminophen group were on a fixed every 4-hour dosing regimen and the remainder of the subjects were on PRN dosing. Of the subpopulation that actually had a PRN dosing regimen, the mean and median time intervals between the adjacent doses were longer than six hours for the IV ibuprofen group. Dr. Fang estimated that the median time between the first and second dose for patients receiving at least 2 doses was 6.6 hours. The time between later doses, i.e., 3rd to 4th, 4th to 5th, etc... increased to up to 9 hours.

Regarding the ability of the study to inform the dosing interval for IV ibuprofen, Dr. Fang noted:

Single-dose and multiple-dose duration are the parameters used in general to define dosing interval. Multiple-dose duration was not assessable due to of lack of efficacy measurements after Hours 6. The single-dose duration measured by median time to the second dose (and/or rescue) in the ITT population would provide a more accurate estimate if patients were all on PRN dosing from the beginning of the study. Because there were no patients receiving rescue and only a subpopulation was on PRN dosing, data from Study 012 were not sufficient even for determination of single-dose duration.

Dr. Fang concluded the following regarding Study 012 in her review:

Ibuprofen injection at 10 mg per kg was able to provide clinically meaningful temperature reduction and normalization in treating fever in hospitalized pediatric patients based on data demonstrating response to the initial dose of 10-minute infusion. Single-dose duration and multiple-dose effects were not assessable due to limitations in study design, conduct, and data collection.

I agree with Dr. Fang's and Ms. Meaker's conclusions that Study 012 provides findings of efficacy for IV ibuprofen in pediatric patients ages 6 months to <17 years for the treatment of fever. In addition to the limitations discussed by Dr. Fang for the study design, conduct, and data collection, the natural history of fever and the underlying illnesses causing the fever may have also contributed to the difficulty defining a dosing interval. Fevers commonly go up and down even in the absence of antipyretic treatment, and generally return to normal with treatment of the underlying condition causing the fever. At least after the first dose, the data in this study point to an approximate 6-hour dosing interval. This finding, combined with the known dosing intervals for the Listed Drugs and for IV ibuprofen in adults, and that ibuprofen is generally dosed on an as needed basis for fever and pain, will inform labeling the dosing interval for pediatric patients as every 4-6 hours as needed.

8. Safety

The safety database contains data from three pediatric studies involving a total of 144 patients exposed to IV ibuprofen 10 mg/kg given by 10-minute infusion. Studies 012 and 005 are the two active-controlled, multiple-dose fever studies conducted in hospitalized pediatric patients as discussed in detail in the Review Section 5. Study 014 is a placebo-controlled study of pre-emptive analgesic effect on post-tonsillectomy pain in patients who received a single dose of study medication before surgery. The following is Dr. Fang's summary of safety from her review.

The type of exposure to IV ibuprofen included single-dose in 82 patients in Study 014, four doses given on a fixed dosing interval within 24 hours in 14 patients in Study 005, and multiple-dose intermittently based on need in 48 patients in Study 012. Multiple-dose experiences in the two fever studies were limited to 45 patients exposed to at least two doses, 36 patients exposed to at least four doses,

and 18 patients exposed to at least six doses. Majority of exposure was in the age group of 6 to <12 years (81 of 144 patients, or 56%). The exposure to IV ibuprofen in the age group of 6 months to <2 years involved only six patients, less than expected.

The pediatric study population consisted of mostly Caucasian (79%) and had slightly more female than male patients. The mean and median body weights of the study population were close to the mid-range weight listed for the corresponding age groups in the Motrin dosing chart. The study population included very sick pediatric patients hospitalized for serious medical conditions such as sepsis, bowel perforation, appendicitis with abscess formation, different types of pneumonia, meningitis, cellulitis, urinary tract infection, severe burn, trauma with bone fracture, toxic shock syndrome, sickle cell anemia, febrile seizure, etc. Some had multiple medical conditions, were on multiple concomitant medications, and were admitted to PICU.

