Office of Clinical Pharmacology Review

NDA or BLA Number	22348
Link to EDR	\\CDSESUB1\evsprod\NDA022348\0170 In addition, the following submissions are pertinent: 1. Study CPI-CL-022 report, including bioanalytical information: \\CDSESUB1\evsprod\NDA022348\0144\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep 2. Dataset (e.g., all xpt) for Study CPI-CL-022: \\CDSESUB1\evsprod\NDA022348\0145\m5\datasets\cpi-cl-022\tabulations\sdtm 3. Dataset (e.g., pharmacokinetics xpt only) for Study CPI-CL-022: \\CDSESUB1\evsprod\NDA022348\0147\m5\datasets\cpi-cl-022\analysis\adam\datasets
Submission Date	7/11/22; PDUFA date: 5/11/2023
Submission Type	10-months review; Supplement 024 Submission Type: Efficacy Supplement Suppl Effect Date Type: Prior Approval Supplement (PAS) Supporting Document Number: 255 eCTD Sequence Number: 0170
Brand Name	CALDOLOR® Injection
Generic Name	Ibuprofen intravenous injection
Dosage Form and Strength	Injection; Strength: 800 mg/8 mL (100 mg/mL); 800 mg/200 mL (4 mg/mL)
Route of Administration	Intravenous
Indication	For the reduction of fever, and the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics
Dosage Regimen	Adults: *For Analgesia (pain):* The dose is 400 mg to 800 mg intravenously every 6 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200 mg. *For Fever:* The dose is 400 mg intravenously, followed by 400 mg every 4 to 6 hours or 100 mg to 200 mg every 4 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200 mg. Pediatric patients: *Ages 12 to 17 years:* The dose is 400 mg intravenously every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 2,400 mg.

	Ages 6 months to 12 years: The dose is 10 mg/kg intravenously up to a maximum single dose of 400 mg every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 40 mg/kg or 2,400 mg, whichever is less.
Applicant	Cumberland Pharmaceuticals Inc.
Associated IND	IND 062605
OND Division	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
OCP Division	Division of Neuropsychiatry Pharmacology (DNP)
OCP Reviewer	David Lee, Ph.D.
OCP Team leader	Yun Xu, Ph.D.
OCP Secondary Review (Division Director)	-

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Neuropsychiatric Pharmacology (OCP/DNP) has reviewed the information submitted in the current Supplement 024, N 22348, an Efficacy Supplement, PAS, for Caldolor® Injection on 7/11/2022. To fulfill PMR 205-5, the results from Study CPI-CL-022 were submitted, which is a pharmacokinetic and safety study in birth to 6 months pediatric patients.

The integrity of the data presented in the Study CPI-CL-022 appear to be acceptable. During the team meeting, it was discussed that limited number of subjects with exposure to the study drug were noted in the following age groups of pediatric patients (from birth to 3 months), which the data do not provide sufficient information for a single dose use in these groups:

1. No PK or safety data in birth to <1 month pediatric group;
2. PK and safety data limited to 1 subject in 1 to <2 months pediatric group; and,
3. PK and safety data limited to 2 subjects in 2 to <3 months pediatric group.

There may be acceptable single dose PK and safety data to support the single dose use in pediatric patients 3 months to <6 months old submitted in this Supplement.

Therefore, from the OCP perspective, the information contained in this Supplement 024 is acceptable provided that a satisfactory agreement can be reached with the Applicant regarding the Labeling, which includes labeling pediatric patients 3 months to <6 months old in this Supplement.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The Applicant submitted a Prior Approval Supplement (PAS), an Efficacy Supplement 024, to fulfill Post Marketing Requirement (PMR) 205-5, for a pediatric study of Caldolor® in the 6-month and under age group, which was added to Caldolor® (N 22348) on 12/24/14 under the Pediatric Research Equity Act (PREA) (Reference ID: 3678476). To fulfill PMR 205-5, the Applicant has conducted and has submitted the results from Study CPI-CL-022, 'A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months.' See below for discussions related to prior submission dates related to Study CPI-CL-022.
General dosing instructions	There are proposed changes to pediatric dosing instructions. There may be there are acceptable single dose PK and safety data to support the single dose use in pediatric patients 3 months to <6 months old submitted in this Supplement. As such dosing recommendation in 3 months to <6 months will be updated, as appropriate.

Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dosing recommendations are proposed to dosing instructions in pediatric patients 3 months to <6 months (Label Section, 2.3 Pediatric Patients): *Ages 3 months to less than 6 months* The dose is 10 mg/kg intravenously up to a maximum single dose of 100 mg. Infusion time must be at least 10 minutes.
Labeling	The Applicant proposed to revise Section 12.3, based on the results from Study CPI-CL-022. The following revisions are recommended in Section 12 Clinical Pharmacology. 1. To be consistent with a typical PK parameter data presentation mode, it is recommended to revise the tables to present standard deviations (SDs), rather than CV%. 2. As well, because the focus is to compare the exposures (e.g., Cmax and AUC) between pediatric and adult patients, and to be consistent with Table 4, it is recommended to delete the PK parameters which are not critical to clinicians. It is also proposed to include the PK information of 3 to <6 months pediatric data with the existing 6 months and older pediatric data in the same table. Noted that Cmax and AUC values are proposed from the reviewer's analysis, whereas T1/2 value is from the Applicant's analysis table. The following source documents are used to support the SDs values in Table 5 below: 1. Standard deviation source for Table 4: adults Study report CPI-CL-001 2. Standard deviation source for Table 5: pediatric Study report CPI-CL-012 ========== **12.3 Pharmacokinetics** …. **Table 4: Pharmacokinetic Parameters of Intravenous Ibuprofen** 400 mg* CALDOLOR Mean (SD) / 800 mg* CALDOLOR Mean (SD) Number of Patients: 12 / 12 AUC (mcg·h/mL): 109.3 (28.9) / 192.8 (35.7) C_{max} (mcg/mL): 39.2 (6.09) / 72.6 (9.61) KEL (1/h): 0.32 (0.06) / 0.29 (0.04) $T_{1/2}$ (h): 2.22 (0.45) / 2.44 (0.31) AUC = Area-under-the-curve Cmax = Peak plasma concentration SD = Standard Deviation KEL = First-order elimination rate constant $T_{1/2}$ = Elimination half-life * = 60 minute infusion time

	The pharmacokinetic parameters of CALDOLOR determined in a study with febrile pediatric patients are presented in Table 5. It was observed that the median T_{max} was at the end of the infusion and that CALDOLOR had a shorter elimination half-life in pediatric patients compared to adults. **Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous** Ibuprofen, Pediatric Patients, by Age Group** 3 months to < 6 months^ Mean (SD) / 6 months to <2 years Mean (SD) / 2 years to <6 years Mean (SD) / 6 years to 16 years Mean (SD) Number of Patients: 20 / 5 / 12 / 25 AUC (mcg·h/mL): 69.63 (19.28) / 71.1 (26.4) / 79.2 (29.3) / 80.7 (29.8) C_{max} (mcg/mL): 59.75 (12.85) / 59.2 (20.6) / 64.2 (22.1) / 61.9 (16.5) T_{max} (min)*: 10 / 10 (10-30) / 12 (10-46) / 10 (10-40) $T_{1/2}$ (h): 1.3 / 1.8 (0.5) / 1.5 (0.6) / 1.55 (0.41) *Median (minimum-maximum) #WT: body weight (kg) ^Open-label study with hospitalized pediatric patients with pain or fever **= 10 minute infusion time …
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.
Other (specify)	Not applicable.

1.2 Phase IV Commitments – Not applicable

1.3 Summary of CPB Findings

Cumberland Pharmaceuticals has submitted a Prior Approval Supplement (PAS), an Efficacy Supplement 024, to fulfill Post Marketing Requirement (PMR) 205-5, for a pediatric study of CALDOLOR in the 6-month and under age group, which was added to Caldolor® (ibuprofen) Injection (N 22348) on 12/24/14 under the Pediatric Research Equity Act (PREA) (Reference ID: 3678476).

To fulfill PMR 205-5, the Applicant has conducted and has submitted the results from Study CPI-CL-022, 'A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months.' See below for discussions related to prior submission dates related to Study CPI-CL-022.

The Applicant proposes to update the current Label as follows based on the information from Study CPI-CL-022 in 0-6 months old age group:

1. Section 1, Indications and Usage;
2. Section 2, Dosage and Administration (to add the 0 – 6 months age group);
3. Section 8.4, Pediatric Use; and
4. Section 12.3, Pharmacokinetics (to include pharmacokinetic results of the clinical study in neonatal pediatric patients], to expand the pediatric age from 'six months and older' to 'from birth (>37 weeks gestational age) and older,'

Caldolor was approved on 6/11/09. Caldolor is approved in adults and pediatric patients 6 months and older for the reduction of fever, and the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics.

It is noted that the efficacy is extrapolated from adults based on PK data, as previously discussed with Pediatric Review Committee meeting held on 9/17/14 (PeRC; DARRTS date 9/29/14). During the meeting, the PeRC commented that:

1) Existing effectiveness data collected in study CPI-CL-012 for fever for pediatric patients aged 6 months to 2 years can be used to support the effectiveness for fever and pain for pediatric patients aged birth to 6 months based on the bridging information described above (i.e., similar bioavailability between oral and i.v. formulations as well as established efficacy for fever and pain in patients 6 months to 2 years of age). The PeRC requested that the Division assure that a sufficient number of patients were studied in CPI-CL-012 between 6 months and 2 years of age before agreeing to this plan;

2) The PeRC also noted that if, upon review, the PK and safety data in patients aged birth to 6 months are not similar to data in patients 6 months to 2 years of age then a full efficacy study may be required.

