

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-348

PHARMACOLOGY REVIEW



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**SUPERVISOR'S SECONDARY REVIEW
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION**

NDA NUMBER: 22-348
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 12/11/2008
PRODUCT: CALDOLOR (Ibuprofen) injection
INTENDED CLINICAL POPULATION: Adults (b) (4)
SPONSOR: Cumberland Pharmaceuticals
REVIEW DIVISION: Division of Anesthesia, Analgesia, and
Rheumatology Products (HFD-170)
PHARM/TOX REVIEWER: Asoke Mukherjee, Ph.D.
PHARM/TOX SUPERVISOR: R. Daniel Mellon, Ph.D.
DIVISION DIRECTOR: Bob A. Rappaport, M.D.
PROJECT MANAGER: Kathleen Davies

Date of review submission to Division File System (DFS): May 19, 2009

Executive Summary

NDA 22-348 was submitted by Cumberland Pharmaceuticals in support of the proposed product CALDOLOR (ibuprofen) injection for intravenous administration. The product is supplied at a concentration of 100 mg/mL and must be diluted to 4 mg/mL or less prior to administration. This product is intended to be added to either normal saline (0.9%), 5% dextrose solutions, or lactated ringer's solution. The proposed indications are analgesia and reduction of fever, for use in adults (b) (4). The maximum daily dose for this product should not exceed 3200 mg/day.

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

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

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

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

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

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

For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Adequate qualification must include:

- a. Minimal genetic toxicology screen (two in vitro genetic toxicology studies e.g. one Ames assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- b. Repeat dose toxicology of appropriate duration to support the proposed indication.

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

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

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

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

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

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

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

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

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

Recommendations

A. Recommendation on approvability

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

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

B. Recommendation for nonclinical studies

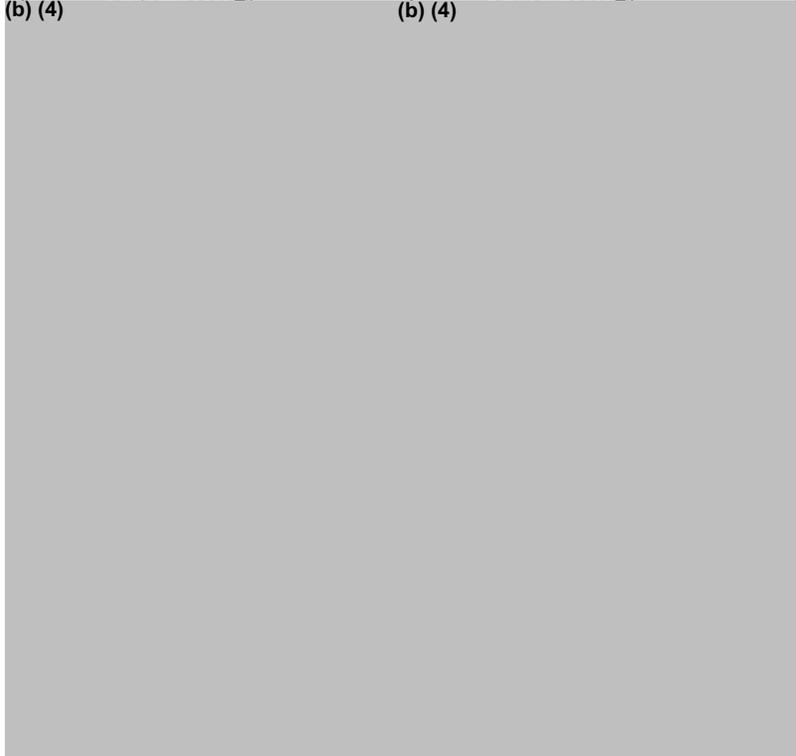
None.