There were no reports of deaths and seven reports of nonfatal serious adverse events (SAEs) in five pediatric patients, three of whom were treated with IV ibuprofen. Based on the review of narratives for all SAEs, the relationship of AE to ibuprofen could not be ruled out in case of the post tonsillectomy hemorrhage at the surgical site. The relationship of AE to ibuprofen could not be completely ruled out in cases of transaminitis and pancreatitis due to concurrent illness and multiple concomitant medications known for drug-induced liver enzyme elevation and pancreatitis. The cases of cardiopulmonary arrest and left pleural pneumothorax were unlikely to be related to ibuprofen treatment because of patient's serious medical conditions involving septic shock and associated respiratory failure and other unstable conditions.

Of the five cases of AE-related dropouts four occurred in the IV ibuprofen group for the reasons of thrombocytopenia, hypothermia/bradycardia, headache, and urticaria, respectively. The case of urticaria was likely related to the ibuprofen treatment as the event commenced seven minutes after the start of the ibuprofen infusion.

In pediatric patients treated by IV ibuprofen the commonly reported individual AEs ($\geq 2\%$) were infusion site pain, vomiting, nausea, anemia, and headache. For the surgical patients treated with a single dose of ibuprofen the common AEs were infusion site pain, nausea, vomiting, and urticaria. The commonly reported AEs in hospitalized febrile pediatric patients were gastrointestinal (GI) symptoms and laboratory test abnormalities in both active treatment groups.

Findings of laboratory (lab) test abnormalities in the two fever studies were similar for the two active treatment groups in general and are hard to interpret due to concurrent serious medical conditions, concomitant medications, lack of placebo control, and age-dependent as well as institution-related variations in defining normal range for the individual lab tests.

Time dependency of AEs could not be adequately assessed due to limited exposure, to a single dose in Study 014 and up to a few doses in the two fever studies.

Subpopulation safety analyses for drug-demographic interactions were not applicable due to limited sample sizes of subpopulations by age, gender, and race.

Based on the review of pediatric safety data there were no new safety signals or major issues identified. Short-term use of IV ibuprofen 10-minute infusion at 10 mg/kg in pediatric patients closely monitored at a hospital setting appears to be reasonably safe. Patients should be well hydrated before receiving IV ibuprofen to minimize the risks for acute renal toxicities. Minimum effective dosage in terms of dose level and dosing interval based on need should be targeted based on the individual response for better tolerance and safety.

I concur with Dr. Fang's review of safety. There were no new or unexpected safety findings in the 144 pediatric patients exposed to IV ibuprofen in the three studies. As with all NSAIDs, the lowest effective dose of IV ibuprofen is recommended for the shortest period of time.

9. Advisory Committee Meeting

An advisory committee was not convened for this application.

10. Pediatrics

Refer to Section 2 (Background) of this memo for details.

11. Other Relevant Regulatory Issues

The Office of Scientific Investigations (OSI) audited Study CPI-CL-012 as the key study in support of efficacy. The study was conducted at 14 US sites, two of which were inspected based on their large contribution to the overall efficacy outcome. There were no special review concerns identified for either site, including protocol violations, adverse event monitoring, or site investigator conflicts of interest. The inspected sites included Samia Khalil, MD, Houston Texas, and Barry Hahn, MD, Staten Island, NY, both of which received no action indicated (NAI) outcomes. Study conduct at both sites appeared adequate and reliable to support the study outcomes.

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators had been made whereby study outcomes affected 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).

There are no other unresolved relevant regulatory issues.

12. Labeling

There was no new review of the approved proprietary name Caldolor.

The Pediatric and Maternal Health Staff, the Office of Prescription Drug Promotion, and the Division of Medication Error Prevention and Analysis provided input into the Caldolor label.