It is also noted that Caldolor is already approved in ages 6 months and up (2015), indicating that there are no issues with efficacy/safety in pediatric 6 months – 2-year olds.

<u>Regulatory background regarding Study CPI-CL-022 information submitted</u>

The information from the Study CPI-CL-022 was submitted (b) (4)

Additionally, there were Information Requests (IRs) sent to the Applicant (via email communications) (b) (4) To that aspect, the Applicant submitted the Responses to IRs on 6/15 and 6/24/2020.

Therefore, for this current submission, S-024, the following information will be reviewed [redacted] (b) (4):

1. The study results from Study CPI-CL-022 submitted on 4/24/2020;
2. The Applicant's Responses to IRs:
    a. Submitted on 6/15/2020 (SDN 0145);
    b. Submitted on 6/24/2020 (SDN 0147).

Results:

Pharmacokinetic findings:

Study CPI-CL-022 was a multi-center, open-label, in-patient, single and/or multiple dose study that assessed the PKs following the first dose and safety during and after the administration of intravenous ibuprofen (10 mg/kg administered intravenously over approximately 10 minutes) in pediatric subjects, aged birth (greater than 37 weeks gestational age) to less than 6 months of age, with a clinical indication of pain and/or fever.

Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters by age (month) are presented in Table 1.

Table 1 Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters by age (month)

Age	# of pediatric patients with PK information	Cmax (µg/mL)		AUC (µg.h/mL)	
		Mean	SD	Mean	SD
[redacted] (b) (4)					
3 to <4	5	58.21	5.18	59.68	13.93
4 to <5	10	56.41	14.16	70.68	22.27
5 to <6	5	68.00	13.81	77.48	15.88

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

There were no apparent trends observed with sex and body weight vs. ibuprofen Cmax and/or AUC values.

During the team meeting, it was discussed that limited drug exposures in the following pediatric patients were noted, which the data do not provide sufficient information for a single dose use in these groups:

1. No PK or safety data in birth to <1 month pediatric group;
2. PK and safety data limited to 1 in 1 to <2 months pediatric group; and,
3. PK and safety data limited to 2 in 2 to <3 months pediatric group.

There may be acceptable single dose PK and safety data to support the single dose use in pediatric patients 3 months to <6 months old submitted in this Supplement. The Table 2 presents only the pediatric patients 3 months to <6 months information

Table 2 Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters 3 months to <6 months information

Age	# of pediatric patients with PK information	Cmax (µg/mL)		AUC (µg.h/mL)	
		Mean	SD	Mean	SD
3 to <4	5	58.21	5.18	59.68	13.93
4 to <5	10	56.41	14.16	70.68	22.27
5 to <6	5	68.00	13.81	77.48	15.88
Grouped 3 - <6 months					
3 to <6	20	59.75	12.85	69.63	19.28

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

In comparison to pediatric patients 6 months and older as presented in the Caldolor® Prescribing Information, the information from Study CPI-CL-022 has been incorporated to the existing PK table (Table 3).

Table 3 Pharmacokinetic Parameters of 10 mg/kg Intravenous** Ibuprofen, Pediatric Patients, by Age Group

	3 months to < 6 months^	6 months to <2 years Mean (SD)	2 years to <6 years Mean (SD)	6 years to 16 years Mean (SD)
Number of Patients	Mean (SD)	5	12	25
AUC (µg·h/mL)	20	71.1 (26.4)	79.2 (29.3)	80.7 (29.8)
C_{max} (µg/mL)	69.63 (19.28)	59.2 (20.6)	64.2 (22.1)	61.9 (16.5)
T_{max} (min)*	59.75 (12.85)	10 (10-30)	12 (10-46)	10 (10-40)
$T_{1/2}$ (h)	10	1.8 (0.5)	1.5 (0.6)	1.55 (0.41)

*Median (minimum-maximum)
#WT: body weight (kg)
^Study CPI-CL-022: Open-label study with hospitalized pediatric patients with pain or fever
**= 10 minute infusion time

Source: Caldolor® Prescribing Information; Section 12.3 Pharmacokinetics; Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous** Ibuprofen, Pediatric Patients, by Age Group;

The mean ibuprofen concentrations across groups showed similar values.

2 QBR

2.1 General Attributes of the Drug

The reader is referred to Caldolor®'s original Clinical Pharmacology Review dated 5/11/09 (in DARRTS).

2.2 General Clinical Pharmacology

The reader is referred to Caldolor®'s original Clinical Pharmacology Review dated 5/11/09 (in DARRTS).

2.3 Intrinsic Factors

2.3.1 What is the ibuprofen exposure information in pediatric patients with Caldolor intravenous injection?

Study CPI-CL-022 was a multi-center, open-label, in-patient, single and/or multiple dose study that assessed the PKs following the first dose and safety during and after the administration of intravenous ibuprofen in pediatric subjects, aged birth (greater than 37 weeks gestational age) to less than 6 months of age, with a clinical indication of pain and/or fever.

The primary objective was to determine the PK profile of Caldolor 10 mg/kg administered intravenously over approximately 10 minutes. The secondary objective of this study is to evaluate the safety of single and repeated doses of intravenous ibuprofen administered to hospitalized pediatric patients by assessing treatment-emergent adverse events, vital signs, and laboratory assessments. The approved dosage regimen of ibuprofen injection for pediatric subjects' ages 6 months to 12 years of age is 10mg/kg intravenously over 10 minutes, with the total daily dose not to exceed 40 mg/kg/day. The study duration was up to 72 hours.

Blood samples were collected using the sparse/staggered sampling scheme:

1. All subjects had samples collected immediately following the first dose; then at 30 min and 2 h;
2. All subjects had samples collected immediately following the first dose; then at 1 h and 4 h.

The proposed primary PK variables included clearance, volume of distribution, elimination half-life, maximum observed concentration (Cmax), and the area under the concentration-time curve from time zero until the last measurable concentration [AUC(0-inf, 0-t)].

Pediatric patients per the age (months) and sex in the study (N=23) are presented in Table 4.

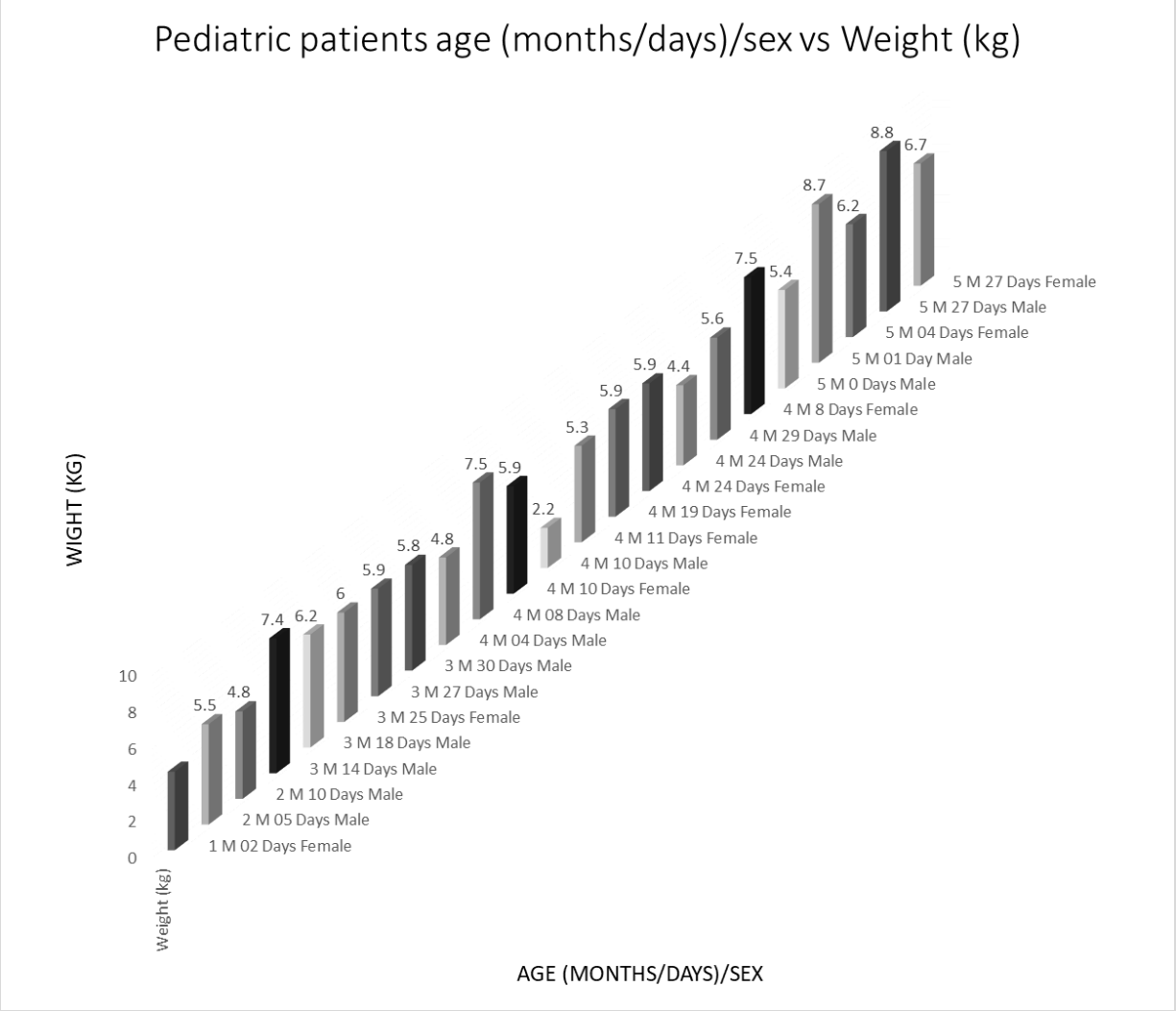
Pediatric patients age (months and days), sex and body weight (kg) in increasing age from 1 months 2 days to 5 months 27 days are presented in Figure 1.