C. Recommendations on labeling

NOTE: Recommended additions are noted in blue text, while recommended deletions are noted in red, crossed-out text. The recommendations below may not reflect final labeling.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
<p>5. WARNINGS AND PRECAUTIONS</p> <p>(b) (4)</p>	<p>5. WARNINGS AND PRECAUTIONS</p> <p>5.9 Pregnancy Starting at 30 weeks gestation, CALDOLOR, and (b) (4) other NSAIDs, (b) (4) should be avoided by pregnant women as (b) (4) (b) (4) premature closure of the ductus arteriosus in the fetus may occur.</p>	<p>(b) (4); The recommended revisions are based on the NSAID class labeling consult dated February 22, 2008.</p>
	<p>CALODOR must be diluted prior to use. Infusion of the drug product without dilution will cause hemolysis.</p>	<p>Dr. Mukherjee has recommended including language in the warnings and precautions section indicating that the product must be diluted. I concur; however, the actual header or location will be discussed with the clinical review team.</p>
<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy</p> <p>(b) (4)</p>	<p>8 USE IN SPECIFIC POPULATIONS</p> <p>8.1 Pregnancy Teratogenic effects - Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.</p> <p>Starting at 30 weeks gestation, CALDOLOR, and other NSAIDS, should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. CALDOLOR can cause fetal harm when administered to a pregnant woman starting at 30 weeks gestation. (b) (4) (b) (4)</p> <p>(b) (4)</p> <p>(b) (4) There are no adequate and well-controlled studies in pregnant women. Prior to 30 weeks gestation, CALDOLOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</p> <p>Reproductive studies conducted in rats and rabbits have not</p>	<p>(b) (4); The recommended revisions are based on the NSAID class labeling consult dated February 22, 2008.</p>

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
	<p>demonstrated evidence of developmental abnormalities.</p> <p>(b) (4)</p>	
<p>8.2 Labor and Delivery</p> <p>(b) (4)</p>	<p>8.2 Labor and Delivery</p> <p>The effects of CALDOLOR on labor and delivery in pregnant women are unknown. In rat studies, maternal exposure to (b) (4) NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, (b) (4) the incidence of dystocia, (b) (4) delayed parturition (b) (4), and decreased pup survival (b) (4)</p>	<p>(b) (4);</p> <p>(b) (4) The recommended revisions are based on the NSAID class labeling consult dated February 22, 2008.</p>
<p>8.3 Nursing Mothers</p> <p>(b) (4)</p>		<p>(b) (4);</p> <p>As the information proposed is entirely clinical, see medical officer recommendations for labeling.</p>
<p>13 NONCLINICAL TOXICOLOGY</p>		
<p>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</p> <p>(b) (4)</p>		<p>Data on carcinogenicity, mutagenicity and impact on fertility does not appear in FDA approved product labels as far back as 1994. As the original pharmacology toxicology reviews and labeling are not available to the review team, it is not clear what original data, if</p>

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/Comment
		any, may have been submitted to the referenced products.
13.2 Animal Toxicology and Pharmacology (b) (4) 	13.2 Animal Toxicology and Pharmacology (b) (4)	These data should be removed from the product labeling, as they do not provide useful information to the physician given the existing human data.

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

/s/

R. Daniel Mellon
5/19/2009 10:58:40 AM
PHARMACOLOGIST



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22-348
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 12/11/2008
PRODUCT: CALDOLOR (ibuprofen) injection
INTENDED CLINICAL POPULATION: Patients suffering from fever, mild to severe pain
SPONSOR: Cumberland Pharmaceuticals, TN 37203
REVIEW DIVISION: Division of Anesthesia, Analgesia and
Rheumatology Drug Products (HFD-170)
PHARM/TOX REVIEWER: Asoke Mukherjee, Ph.D.
PHARM/TOX Team Leader: Daniel Mellon, Ph.D.
DIVISION DIRECTOR: Bob Rappaport, M.D.
PROJECT MANAGER: Kathleen Davies

Date of review submission to Division File System (DFS): May 15, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: From the nonclinical pharmacology toxicology perspective, this NDA may be approved.

B. Recommendation for nonclinical studies: Nil

C. Recommendations on labeling:

The sponsor did not submit the proposed label of Amelior (ibuprofen injection) in a PLR format. However, following recommendations are given for the non-clinical label according to the PLR format and considering the comments from the maternal health on NSAID labels.