Changes to the previously approved label as a result of this supplement include dosing instructions for ages 6 months to 17 years in Section 2 Dosage and Administration, the addition of adverse event data from the submitted pediatric studies to Section 6.1 Clinical Study Experience, update to Section 8 to comply with PLLR, addition of the PK data from Study 012 to Section 12.3 Pharmacokinetics, updates to Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility, and inclusion of the clinical study data from Study 012 into Section 14, Clinical Studies.

This product does not include the class-wide NSAID MedGuide as it is used only in inpatients.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action Approval

- Risk Benefit Assessment

Caldolor was approved on June 11, 2009 for the reduction of fever, the management of mild-to-moderate pain, and the management of moderate-to-severe pain as an adjunct to opioid analgesics in adults. This supplement is intended to fulfill two of the three required post marketing studies under PREA that were issued on December 24, 2014. The goal of this supplement is to obtain the indications and labeling for the use of Caldolor for treatment of pain and fever in pediatric patients ages 6 months to less than 17 years of age. This approval represents the first IV NSAID approved for use in pediatric patients. There is a huge public health need data that informs the use of analgesics in pediatrics.

Efficacy and safety of Caldolor at a dose of 10 mg/kg administered every 4 to 6 hours as needed for fever were demonstrated in one adequate and well-controlled clinical trial of febrile pediatric patients ages 6 months to 17 years, with additional safety data obtained from a small exploratory study in febrile pediatric patients and a study of preemptive analgesia in pediatric patients undergoing tonsillectomy. No new or unexpected safety signals were detected.

With regard to determination of the dosing interval, data from Study 012 was limited due to study design and the collection of efficacy data as noted by Dr. Fang. However, based on the data from Study 012, similar pharmacokinetic profiles for pediatric patients and adults, and the approved dosing intervals for Caldolor in adults and the

oral ibuprofen Listed Drugs in adults and children, a dosing interval of every 4 to 6 hours as needed for pain or fever is appropriate.

The original pediatric drug development requirements under PREA, as issued with the approval of Caldolor in adults, included a pain study and a fever study, each in pediatric patients ages birth to less than 17 years of age. Upon further internal discussion between the Division and the Pediatric Research Committee, the determination was made that an efficacy study in fever could be used to support the efficacy of Caldolor for pain in pediatric patients ages 6 months to less than 17 years of age and that the efficacy studies in pain in this age group were no longer needed. This decision was based in part on the extreme difficulty the Applicant had recruiting pediatric patients into a study assessing treatment of pain, as well as what is known about ibuprofen use in pediatric patients.

The Division determined that efficacy findings for analgesia in adults for Caldolor could be extrapolated to pediatric patients down to 2 years of age as long as the pharmacokinetic profiles and exposure were similar. For patients ages 6 months to 2 years, efficacy for pain can be extrapolated from pediatric patients ages 2 to 11 years based on the labeling from the Listed Drug Children's Motrin oral suspension, the similarity in the pharmacokinetic profile for this age group and patients 2 years to <17 years in the Caldolor fever study, and the fact that the doses used for pain and fever in pediatric patients for oral ibuprofen products are the same. For patients ages 6 months to <17 years, findings from the fever study (012) could inform dosing and administration for both fever and pain. A remaining PMR in pediatric patients from birth to 6 month of age assessing PK, safety and efficacy in patients with pain or fever is currently pending.

The benefits for Caldolor outweigh the risks for use in hospitalized pediatric patients for the treatment of pain and fever. It is likely that this product will be utilized for relatively short periods of time on an as needed basis, and will provide another option for treatment of pain and fever in patients who require parenteral treatment.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None
- Recommendation for other Postmarketing Requirements and Commitments

The Applicant will be reminded that the following PMR is pending:

205-5: A deferred pharmacokinetic (PK) and safety study of Caldolor (ibuprofen) Injection for reduction in fever, or management of mild-to-moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics, in pediatric patients aged birth to 6 months. [Final study report due: December 2018]

This supplement fulfills the requirements of PMRs 205-4 and 205-5

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/s/

ELLEN W FIELDS
11/19/2015