Table 4 Number of pediatric patients per the age month and sex: N=23

Month	N	Sex	
		Male	Female
0 – 1	0	-	-
1 – 2	1	-	1
2 – 3	2	2	-
3 – 4	5	4	1
4 – 5	10	5	5
5 – 6	5	3	2

Source: Reviewer's data

Figure 1 Pediatric patients age (months and days), sex and body weight (kg) in increasing age from 1 months 2 days (bottom left) to 5 months 27 days (top right)



Source: Reviewer's data

Pediatric individual patients' ibuprofen plasma concentration vs. timepoints are presented in Table 5.

Table 5 Ibuprofen plasma concentration (µg/mL) vs Timepoints (h)

	Sampling timepoints (h)				
	0.167	**0.500**	**1.00**	**2.00**	**4.00**
Subject	**Concentration (µg/mL)**				
(b) (6)					
N	23	12	11	12	9
Mean	56.28	37.50	23.42	15.40	5.39
SD	13.27	15.03	6.66	7.17	2.68
Min	28.76	13.62	10.93	5.44	1.41
Median	58.48	37.24	25.23	14.09	5.04
Max	88.48	76.11	31.72	32.30	9.10
CV%	23.58	40.08	28.44	46.56	49.69

Source: \\CDSESUB1\evsprod\NDA022348\0144\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\cpi-cl-022\cpi-cl-022-body.pdf, p.51/119

The Applicant presented plots of individual and mean ibuprofen plasma concentration vs time profile in Figures 2 and 3 using linear and semi-log scales, respectively.

Figure 2 Mean (±SEM) ibuprofen plasma concentration - linear scale

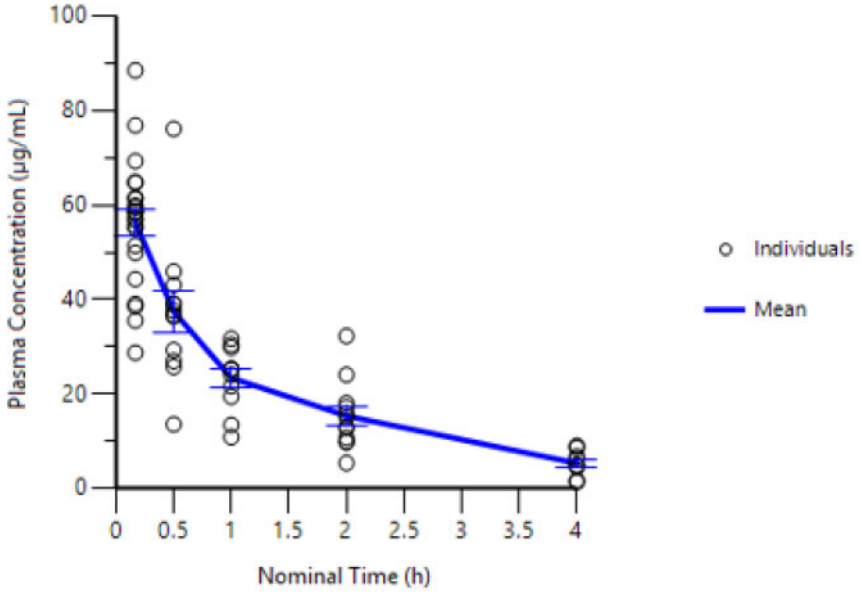


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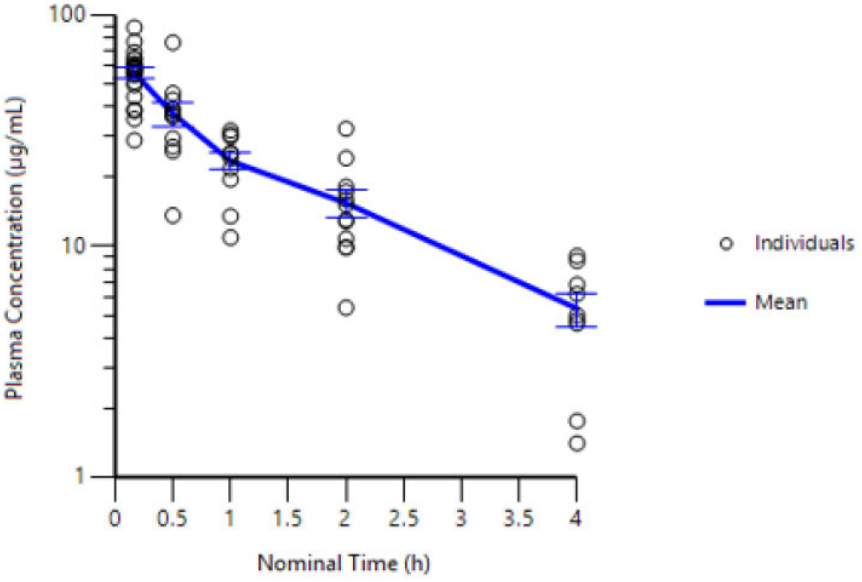
Figure 3 Mean (±SEM) ibuprofen plasma concentration - log scale



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The following pharmacokinetic information was presented by the Applicant in pediatric subjects from age birth to 6 months in Table 6.

Table 6 Ibuprofen plasma pharmacokinetic parameters of 10 mg/kg intravenous CALDOLOR in pediatric patients from age birth to 6 months

Treatment	AUC0-t (SE) (h*µg/mL)	AUC0-inf (h*µg/mL)	Cmax (SE) (µg/mL)	Residual Area (%)	Tmax (min)	T½ el (h)	Kel (1/h) (h)	Kel Lower	Kel Upper (h)	Correlation	Vz (mL)	Cl (mL/h)	Cl/WT (mL/hr/kg)	Vz/WT (mL/kg)
Caldolor	75 74 (4 09)	85 87	56 28 (2 77)	11 80	10 1 30		0 5317	0 500	4 000	-0 9948	1309 71	696 39	116 45	219 02

mg= milligram; kg= kilogram; AUC= area under the curve; SE = Standard error; h= hour; µg= microgram; mL= milliliter; Cmax= maximum concentration; Tmax= time to maximum concentration; min= minutes; T 1/2el= terminal half-life; Kel= terminal elimination rate constant; Vz= apparent volume of distribution; Cl= clearance; WT = mean weight;
Source: \\CDSESUB1\evsprod\NDA022348\0144\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\cpi-cl-022\cpi-cl-022-body.pdf, p.52/119

Noted that in the reported Table 6, for AUC0-t and Cmax parameters only, SE values were reported; no SE values were reported for other PK parameters. The Applicant stated that the analysis method (Phoenix WinNonlin when sparse sampling schedule) employed "…treated the sparse data as a special case..." and "first calculates the mean concentration curve of the data, by taking the mean concentration value for each unique time value for plasma data. The standard error of the data is also calculated for each unique time. Using the mean concentration curve, NCA [noncompartmental analysis] will calculate all of the usual plasma parameters." (The Applicant's email Response/communication dated 12/19/2022 of the Agency's Information Request dated 12/15/2022)

Reviewer's additional analysis

Additional analysis was conducted with Phoenix 64 v.8.3.4.295, utilizing the individual pediatrics ibuprofen concentration-time data.

All pediatric patients' individual ibuprofen plasma concentration vs. time profiles are presented in Figure 4.

Figure 4 All pediatric patients' individual ibuprofen plasma concentration vs. time profiles

All pediatric patients' ibuprofen individual and mean pharmacokinetic parameters are presented in Table 7.

Table 7 All pediatric ibuprofen individual pharmacokinetic parameters (Phoenix 64 v.8.3.4.295) (N=23)

Subject ID	# Samples	Tmax (h)	Cmax (ug/mL)	AUCall (ug h/mL)	Tlast (h)	Age	Sex	WT (kg)	Dose mg (10mg/kg)
(b) (6)									

(b) (6)

Mean		-	58.04	65.74	-				
SD		-	13.08	20.89	-				
%CV		-	22.54	31.78	-				
min		-	28.76	29.79	1.00				
max		-	88.48	108.66	4.00				
median		0.17	58.55	62.76	2.00				

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters by age (month) are presented in Table 8.

Table 8 Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters by age (month)

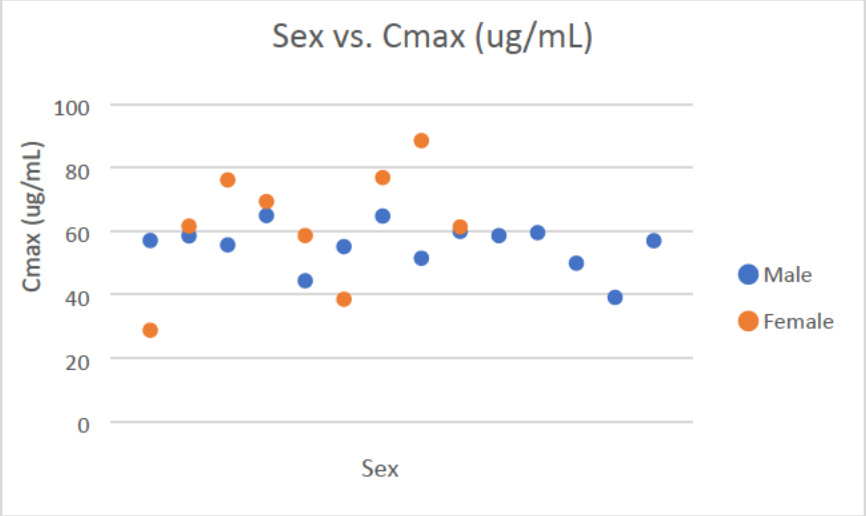
Age	# of pediatric patients with PK information	Cmax (ug/mL)		AUC (ug.h/mL)	
		Mean	SD	Mean	SD
(b) (4)					
3 to <4	5	58.21	5.18	59.68	13.93
4 to <5	10	56.41	14.16	70.68	22.27
5 to <6	5	68.00	13.81	77.48	15.88

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

All pediatric patients' individual ibuprofen sex vs. Cmax(a) and AUC(b) values are presented in Figure 5.