Sponsor's Proposed Labeling	Recommended labeling	Rationale/Comment
Nothing proposed	5.0 Warnings and Precautions 5.1 Hematological Adverse Reactions: Amelior should not be used without dilution as recommended because it may cause hemolysis.	In vitro data in human blood showed hemolysis at 100 mg/mL.
8 Use in specific populations (b) (4)	8 Use in specific populations 8.1 Pregnancy Pregnancy <i>Teratogenic Effects. Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.</i> Prior to 30 weeks gestation, CALDOLOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Starting at 30 weeks gestation, NSAIDS including CALDOLOR should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. There are no	Based on the recommendation from maternal health consult for the NSAID label

Sponsor's Proposed Labeling	Recommended labeling	Rationale/Comment
(b) (4) 8.3 Nursing mothers	adequate and well-controlled studies in pregnant women. Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. 8.3 Nursing mother	
(b) (4)	(b) (4)	The change was made to incorporate the information on nursing mothers from the 2002 approved label (b) (4) (b) (4)
(b) (4)	(b) (4) remove this section from the label.	Because no information is available For these data in the package insert of referenced NDA.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings: Ibuprofen induced GI erosion and ulcers in dogs when given by IV route for 28 days. The procedure also showed local injection site inflammation, thrombosis, edema and erythema due to irritational nature of the formulation and the procedure. Ibuprofen injection showed hemolytic potential at 1:1 ratio by volume between 100 mg/mL solution and heparinized blood. Therefore, it is recommended that the drug product should not be used without dilution as mentioned in the package insert.

- B. Pharmacologic activity:** Pharmacological activity of ibuprofen injections to reduce fever is due to inhibition of COX-1 and COX-2 enzymes. The sponsor did not conduct any pharmacology experiments. However, the sponsor provided a summary of published data on the anti-pyretic, analgesic and anti-inflammatory effects of ibuprofen.
- C. Nonclinical safety issues relevant to clinical use:** The drug product can induce irritation, thrombosis and inflammation at the site of injections. Also, the product should not be injected intravenously without further dilution (1:25 or greater) with saline or any suitable vehicle. Ibuprofen also showed GI and kidney inflammation in the non-clinical toxicity studies. However, these effects are expected from NSAIDs.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-348

Review number: One

Sequence number/date/type of submission: Jan 19, 2008, serial # 000 and April 20, 2009; serial #0014; 505(b)(2)

Information to sponsor: Yes () No (x)

Sponsor and/or agent: Cumberland Pharmaceuticals, TN 37203

Manufacturer for drug substance:

(b) (4)

Reviewer name: Asoke Mukherjee, Ph.D.

Division name: Division of Analgesia, Anesthesia, and Rheumatology Products

HFD #: 170

Review completion date: May 1, 2009

Drug:

Trade name: CALDOLOR

Generic name: Ibuprofen Injection

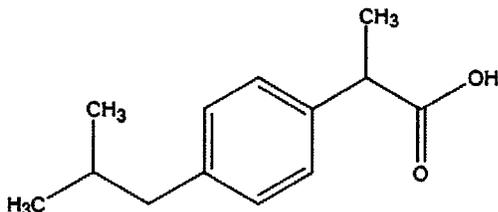
Code name: 9420

Chemical name: (RS)-2-(4-isobutyl) propionic acid

CAS registry number: 15687-27-1

Molecular formula/molecular weight: C₁₃H₁₈O₂, 206.28

Structure:



Relevant INDs/NDAs/DMFs:

NDA#	Drug Name	Div	Strength (route)	Marketing Status	AP Date	Indication	Company
17-463	Motrin	DAARP (170)	400, 600, 800 mg (oral tablet)	AP	9/19/1974	Signs and symptoms of rheumatoid arthritis and osteoarthritis mild to moderate pain primary	McNeil Consumer & Specialty Pharmaceuticals

						dysmenorrhea	
20-402	Advil Liqui-gels	560	200 mg (oral capsule)	AP	4/20/1995	Migraine	Wyeth Consumer Healthcare
20-516	Children's Motrin Drops	560	50 mg (oral suspension)	AP	6/16/1995	Fever Reduction and pain relief	McNeil Consumer & Specialty Pharmaceuticals