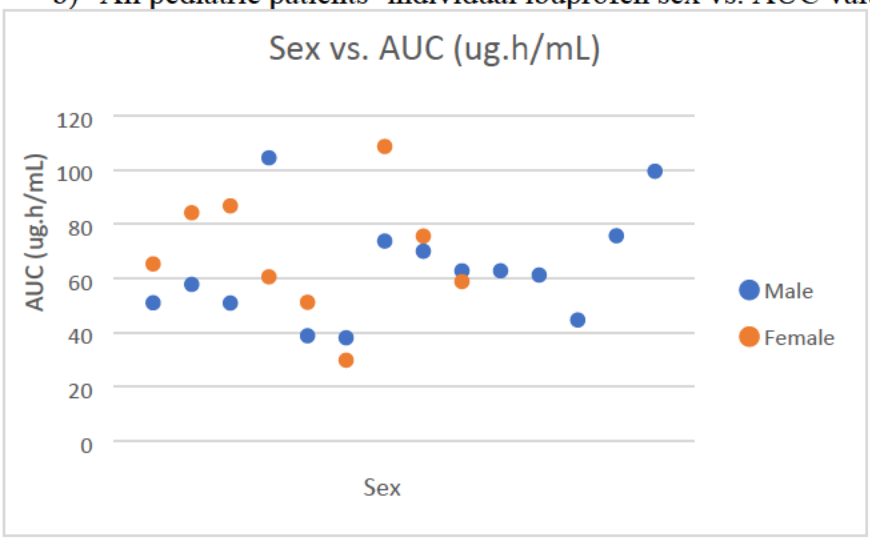
Figure 5 All pediatric patients' individual ibuprofen sex vs. Cmax(a) and AUC(b) values

a) All pediatric patients' individual ibuprofen sex vs. Cmax values



Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

b) All pediatric patients' individual ibuprofen sex vs. AUC values

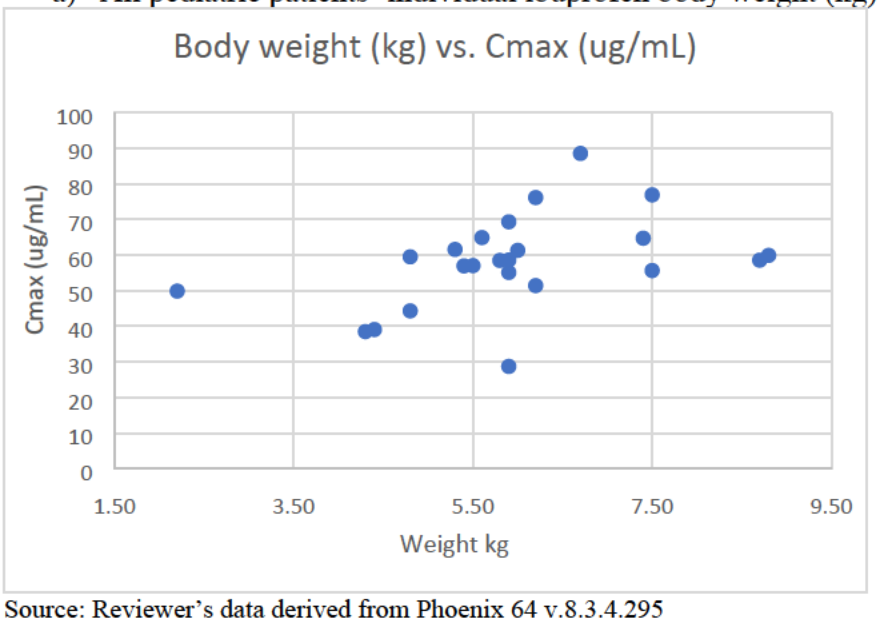


Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

All pediatric patients' individual ibuprofen body weight (kg) vs. Cmax(a) and AUC(b) values are presented in Figure 6.

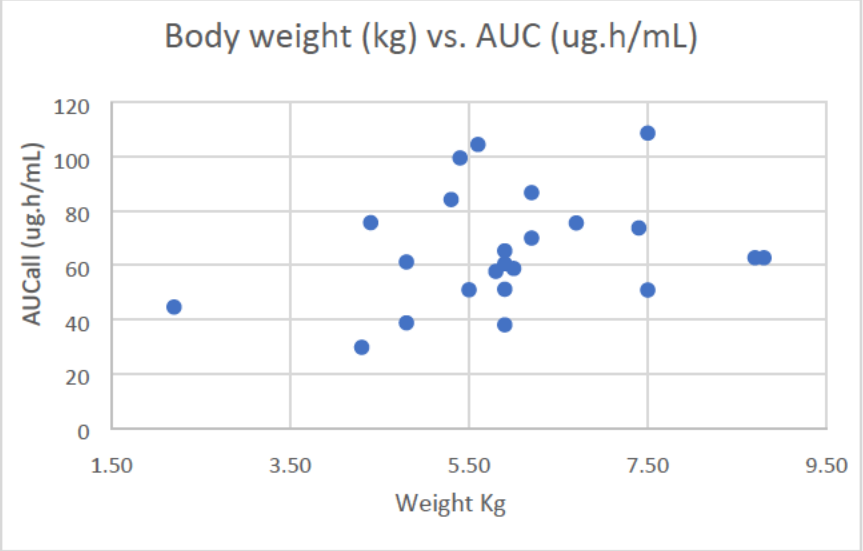
Figure 6 All pediatric patients' individual ibuprofen body weight (kg) vs. Cmax(a) and AUC(b)

a) All pediatric patients' individual ibuprofen body weight (kg) vs. Cmax values



Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

b) All pediatric patients' individual ibuprofen body weight (kg) vs. AUC values



Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters comparison by sex are presented in Table 9.

Table 9 Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters comparison by sex

	Phoenix 64 data					
	Pediatric male patients			Pediatric female patients		
Statistic	Tmax (h)	Cmax (µg/mL)	AUClast* (µg.h/mL)	Tmax (h)	Cmax (µg/mL)	AUC0-last* (µg.h/mL)
Mean	-	55.39	63.66		62.16	68.98
SD	-	7.19	20.08	-	18.85	22.93
%CV	-	12.99	31.54	-	30.32	33.24
min	-	39.10	38.06	-	28.76	29.79
max	-	64.89	104.47	-	88.48	108.66
median	0.17	56.99	61.98	0.17	61.56	65.31
*same for AUC0-inf						

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

There were no apparent trends observed with sex and body weight vs. ibuprofen Cmax and/or AUC values, as shown in Figures x and y, and Table x.

2.3.2 What does ibuprofen exposure in pediatric patients birth to <6 months old look like when compared to pediatric patients 6 months and older?

The mean ibuprofen parameters after 10 mg/kg intravenous injection in pediatric patients 6 months to 16 years (6 months to < 2 years, 2 years to < 6 years, and 6 years to 16 years) are included in Caldolor's Prescribing Information (reproduced here: "Table 5").

Caldolor® Prescribing Information:
Reproduced Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous Ibuprofen, Pediatric Patients, by Age Group

	6 months to < 2 years Mean (b) (4)	2 years to < 6 years Mean (b) (4)	6 years to 16 years Mean (b) (4)
Number of Patients	5	12	25
AUC (mcg h/mL)	71.1 (b) (4)	79.2 (b) (4)	80.7 (b) (4)
Cmax (mcg/mL)	59.2 (b) (4)	64.2 (b) (4)	61.9 (b) (4)
Tmax (min)*	10 (10-30)	12 (10-46)	10 (10-40)
T1/2(h)	1.8 (b) (4)	1.5 (b) (4)	1.55 (b) (4)
(b) (4)			

mg= milligram; kg= kilogram; (b) (4) AUC= area under the curve; h= hour; mcg= microgram; mL= milliliter; Cmax= maximum concentration; Tmax= time to maximum concentration; min= minutes; T 1/2= half-life; Cl= clearance; Vz= apparent volume of distribution; WT = mean weight
source: Caldolor Prescribing Information; Drugs@FDA
Source: Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous** Ibuprofen, Pediatric Patients, by Age Group; Caldolor® Prescribing Information; Section 12.3 Pharmacokinetics

Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters by age (month) are re-presented again below (Table 10).

Table 10 Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters by age (month)

Age	# of pediatric patients with PK information	Cmax (ug/mL)		AUC (ug.h/mL)	
		Mean	SD	Mean	SD
(b) (4)					
3 to <4	5	58.21	5.18	59.68	13.93
4 to <5	10	56.41	14.16	70.68	22.27
5 to <6	5	68.00	13.81	77.48	15.88

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

During the team meeting, it was discussed that limited drug exposures in the following pediatric patients were noted, which the data do not provide sufficient information for a single dose use in these groups:

4. No PK or safety data in birth to <1 month pediatric group;
5. PK and safety data limited to 1 in 1 to <2 months pediatric group; and,
6. PK and safety data limited to 2 in 2 to <3 months pediatric group.

There may be acceptable single dose PK and safety data to support the single dose use in pediatric patients 3 months to <6 months old submitted in this Supplement. The Table 11 presents only the pediatric patients 3 months to <6 months information.

Table 11 Pediatric patients' ibuprofen mean Cmax and AUC pharmacokinetic parameters 3 months to <6 months information

Age	# of pediatric patients with PK information	Cmax (ug/mL)		AUC (ug.h/mL)	
		Mean	SD	Mean	SD
3 to <4	5	58.21	5.18	59.68	13.93
4 to <5	10	56.41	14.16	70.68	22.27
5 to <6	5	68.00	13.81	77.48	15.88
Grouped 3 - <6 months					
3 to <6	20	59.75	12.85	69.63	19.28

Source: Reviewer's data derived from Phoenix 64 v.8.3.4.295

In comparison to pediatric patients 6 months and older as presented in the Caldolor® Prescribing Information, the information from Study CPI-CL-022 has been incorporated to the existing PK table (Table 12).

Table 12 Pharmacokinetic Parameters of 10 mg/kg Intravenous** Ibuprofen, Pediatric Patients, by Age Group

	3 months to < 6 months^	6 months to <2 years Mean (SD)	2 years to <6 years Mean (SD)	6 years to 16 years Mean (SD)
Number of Patients	Mean (SD)	5	12	25
AUC (µg·h/mL)	20	71.1 (26.4)	79.2 (29.3)	80.7 (29.8)
C_{max} (µg/mL)	69.63 (19.28)	59.2 (20.6)	64.2 (22.1)	61.9 (16.5)
T_{max} (min)*	59.75 (12.85)	10 (10-30)	12 (10-46)	10 (10-40)
$T_{1/2}$ (h)	10	1.8 (0.5)	1.5 (0.6)	1.55 (0.41)

*Median (minimum-maximum)
#WT: body weight (kg)
^Study CPI-CL-022: Open-label study with hospitalized pediatric patients with pain or fever
**= 10 minute infusion time
Source: Caldolor® Prescribing Information; Section 12.3 Pharmacokinetics; Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous** Ibuprofen, Pediatric Patients, by Age Group;

The mean ibuprofen concentrations across groups showed similar values.

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics – Not applicable

2.6 Analytical Section

2.6.1 What active moieties were measured in the plasma in the clinical pharmacology and biopharmaceutics studies and what bioanalytical methods are used to assess concentrations?

Blood samples were analyzed using a validated high performance liquid chromatographic method with tandem mass spectrometry detection (Validation Report No. 115102AEEP: Validation of a High Performance Liquid Chromatographic Method using Tandem Mass Spectrometry Detection for the Determination of Ibuprofen in Human EDTA K2 Plasma). The concentration ranges for the standard curves and quality control samples were 1 to 100 µg/mL. Tables 13-15 present bioanalytical analysis information from Study CPI-CL-022.

Table 13 Description of the analytical method

Method SOP No.:	ANI 10272.02
Method SOP Title:	Determination of Ibuprofen in Human EDTA K_2 Plasma over a Concentration Range of 1 to 100 µg/mL using High Performance Liquid Chromatographic Method with Tandem Mass Spectrometry Detection
Analyte:	Ibuprofen

Internal Standard:	Ibuprofen-d_3
Calibration Range:	1 to 100 µg/mL
Biological Matrix:	Human EDTA K_2 plasma
Assay Volume Required:	0.025 mL
Sample Extraction:	Liquid-liquid extraction
Type of Assay:	LC/MS/MS (API 4000)
Column:	ACE 3 C18, 30 x 4.6 mm, 3 µm
Column Temperature:	25°C
Mobile Phase A:	Milli-Q type water / methanol with ammonium acetate and acetic acid
Mobile Phase B:	Methanol
Chromatographic Mode:	Isocratic with column flush
Flow Rate:	1.000 mL/min
Chromatographic Integration / Acquisition Data System:	Analyst 1.6.3, AB Sciex
LIMS:	Watson version 7.4.1, Thermo Fisher Scientific Corporation
Quantitation Method:	Peak area ratio
Calibration Regression:	Linear
Weighting Factor:	$1/C^2$ [Peak area ratios (analyte/internal standard) versus the nominal concentration of the calibration standards]
Calibration equation:	y = mx + b
Coefficient of determination:	r^2

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Table 14 Analytical Performance: Back-Calculated Concentrations of Calibration Standards for Ibuprofen in Human EDTA K2 Plasma (190125AVFG)

Injection Date	Run ID	CS1 1.00 (µg/mL)	CS2 2.00 (µg/mL)	CS3 5.00 (µg/mL)	CS4 10.00 (µg/mL)	CS5 20.00 (µg/mL)	CS6 40.00 (µg/mL)	CS7 80.00 (µg/mL)	CS8 100.00 (µg/mL)
05-JUL-2019	1AVFG	1.05	2.13	5.13	9.59	19.78	39.63	82.90	98.10
		0.94	1.91	5.20	9.57	19.51	39.66	80.83	103.74
n		2	2	2	2	2	2	2	2
Intra-Run Mean		1.00	2.02	5.17	9.58	19.65	39.65	81.87	100.92
Intra-Run SD		0.08	0.16	0.05	0.01	0.19	0.02	1.46	3.99

Intra-Run CV(%)		8.00	7.92	0.97	0.10	0.97	0.05	1.78	3.95
Intra-Run % Bias		0.00	1.00	3.40	-4.20	-1.75	-0.88	2.34	0.92
09-JUL-2019	2AVFG	0.97	1.87	4.82	9.43	18.70	37.83	82.44	105.14
		1.07	2.04	5.11	9.83	20.31	41.72	80.12	107.65
n		2	2	2	2	2	2	2	2
Intra-Run Mean		1.02	1.96	4.97	9.63	19.51	39.78	81.28	106.40
Intra-Run SD		0.07	0.12	0.21	0.28	1.14	2.75	1.64	1.77
Intra-Run CV(%)		6.86	6.12	4.23	2.91	5.84	6.91	2.02	1.66
Intra-Run % Bias		2.00	-2.00	-0.60	-3.70	-2.45	-0.55	1.60	6.40
n		4	4	4	4	4	4	4	4
Inter-Run Mean		1.01	1.99	5.07	9.61	19.58	39.71	81.57	103.66
Inter-Run SD		0.06	0.12	0.17	0.17	0.67	1.59	1.31	4.04
Inter-Run CV(%)		5.94	6.03	3.35	1.77	3.42	4.00	1.61	3.90
Inter-Run % Bias		1.00	-0.50	1.40	-3.90	-2.10	-0.73	1.96	3.66

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Table 15 Within-Run and Between-Run Accuracy and Precision of Quality Controls for Ibuprofen in Human EDTA K2 Plasma (190125AVFG)

Injection Date	Run ID	QC1 3.00 (µg/mL)	QC4 7.50 (µg/mL)	QC2 50.00 (µg/mL)	QC3 75.00 (µg/mL)
05-JUL-2019	1AVFG	2.97	7.66	50.13	73.77
		2.93	7.68	52.18	74.25
n		2	2	2	2
Intra-Run Mean		2.95	7.67	51.16	74.01
Intra-Run SD		0.03	0.01	1.45	0.34
Intra-Run CV(%)		1.02	0.13	2.83	0.46
Intra-Run % Bias		-1.67	2.27	2.32	-1.32
09-JUL-2019	2AVFG	3.11	7.68	51.38	78.64
		2.74	7.85	46.77	73.06
n		2	2	2	2
Intra-Run Mean		2.93	7.77	49.08	75.85
Intra-Run SD		0.26	0.12	3.26	3.95
Intra-Run CV(%)		8.87	1.54	6.64	5.21
Intra-Run % Bias		-2.33	3.60	-1.84	1.13
n		4	4	4	4
Inter-Run Mean		2.94	7.72	50.12	74.93

Inter-Run SD	0.15	0.09	2.38	2.52
Inter-Run CV(%)	5.10	1.17	4.75	3.36
Inter-Run % Bias	-2.00	2.93	0.24	-0.09

Source: \\CDSESUB1\evsprod\NDA022348\0144\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\cpi-cl-022\cpi-cl-022-e3-16-2-05-ba.pdf, p.33/233

2.7 Office of Study Integrity and Surveillance (OSIS) inspection request

Study CPI-CL-022 intended to serve as the basis for extrapolation of efficacy in 0-6months old age group by showing the comparable bioavailability between 0-6 months and 6 months-2-year old age groups. The efficacy/safety has been shown in 6 months - 2-year old age group, and Caldolor is already approved in adults and pediatric patients 6 months and older. Since the efficacy in the pediatric patients is extrapolated from adults based on PK data, i.e., based on similar systemic exposure, there is a need to inspect the clinical and analytical sites used in the study.

From the clinical pharmacology perspective, the results from the submitted PK study will be reviewed as an essential assessment for this Supplement. A request to Office of Study Integrity and Surveillance (OSIS) was made to inspect the clinical and analytical study sites for Study CPI-CL-022 (OSIS Consult Request for Biopharmaceutical Inspections form submitted on 9/1/2022). There were 4 clinical sites participated in Study CPI-CL-022. Out of the 4 clinical sites, the clinical Site 3 (N=9; Children's Medical Center Dallas, Dallas, TX) was requested to be inspected. Additionally, the analytical site ((b) (4)) was requested to be inspected.

Results:

1. Clinical Site 3: Children's Medical Center Dallas, Dallas, TX)

   According to the Memorandum, the Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection of the clinical site was not needed at this time (DARRTS date 10/27/2022). The rationale for this decision is noted below.

   Memorandum:

   The Office of Regulatory Affairs (ORA) conducted an Inspection for the site in March 2021, which falls within the surveillance interval. The inspection was conducted under the following submissions:

   NDAs 201194/S-009, 200534/S-010, and 200535/S017.

   The following items were discussed with the site during the inspection:

- 1 subject was enrolled in the study although the subject had an elevated alkaline phosphatase level that should have led to a screening failure
- For 1 subject, an IV was removed before samples for the 24 hr PK and CMP could be collected, which was not added to the protocol deviation log.