IND#	Drug	Status	Division	Indication	Stamp Date	Sponsor
62-605	Ibuprofen Injection	Active	DAARP	Antipyretic/Agent in febrile adults and children who can not take oral medication	5/7/2001	Cumberland Pharmaceuticals

DMF#	Subject of DMF	Holder	Submit Date	Reviewer's Comment
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(b) (4)

Drug class: NSAID

Intended clinical population: Adults (b) (4) with fever and pain

Clinical formulation:

Table P.1-1. Composition of Ibuprofen Injection

Presentation		100 mg/mL,			
Strength		100 mg/mL			
Product Description		A clear, colorless to slightly yellow solution.			
	Ref.	Each mL contains	Each 4 mL contains	Each 8 mL contains	Function
Ibuprofen	USP	100 mg	400 mg	800 mg	Active Ingredient
Arginine	USP	78.0 mg	312 mg	624 mg	(b) (4)
WFI	USP	qs 1.0 mL	qs 4.0 mL	qs 8.0 mL	(b) (4)
(b) (4)	USP	-	-		(b) (4)
	NF	-	-		(b) (4)
	NF	-	-		(b) (4)
Container Description		(b) (4)			
		- (b) (4) clear glass vial (400mg presentation)			
		(b) (4) (b) (4) clear glass vial (800mg presentation)			
Closure Description		(b) (4) closure			

All of the above excipients have been used in previously FDA approved drug products via the intravenous route of administration at comparable to higher levels. There are no nonclinical safety concerns with the excipients in this formulation.

Route of administration: Intravenous

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-348 are owned by Cumberland Pharmaceuticals Inc. or are data for which Cumberland Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 22-348 that Cumberland Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that Cumberland Pharmaceuticals does not own (or from FDA reviews or

summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-348.

This is a 505(b)(2) NDA and the sponsor is referencing the Agency's previous findings of safety and efficacy of NDAs 17-463 and 20-516 from McNeil Consumer & Specialty Pharmaceuticals and NDA 20-402 from Wyeth Consumer Healthcare for the non-clinical data.

Studies reviewed within this submission:

A 28-day intravenous or oral toxicity study in beagle dogs

Rabbit vein irritation study

Evaluation of a test article to induce hemolysis in human blood

Evaluation of a test article to induce flocculation in human plasma and serum

Stopper extractables and leachables in ibuprofen for injection

Studies not reviewed within this submission: None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: The sponsor provided a brief summary on the mode of action of ibuprofen. Ibuprofen is a non-selective nonsteroidal anti-inflammatory agent (NSAID) and inhibits COX-1 and COX-2 enzymes.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: The effect of ibuprofen resulted from the inhibition of prostaglandin synthesis. The sponsor submitted literature findings to support that 5 mg infusion of ibuprofen reduced the pyrexia induced by 0.1 ug/kg endotoxins in male Hartley guinea-pigs by about 0.4 to 0.8°C. In another study, a shock-like syndrome of hypotension, pyrexia, leucopenia and thrombocytopenia was induced by IV injections of IL-1 beta (5 ug/kg) or TNF (1 ug/kg) in rabbits. Above changes were partly induced by the release of inducible forms of prostaglandins. Pretreatment with Ibuprofen IV injections at 10 mg/kg prevented hemodynamic changes induced by the cytokines. The effect of ibuprofen on several models of experimental pain and inflammation was discussed also.

Drug activity related to proposed indication: See above

2.6.2.3 Secondary pharmacodynamics: No secondary pharmacology data were provided in the NDA.

2.6.2.4 Safety pharmacology: No new safety pharmacology data were provided in the NDA.

2.6.2.5 Pharmacodynamic drug interactions: No pharmacodynamic drug interaction study was provided in the NDA.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

The sponsor did not conduct any pharmacodynamic study. However, a summary was provided from the published literature. The following table in the sponsor’s submission provides information and sources of the data.

2.6.3.1 Pharmacology Overview

Table 2.6.3.1 Pharmacology Overview					
Overview					Test Article: Ibuprofen
Type of Study	Test System	Method of Administration	Testing Facility¹⁻⁹	Report No./Journal Reference	Location in CTD
Primary Pharmacodynamics					
<i>In Vivo</i>					
Effect of Ibuprofen on Fever and Metabolic Changes Induced by Continuous Infusion of Leukocytic Pyrogen (Interleukin 1) or Endotoxin	Hartley guinea pigs	60-Minute intravenous infusion	1/2	Sobrado, 1983	4.3
Shock like State in Rabbits Induced by Interleukin 1	New Zealand rabbit	Intravenous	3/4/5	Okazawa, 1988	4.3
Pharmacological Evaluation of Mild Analgesics	Mouse, rat, guinea pig	Oral, subcutaneous	6	Romze, 1980	4.3
A Rapid Method for Evaluation of Analgesin and Anti-Inflammatory Activity in Rats	Wistar strain albino rats	Oral gavage	7	Rao, 1991	4.3
Inflammation-Induced Reduction of Spontaneous Activity by Adjuvant: A Novel Model to Study the Effect of Analgesics in Rats	Sprague-Dawley rats	Oral	8	Marsou, 2007	4.3
An Evaluation of Analgesic Regimens for Abdominal Surgery in Mice	Mice C57BL/6J	Oral (drinking water)	9	Hayes, 2000	4.3
1. Nutrition Metabolism Laboratory, Cancer Research Institute, New England Deaconess Hospital, Harvard Medical School, Boston, Massachusetts 2. Division of Experimental Medicine, Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts 3. Department of Medicine, Division of Geographic Medicine and Infectious Diseases, Tufts University and New England Medical Center Hospital, Boston, Massachusetts 4. Department of Surgery, Trauma Service, Massachusetts General Hospital, Boston, Massachusetts 5. Department of Surgery, New England Medical Center Hospitals, Boston, Massachusetts 6. Preclinical Research Department, Pharmaceutical Division, Sandoz AG, Basel, Switzerland 7. Department of Pharmacology, IDPL Research Centre, Hyderabad, India 8. Dep. Of Pharmacology, Biochemistry, and Molecular Biology, Neurogen Corporation, Farmford, Connecticut 9. Animal Resources Center, St. Jude Children’s Research Hospital, Memphis, TN 38163					

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: PK data are summarized under individual study reports.

2.6.4.2 Methods of Analysis: Ibuprofen was extracted from the plasma by liquid/liquid extraction and assayed by HPLC using UV detection.

2.6.4.3 Absorption: The drug is administered by IV injections. Therefore, there was no absorption issue related to the product.

2.6.4.4 Distribution: No distribution study was submitted to the NDA.

2.6.4.5 Metabolism: No distribution study was submitted to the NDA.

2.6.4.6 Excretion: No distribution study was submitted to the NDA.

2.6.4.7 Pharmacokinetic drug interactions: No drug interaction study was submitted in the NDA.

2.6.4.8 Other Pharmacokinetic Studies: None

2.6.4.9 Discussion and Conclusions: See overall discussion and conclusion

2.6.4.10 Tables and figures to include comparative TK summary

There were no tables supplied by the Sponsor of this NDA.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Summary of toxicokinetic data are provided in the individual study reports. In addition, plasma protein binding of ibuprofen in several animal species was summarized by the sponsor in the following table.

2.6.5.6 Pharmacokinetics: Plasma Protein Binding

Table 2.6.5.6 Pharmacokinetics: Plasma Protein Binding				Test Article: Ibuprofen
Study system: Rat plasma, dog plasma				
Target entity, Test system and method: Not reported				
				Location in CTD
Species	Conc. tested	% Bound	Report No./Journal Reference	
Rat (plasma)	≤ 100 µg/mL	> 90%	Davies, 1971	4.3
Dog (plasma)	≤ 100 µg/mL	> 90%	Davies, 1971	4.3
Dog (serum)	20 and 50 µg/mL	96% at both concentrations	Scherkl, 1987	4.3

2.6.6 TOXICOLOGY**2.6.6.1 Overall toxicology summary**

See overall discussion and conclusion for toxicity to the ibuprofen injection.