After receiving a written response from the site, OSIS recommended that all study data be accepted for Agency review.

Site:

Facility Type	Facility Name	Facility Address
Clinical	Children's Medical Center Dallas	University of Texas Southwestern Medical School, 1935 Medical District Drive, Dallas, TX

2. Analytical site: (b) (4)

According to the Memorandum, the Office of Study Integrity and Surveillance (OSIS) determined that there were no 'objectionable conditions during the RRA' (remote regulatory assessment), and that 'data from the audited studies are reliable' from the analytical site (DARRTS date 02/22/2023).

Memorandum:

SUBJECT: Remote regulatory assessment (RRA) of (b) (4)

The Office of Study Integrity and Surveillance (OSIS) conducted a remote regulatory assessment (RRA) of the analytical portion of Studies 190125AVFG (NDA 022348/S024, Ibuprofen), (b) (4)

I did not observe any objectionable conditions during the RRA. Therefore, I conclude that data from the audited studies are reliable.

2. Reviewed Studies
Study 190125AVFG (NDA 022348/S024)
A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months
Sample Analysis Period: 07/05/2019 – 07/09/2019

3. Scope of RRA
OSIS scientist Monica Javidnia, Ph.D. reviewed the analytical portion of the above studies conducted at (b) (4)

from [redacted] (b) (4) The RRA included an examination of records and processes for method validation, and study sample analysis. The RRA also included interviews with the firm's management and staff and a facility tour. Additionally, the RRA included a review of study related SOPs, study-related correspondence, sample receipt, raw study data, audit trails, chromatograms, sample processing forms, select training records for study staff, calibration and maintenance records, and interviews with staff about IT, data
security, and archiving processes.

4. RRA Observations
At the conclusion of the RRA, I did not observe any objectionable conditions. No items were discussed with firm's management during the RRA close-out meeting.

Reviewer's comment: Acceptable and there are no further communications needed to be forwarded to the Applicant.

3 Detailed Labeling Recommendations

The following dosing recommendations are proposed to dosing instructions in pediatric patients 3 months to <6 months (Label Section, 2.3 Pediatric Patients):

Ages 3 months to less than 6 months

The dose is 10 mg/kg intravenously up to a maximum single dose of 100 mg. Infusion time must be at least 10 minutes.

The following revisions are recommended from the clinical pharmacology perspective, in Section 12 Clinical Pharmacology.

To be consistent with a typical PK parameter data presentation mode, it is recommended to revise the tables to present standard deviations (SDs), rather than CV%.

As well, because the focus is to compare the exposures (e.g., Cmax and AUC) between pediatric and adult patients, and to be consistent with Table 4, it is recommended to delete the parameters which are not critical to clinicians.

It is also proposed to combine the information of 3 to <6 months pediatric data with the existing 6 months and older pediatric data in the same table. Noted that Cmax and AUC values are proposed from the reviewer's analysis, whereas T1/2 value is from the Applicant's analysis table.

The following source documents are used to support the SDs values in Table 5 below:

1. Standard deviation source for Table 4: adults Study report CPI-CL-001
2. Standard deviation source for Table 5: pediatric Study report CPI-CL-012

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12.3 Pharmacokinetics

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Table 4: Pharmacokinetic Parameters of Intravenous Ibuprofen		
	400 mg* CALDOLOR Mean (SD)	800 mg* CALDOLOR Mean (SD)
Number of Patients	12	12
AUC (mcg·h/mL)	109.3 (28.9)	192.8 (35.7)
C_{max} (mcg/mL)	39.2 (6.09)	72.6 (9.61)
KEL (1/h)	0.32 (0.06)	0.29 (0.04)
$T_{1/2}$ (h)	2.22 (0.45)	2.44 (0.31)

AUC = Area-under-the-curve
Cmax = Peak plasma concentration
SD = Standard Deviation
KEL = First-order elimination rate constant
$T_{1/2}$ = Elimination half-life
* = 60 minute infusion time

The pharmacokinetic parameters of CALDOLOR determined in a study with febrile pediatric patients are presented in Table 5. It was observed that the median T_{max} was at the end of the infusion and that CALDOLOR had a shorter elimination half-life in pediatric patients compared to adults.

Table 5: Pharmacokinetic Parameters of 10 mg/kg Intravenous Ibuprofen, Pediatric Patients, by Age Group**				
	3 months to < 6 months^ Mean (SD)	6 months to <2 years Mean (SD)	2 years to <6 years Mean (SD)	6 years to 16 years Mean (SD)
Number of Patients	20	5	12	25
AUC (mcg·h/mL)	69.63 (19.28)	71.1 (26.4)	79.2 (29.3)	80.7 (29.8)
C_{max} (mcg/mL)	59.75 (12.85)	59.2 (20.6)	64.2 (22.1)	61.9 (16.5)
T_{max} (min)*	10	10 (10-30)	12 (10-46)	10 (10-40)
$T_{1/2}$ (h)	1.3	1.8 (0.5)	1.5 (0.6)	1.55 (0.41)

*Median (minimum-maximum)
#WT: body weight (kg)
^Open-label study with hospitalized pediatric patients with pain or fever
**= 10 minute infusion time

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4 Appendices

4.1 Proposed Package Insert

The following Label is proposed by the Applicant.

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4.2 Individual Study Review

4.2.1 Study CPI-CL-022: A Multi-Center, Open-Label, Pharmacokinetic, and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months

Synopsis provided by the Applicant:

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Additional relevant information from the study report, which are not in the study synopsis:

1. CPI-CL-022 **pharmacokinetic** demographics

Number of subjects per the age month: N=23

Month	Pediatric patients N
0 – 1	0
1 – 2	1
2 – 3	2
3 – 4	5
4 – 5	10
5 – 6	5

Noted: The screening population (n=30) includes all subjects who provided informed consent and provided demographic and/or baseline screening assessments in the trial.

Sorted by Age:

PK subjects	N=23					
Subject No.	Age	Sex	Date of birth	Ethnicity	Race	Weight (kg)
(b) (6)	1 Month 02 Days	Female	(b) (6)	Non-Hispanic or Non-Latino	Other	4.3
	2 Months 05 Days	Male		Non-Hispanic or Non-Latino	White	5.5
	2 Months 10 Days	Male		Hispanic Or Latino	White	4.8
	3 Months 14 Days	Male		Hispanic Or Latino	Other	7.4
	3 Months 18 Days	Male		Non-Hispanic or Non-Latino	White	6.2

(b) (6)	3 Months 25 Days	Female	(b) (6)	Non-Hispanic or Non-Latino	White	6
	3 Months 27 Days	Male		Non-Hispanic or Non-Latino	White	5.9
	3 Months 30 Days	Male		Non-Hispanic or Non-Latino	White	5.8
	4 Months 04 Days	Male		Non-Hispanic or Non-	White	4.8
	4 Months 08 Days	Male		Non-Hispanic or Non-Latino	White	7.5
	4 Months 10 Days	Female		Non-Hispanic or Non-Latino	White	5.9
	4 Months 10 Days	Male		Non-Hispanic or Non-Latino	Black or African American	2.2
	4 Months 11 Days	Female		Hispanic Or Latino	Other	5.3
	4 Months 19 Days	Female		Non-Hispanic or Non-Latino	White	5.9
	4 Months 24 Days	Female		Non-Hispanic or Non-Latino	White	5.9
	4 Months 24 Days	Male		Non-Hispanic or Non-Latino	White	4.4
	4 Months 29 Days	Male		Non-Hispanic or Non-Latino	White	5.6
	4 Months 8 Days	Female		Non-Hispanic or Non-Latino	White	7.5
	5 Months 0 Days	Male		Non-Hispanic or Non-Latino	Black or African American	5.4
	5 Months 01 Day	Male		Non-Hispanic or Non-Latino	White	8.7
	5 Months 04 Days	Female		Hispanic Or Latino	White	6.2
	5 Months 27 Days	Male		Non-Hispanic or Non-Latino	Black or African American	8.8
	5 Months 27 Days	Female		Hispanic Or Latino	Other	6.7

2. Study design

7.5 Rationale for Current Study Design

For the pediatric patient population, there are multiple oral over-the-counter (OTC) ibuprofen products available for the treatment of pain in children. Motrin® (McNeil Consumer Healthcare, Fort Washington, Pennsylvania) is one of the most commonly used oral ibuprofen products currently marketed. The recommended dose for Motrin for treatment of pain in children 6 months to 12 years of age is 10 milligrams per kilogram (mg/kg) with the recommended maximum daily dose of 40 mg/kg. The recommended dosing for children 12 years of age and older is the same as that used for adults, 200 to 800 mg up to four times daily, with a maximum of 3200 mg per day.

The approved dosage regimen of ibuprofen injection for pediatric subjects' ages 6 months to 12 years of age is 10mg/kg intravenously over 10 minutes, up to a maximum single dose of 400 mg every 4 to 6 hours as necessary, for pain and fever.

Based on the approved dosing for the ibuprofen injection in pediatric patients greater than 6 months, as well as published results from clinical studies, the dose selected for this study was 10.0 mg/kg of intravenous ibuprofen. The total daily dose would not exceed 40 mg/kg/day.

9.2 Overall Study Design

This was an multi-center, open-label, single and/or multiple dose clinical study that assessed the pharmacokinetics following the first dose and safety during and after the administration of intravenous ibuprofen. A total of twenty-four subjects, between the ages of birth (> 37 weeks gestational age) to less than six months of age, were enrolled at up to five clinical centers. The study duration was up to 72 hours.

9.3.6 Treatment Period
The Treatment Period began at Hour 0 when the initial dose of investigational medicinal product was administered. Subsequent doses of IMP were administered, at the investigators discretion, every 6 to 8 hours, as needed, during the 48 hour treatment period. The total daily dose would not exceed 40 mg/kg/day.

9.5.8 Selection of Doses in the Study
The dose in this study was selected using the results generated from three previous clinical studies in pediatric subjects conducted by Cumberland and by the current recommended available dosing information.

9.6.5 Pharmacokinetic Variables
The primary pharmacokinetic variables included clearance, volume of distribution, elimination half-life (T1/2), maximum observed concentration (Cmax), and the area under the concentration-time curve from time zero until the last measurable concentration [AUC(0-□, 0-t)].

9.6.7.1 PK Blood Sample Collection and Processing
PK samples were collected on all subjects immediately (± 5 minutes) following completion of the first dose of intravenous ibuprofen; then alternating subjects had PK sampling performed either at 30 minutes and 2 hours or at 1 hour and 4 hours following the first dose of intravenous ibuprofen (12 subjects had samples collected immediately following the first dose, then at 30 minutes and 2 hours; and, 12 subjects had samples collected immediately following the first dose, then at 1 hour and 4 hours).
Samples were processed by (b) (4)

9.6.7.2 Shipment and Assay of Biological Samples
Each site retained the samples at their site until completion of the study. Sample shipment was arranged by (b) (4)

The assay, bioanalytical (BA) and PK modeling report were performed and completed by (b) (4)

9.8.5.2.1 Handling of Below the Lower Limit of Quantitation (BLQ), No Reportable Concentration Values and Missing Data
All concentration values BLQ were set to zero. Samples with no reportable value occurring prior to dosing were replaced by "0.00" otherwise they were set to missing for tabulation, graphical representation and calculation purposes, all samples with no reportable value observed after dosing were set to missing.
For PK calculation, only observed data were used in the analysis except for concentration values BLQ and samples with no reportable value occurring prior to dosing as described above.

There was no extrapolation or imputation of missing data. This procedure is described in the Summary PK report (Listing 16.2.5.4)

9.8.5.3 PK Parameters

The following PK parameters were calculated from the mean ibuprofen plasma drug concentration-time data using standard non-compartmental methods consistent with the intravenous infusion route of administration:

AUC0-t: Area under the concentration-time curve from time zero until the last measurable concentration. AUC0-t was calculated using the trapezoidal method.

AUC0-inf: Area under the concentration-time curve from time zero to infinity (extrapolated), calculated as AUC0-t + Clast/Kel, where Clast is the last measurable concentration.

Residual area: Residual area, calculated as 100*(1- AUC0-t / AUC0-inf).

Cmax: Maximal measured serum concentration, taken from the plasma concentration time profile.

Tmax: Time when the maximal serum concentration was observed, taken from the serum concentration-time profile.

Kel: Terminal elimination rate constant. This parameter is the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. At least 3 concentration points were used in estimating Kel. The sampling time where ln-linear Kel calculation begins (Kel Lower) and the sampling time of the last quantifiable concentration used to estimate the Kel (Kel Upper) were reported with the correlation coefficient from the linear regression to calculate Kel (Correlation).

T½ el: Terminal elimination half-life, calculated as ln(2)/Kel.

Cl: Apparent clearance, calculated as Dose/AUC0-inf

Cl/WT: Apparent clearance, calculated as Dose/AUC0-inf/Weight. The mean body weight was used.

Vz: Apparent volume of distribution, calculated as Dose/(Kel x AUC0-inf)

Vz/WT: Apparent volume of distribution, calculated as Dose/(Kel x AUC0-inf)/Weight. The mean body weight was used.

The nominal time of infusion (10 minutes) and nominal dose were used for the derivation of PK parameters. The nominal dose was calculated using the mean weight as (10 mg/kg x mean body weight = 10 x 5.98 kg = 5.98 mg).

11.4.7 Analysis of Pharmacokinetic Parameters

Descriptive statistics including number of observations [N], mean, median, standard deviation [SD], standard error on the mean (SEM), minimum [Min], and maximum [Max]) were calculated from plasma concentration for each subject. These results are shown in Table 11-4.

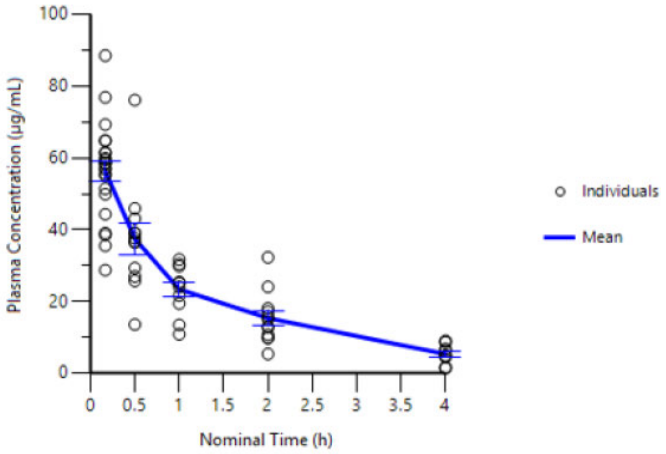
Table 11–4 Ibuprofen Plasma Concentration (µg/mL) vs Nominal Time (h)

	Relative Nominal Time (h)				
	0.167	0.500	1.00	2.00	4.00
Subject	Concentration (µg/mL)				
(b) (6)					

N	23	12	11	12	9
Mean	56.28	37.50	23.42	15.40	5.39
SD	13.27	15.03	6.66	7.17	2.68
SEM	2.77	4.34	2.01	2.07	0.89
Min	28.76	13.62	10.93	5.44	1.41
Median	58.48	37.24	25.23	14.09	5.04
Max	88.48	76.11	31.72	32.30	9.10
CV%	23.58	40.08	28.44	46.56	49.69
Geometric Mean	54.67	34.87	22.37	14.00	4.61

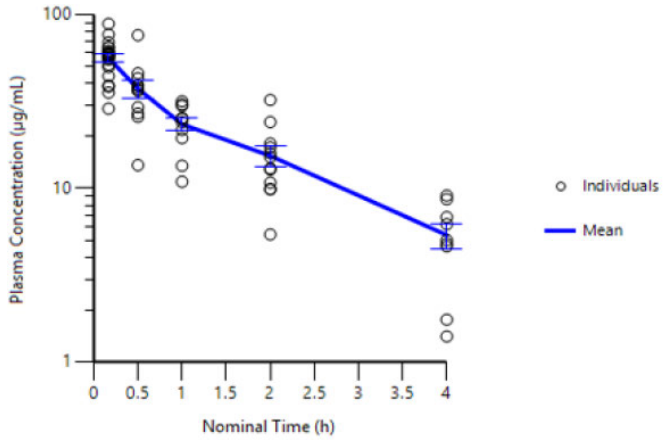
- = Not collected; N = Number of observations; SD = Standard deviation; SEM = Standard error on the mean; CV = Coefficient of variation; Min = Minimum; Max = Maximum
*No detectable concentrations were obtained for subject 03-2011. The information is presented in the table but removed from the descriptive statistics.

Figure S1: Mean (±SEM) Ibuprofen Plasma Concentration - Linear Scale



Treatment: CALDOLOR® (ibuprofen) injection, 10 mg/kg
SEM= standard error of the mean; µg= microgram; mL= milliliter; h= hour; mg= milligram; kg= kilogram

Figure S2: Mean (±SEM) Ibuprofen Plasma Concentration - Log Scale



Treatment: CALDOLOR (ibuprofen) injection, 10 mg/kg
SEM= standard error of the mean; µg= microgram; mL= milliliter; h= hour; mg= milligram; kg= kilogram

The ibuprofen PK parameters (AUC0-t, AUC0-inf, Cmax, Residual area, Tmax, T½ el, Kel, Kel Lower, Kel Upper, Correlation, Cl, Vz, Cl/WT and Vz/WT) calculated from the mean PK profile of pediatric subjects aged from birth to 6 months appear in Table 11-5.

Table 11–5 Ibuprofen Plasma PK Parameters of 10 mg/kg Intravenous CALDOLOR in Pediatric Subjects from Age Birth to 6 Months

Treatment	AUC_{0-t} (SE) (h*µg/mL)	AUC_{0-inf} (h*µg/mL)	C_{max} (SE) (µg/mL)	Residual Area (%)	T_{max} (min)	$T_{½ el}$ (h)	K_{el} (1/h)	K_{el} Lower (h)	K_{el} Upper (h)	Correlation	Vz (mL)	Cl (mL/h)	Cl/WT (mL/hr/kg)	Vz/WT (mL/kg)
Caldolor	75.74 (4.09)	85.87	56.28 (2.77)	11.80	10	1.30	0.5317	0.500	4.000	-0.9948	1309.71	696.39	116.45	219.02

mg= milligram; kg= kilogram; AUC= area under the curve; SE = Standard error; h= hour; µg= microgram; mL= milliliter; Cmax= maximum concentration; Tmax= time to maximum
concentration; min= minutes; T 1/2el= terminal half-life; Kel= terminal elimination rate constant; Vz= apparent volume of distribution; Cl= clearance; WT = mean weight

The mean PK Parameters of 10 mg/kg Intravenous Ibuprofen of pediatric patients in older age groups (6 months to < 2 years, 2 years to < 6 years, and 6 years to 16 years) are published in the prescribing information of CALDOLOR (ibuprofen) injection for IV use and are presented in Table 11-6.