2.6.6.2 Single-dose toxicity

No single dose toxicity study was conducted for the NDA. However, a summary of published data provided by the sponsor suggested that acute toxicity was about 800 and 1600 mg/kg/oral in mice and rats, respectively. GI toxicity was noted in acute toxicity studies. The following table provided by the sponsor summarized acute toxicity to ibuprofen.

Species (Strain)	Route of Administration	LD ₅₀ (mg/kg bw)	Symptoms of Toxicity	Reference
Mouse (not specified)	Oral	800	Prostration. Death occurred within 3 days from perforated gastric ulcer.	Adams (1969)
Mouse (albino)	Intraperitoneal	320	Prostration. Death occurred within 3 days from perforated gastric ulcer.	Adams (1969)
Rats (not specified)	Oral	1600	Sedation, prostration, loss of righting reflex and labored respiration.	Adams (1969)
Rats (not specified)	Oral		Delayed death observed at 1,600 mg/kg during days 1 to 6. Death between 4 to 8 days for 1,000 mg/kg.	Elliott (1988)
Rats (not specified)	Subcutaneous	1300	Sedation, prostration, loss of righting reflex and labored respiration. Death occurred within 3 days from intestinal ulceration	Adams (1969)
Rats (not specified)	Intraperitoneal	400	Death after 2 days following administration. Abdominal adhesions at both doses (320 and 400 mg/kg)	Elliott (1988).
Rats (not specified)	Intravenous	Not specified	Gastric and intestinal ulcers/erosion were observed at 270 and 530 mg/kg.	Elliott (1988).
Rats (Long-Evans)	Intravenous and oral	Not specified	Greater toxicity by the oral route <i>versus</i> intravenous route. Mild prostration, slight motor incoordination and dyspnea observed 10 -20 minutes following iv at 100 and 150 mg/kg. These CNS effects not observed following oral administration at same doses	Cioli (1979)

2.6.6.3 Repeat-dose toxicity

Study title: A 28-day intravenous or oral toxicity study in beagle dogs

Key study findings: Liquid feces were observed at 15 mg/kg/day/IV and higher doses. Kidney inflammation was noted at 15, 30 and 45 mg/kg/day/IV. The GI histopathology was restricted to 45 mg/kg doses. NOEL was not established. The highest dose tolerated was 45 mg/kg/day.

Study no.: 2001-4932

Volume # M4 and page #: 1

Conducting laboratory and location^{(b) (4)}

Date of study initiation: Jan 3, 2003

GLP compliance: Yes

QA report: yes (x) no ()

Drug: Ibuprofen, lot # L019420, and % purity: Purity of the injection solution was 100.5% for ibuprofen as stated in the certificate of analysis, individual impurity was

(b) (4) and total impurities were (b) (4) The injection was 100 mg/mL. The certificate of analysis from the sponsor's submission is shown below.

(b) (4)



Oral dosing was done by using commercially available pediatric suspensions at 20 mg/mL. The Batch # for pediatric suspensions was FEM123 and FEM053.

Methods

Doses: There were five dose groups as shown below. The control animals received IV injections of saline. However, there was no control group for the oral dose. The study design is shown from the sponsor's table.

Group (Route of Administration)	Dose Conc. (mg/ml)	Dose Volume (mL/kg/admin.)	Total Dose Volume (mL/kg/day)	Dose Level (mg/kg/admin.)	Total Dose Level (mg/kg/day)	Number of Animals	
						Males	Females
1. Control (i.v.)	0	3.75	11.25	0	0	3	3
2. Ibuprofen (i.v.)	4	1.25	3.75	5	15	3	3
3. Ibuprofen (i.v.)	4	2.50	7.5	10	30	3	3
4. Ibuprofen (i.v.)	4	3.75	11.25	15	45	3	3
5. Ibuprofen (p.o.)	20	0.75	2.25	15	45	3	3

Admin=administration; Conc=concentration; i.v.=intravenous; p.o.=per os;

Group 1 (Control) animals received only the vehicle (0.9% Sodium Chloride for Injection, USP).

Group 5 animals received Motrin's Pediatric Formulation.