Table 11–6 Pharmacokinetic Parameters of 10 mg/kg Intravenous CALDOLOR in Pediatric Patients by Age Group

	6 months to < 2 years Mean (b) (4)	2 years to < 6 years Mean (b) (4)	6 years to 16 years Mean (b) (4)
Number of Patients	(b) (4)	12	25
AUC (mcg h/mL)	71.1 (b) (4)	79.2 (b) (4)	80.7 (b) (4)
C_{max} (mcg/mL)	59.2 (b) (4)	64.2 (b) (4)	61.9 (b) (4)
T_{max} (min)*	10 (10-30)	12 (10-46)	10 (10-40)
$T_{1/2}$(h)	1.8 (b) (4)	1.5 (b) (4)	1.55 (b) (4)
(b) (4)			

mg= milligram; kg= kilogram; (b) (4) AUC= area under the curve; h= hour; mcg= microgram; mL= milliliter; Cmax= maximum
concentration; Tmax= time to maximum concentration; min= minutes; T 1/2= half-life; Cl= clearance; Vz= apparent volume of distribution; WT =
mean weight

11.4.8 Pharmacokinetic Conclusions

The pharmacokinetics of ibuprofen following a 10.0 mg/kg IV infusion in children ages birth to less than 6 months of age was evaluated. It was observed that the time to peak ibuprofen concentration (Tmax) was observed at the end of the 10 minute IV infusion. Following the infusion, ibuprofen plasma levels declined rapidly with elimination half-life (T½ el) of 1.30 hours. Following the 10 minute infusion, the peak ibuprofen concentration was 56.28 µg/mL.

The AUC0-t and AUC0-inf was 75.74 h*µg/mL and 85.87 h*µg/mL, respectively for 10.0 mg/kg IV infusion and the volume of distribution was 0.22 L/kg.

The median Tmax observed in this study was comparable to data from the Caldolor prescribing information. The volume of distribution as well as the clearance was lower in subjects from birth to 6 months compared to older pediatric patients. However, clearance and volume of distribution normalized by body weight were similar among age groups. Finally, the AUC, Cmax and T½ el obtained were comparable to the data for older pediatric patients.

Listing 16.2.5.1 contains the Bioanalytical Report, Listing 16.2.5.2 contains the Representative Chromatograms, Listing 16.2.5.3 contains the Analytical Method Validation Report, and Listing 16.2.5.4 contains the Summary PK Report.

4.3 Consult Review (including Pharmacometric Reviews) – Not applicable

4.4 Cover Sheet and OCP Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	22348; 505(b)(2); Supplement 024 (Efficacy); Post Marketing Requirement 205-5	**SDN Seq.N**	255 0170
Applicant	Cumberland Pharmaceuticals Inc.	**Submission Date**	7/11/2022
Generic Name	Ibuprofen Injection	**Brand Name**	CALDOLOR®
Drug Class	Analgesia		
Proposed Indication	For the reduction of fever, and the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics		
Dosage Regimen	Adults: *For Analgesia (pain):* The dose is 400 mg to 800 mg intravenously every 6 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200 mg. *For Fever:* The dose is 400 mg intravenously, followed by 400 mg every 4 to 6 hours or 100 mg to 200 mg every 4 hours as necessary. Infusion time must be at least 30 minutes. Maximum daily dose is 3,200 mg. Pediatric patients: *Ages 12 to 17 years:* The dose is 400 mg intravenously every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 2,400 mg. *Ages 6 months to 12 years:* The dose is 10 mg/kg intravenously up to a maximum single dose of 400 mg every 4 to 6 hours as necessary. Infusion time must be at least 10 minutes. Maximum daily dose is 40 mg/kg or 2,400 mg, whichever is less.		
Dosage Form /Strengths	Injection; Strength: 800 mg/8 mL (100 mg/mL); 800 mg/200 mL (4 mg/mL)	**Route of Administration**	Intravenous
OCP Division	DNP	**OND Division**	DAAP
OCP Review Team	**Primary Reviewer(s)** David Lee	**Secondary Reviewer/ Team Leader** Yun Xu	
Pharmacometrics	-		
Genomics	-		
Review Classification	☑ Standard ☐Priority ☐ Expedited		

Filing Date	9/9/2022; Filing meeting: 8/18/2022	**74-Day Letter Date**	9/23/2022
Review Due Date	Primary 4/4/2023; Secondary 4/11/2023	**PDUFA Goal Date**	5/11/2023

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑Yes

☐No

If no list reason(s):

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐Yes

☑No

Is there a need for clinical trial(s) inspection?

☑Yes

☐No

If yes explain: The Applicant has submitted the results from 1 PK study (Study CPI-CL-022) in pediatric patients 0-6 months. Since the efficacy is extrapolated from adults based on PK data, there is a need to inspect the clinical and analytical sites used in the study (see Filing Memo below for further discussion).

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑Yes ☐ No ☐N/A
Bioanalytical and Analytical Methods	☑Yes ☐ N/A	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		

☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☑ Single Dose		
	☐Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☑ Pediatrics		1	The Applicant has submitted results from 1 PK study, Study CPI-CL-022 entitled “A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months”
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			

☐ Population Pharmacokinetics					
☐ Exposure-Efficacy					
☐ Exposure-Safety					
Total Number of Studies		**In Vitro**	-	**In Vivo**	1
Total Number of Studies to be Reviewed			-		1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑ N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑ N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐ N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑ N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐ N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑ N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑ N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☐Yes ☐No ☑ N/A	

9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐ N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐ N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐ N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑ N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐ N/A	The Applicant has submitted the results from 1 PK study, in pediatric patients 0-6 months, Study CPI-CL-022 entitled "A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months," to fulfill the last PMR under PREA, PMR 205-5.

		Study CPI-CL-022 was an open-label PK and safety study intended to serve as the basis for extrapolation of efficacy in 0-6months old age group by showing the comparable bioavailability between 0-6 months and 6 months - 2-year old age groups, if efficacy/safety has been shown in 6 months - 2-year old age group. There are no issues with efficacy/safety in 6 months-2-year old age group, since Caldolor is already approved in ages 6 months and up (see Filing Memo below for further discussion). From the clinical pharmacology perspective, the results from the submitted PK study will be reviewed as an essential assessment for this Supplement. The Applicant proposes to update the current Caldolor® Label, to include PK information in 0-6 months old age group. Noted that the data from the Study CPI-CL-022 was submitted (b) (4) [redacted] Just to clarify, for this current submission, the study results from Study CPI-CL-022 submitted in 4/24/2020 will be reviewed (see Filing Memo below for further discussion).
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization	☐Yes ☐No ☑ N/A	

strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑ N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑ N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑ N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐ N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑ N/A	

Filing Memo

Caldolor® (ibuprofen) Injection (N22348) was approved on 6/11/09. Caldolor is indicated in adults and pediatric patients 6 months and older for the reduction of fever, and the management of mild to moderate pain and management of moderate to severe pain as an adjunct to opioid analgesics.

In order to fulfill Caldolor's Postmarketing Requirement (PMR) 205-5 [Pediatric Research Equity Act (PREA) (Reference ID: 3678476); 12/24/14] for a pediatric study in the 6-month and under age group, the Applicant has conducted and has submitted the results from Study CPI-CL-022, 'A Multi-Center, Open-Label Pharmacokinetic and Safety Study for Reduction in Fever or Management of Pain in Pediatric Subjects Aged Birth to Six Months.' The Applicant proposes to update the current Caldolor® Label, to include PK information from Study CPI-CL-022 in 0-6 months old age group.

The Applicant has submitted the results from 1 PK study (Study CPI-CL-022) in pediatric subjects aged birth to six months.

It is noted that the efficacy is extrapolated from adults based on PK data, as previously discussed with Pediatric Review Committee meeting held on 9/17/14 (PeRC; DARRTS date 9/29/14). During the meeting, the PeRC commented that:

- Existing effectiveness data collected in study CPI-CL-012 for fever for pediatric patients aged 6 months to 2 years can be used to support the effectiveness for fever and pain for pediatric patients aged birth to 6 months based on the bridging information described above (i.e., similar bioavailability between oral and i.v. formulations as well as established efficacy for fever and pain in patients 6 months to 2 years of age). The PeRC requested that the Division assure that a sufficient number of patients were studied in CPI-CL-012 between 6 months and 2 years of age before agreeing to this plan.

- The PeRC also noted that if, upon review, the PK and safety data in patients aged birth to 6 months are not similar to data in patients 6 months to 2 years of age then a full efficacy study may be required.

Caldolor is already approved in ages 6 months and up, indicating that there are no issues with efficacy/safety in pediatric 6 months – 2-year olds.

1. Clarification of the location of the study results from Study CPI-CL-022

Noted that the information from the Study CPI-CL-022 was submitted (b) (4) [redacted]

Therefore, for this current submission, Supplement 024, S-024, the study results from Study CPI-CL-022 submitted in 4/24/2020 will be reviewed.

Additionally, there were Information Requests (IRs) sent to the Applicant (via email communications) (b) (4) [redacted] The Applicant submitted the requested information under submissions, SDN 0145 (submission date 6/15/2020) and 0147 (submission date 6/24/2020). The information submitted in SDN 0145 and 0147 will also be reviewed in this current supplement.

2. Office of Study Integrity and Surveillance (OSIS) inspection request

A request to Office of Study Integrity and Surveillance (OSIS) is needed to inspect the clinical and analytical study sites for Study CPI-CL-022. The OSIS Consult Request for Biopharmaceutical Inspections form will be filled out and send to the regulatory project manager.

Study CPI-CL-022 was an open-label PK and safety study intended to serve as the basis for extrapolation of efficacy in 0-6months old age group by showing the comparable bioavailability between 0-6 months and 6 months-2-year old age groups, if efficacy/safety has been shown in 6 months - 2-year old age group. Since the efficacy is extrapolated from adults based on PK data, there is a need to inspect the clinical and analytical sites used in the study.

There were 4 clinical sites participated in Study CPI-CL-022. Out of the 4 clinical sites, the clinical Site 3 (N=9; Children's Medical Center Dallas, Dallas, TX) will be requested to be inspected. Additionally, the analytical site will be requested to be inspected (b) (4)).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID J LEE
04/11/2023 11:46:14 AM

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