The doses were selected on the basis of a dose finding study that showed fecal occult blood at 20 mg/kg/IV tid regimen.

Species/strain: Beagle dogs

Number/sex/group or time point (main study): see study design

Route, formulation, volume, and infusion rate: Slow intravenous bolus injections in sterile 0.9% sodium chloride solution. Injections were made three times daily at 4-hour intervals in cephalic or saphenous veins. The stability and content of ibuprofen in 4.0 and 20.0 mg/mL of dosing solutions were verified by analytical methods. Data showed that ibuprofen contents from several layers of the solution from samples used on injection days 1 and 28 were between 89.8 to 99.8% of the nominal concentrations. The control animals received the saline.

Oral gavage doses were given three times daily at every 4-hour intervals. The dose volumes were between 0.75 to 3.75 mL/kg for groups 1 to 5. The dosage groups are shown in the study design.

Satellite groups used for toxicokinetics or recovery: Main study animals were used for toxicokinetics, there was no recovery groups.

Age: Dogs were 8-11 months old at the beginning of dosing.

Weight: The body weight of male dogs was between 9.4 to 11.2 kg and that for female dogs was 7.3 to 11.4 kg.

Sampling times: Blood samples were collected at predose and before necropsy for hematology, coagulation and blood chemistry. About one mL of blood samples were collected on the study day 1 and 27 at several time points from groups 2-5 for the toxicokinetics.

Unique study design or methodology (if any): nil

Observations and times:

Mortality: Mortality and clinical signs were observed 1-2 times daily. Animals were examined at pretreatment and prior to first dosing on each day.

Clinical signs: see above

Body weights: The body weight was recorded at pre treatment, once weekly and before the necropsy.

Food consumption: The food consumption was recorded daily at pretreatment and during the treatment period.

Ophthalmoscopy: Not examined

EKG: Not recorded

Hematology: Hematology and coagulation was conducted at pretreatment and at necropsy using standard parameters.

Clinical chemistry: Standard parameters of clinical chemistry were measured at pretreatment and at the end of treatment period.

Urinalysis: Urine samples were collected for 16 hours before the initiation of treatment and before necropsy.

Gross pathology: All animals were euthanized on day 29 by overdose with IV sodium pentobarbital. External surfaces and internal organs were examined for any gross changes.

Organ weights (specify organs weighed if not in histopath table): Protocol specified organ weights were recorded. Organs were fixed in 10% formalin. Lungs were infused with formalin for fixation. Bone marrow smears were stained with Wright's stain to examine erythroid and myeloid cells. Histopathological examinations were done following hematoxylin and eosin staining of slides. The sponsor stated that histopathological examinations of 3 sections around the injection site were conducted.

Histopathology: Adequate Battery: yes (x), no ()—explain

Peer review: yes (), no (x)

Results

Mortality: No ibuprofen-related mortality was reported in the study.

Clinical signs: Salivation and black feces were observed from day 2 at 45 mg/kg/IV dose. Liquid feces were also observed at 15, 30 mg/kg/IV and 45 mg/kg/oral doses. Swelling and redness was noted in the injection site in control and treated animals.

Body weights: No treatment related change in the average body weight was noted in the male and female dogs.

Food consumption: Data on average food consumption (g/day) on day 1 and day 28 are shown below. Data suggest that the food consumption was reduced at 45 mg/kg dose in male and female dogs. Male dogs also showed a reduction in the food consumption at 15 and 30 mg/kg/IV when compared to the control.

Group	Sex	Day 1	Day 28	Difference
1	M	212	324	+112
2	M	273	281	+8
3	M	345	214	-129
4	M	270	226	-44

5	M	303	222	-81
1	F	308	313	+5
2	F	204	288	+84
3	F	204	211	+7
4	F	261	210	-51
5	F	361	245	-116

Hematology: Hematology data did not show treatment related change in male and female animals. However, the sponsor stated that Male 4002D at 45 mg/kg/IV showed a reduction in the RBC parameters. A reduction in the RBC counts due to NSAID treatment is a known toxicity of this group of drugs. However, the average data did not show any significant trend to the RBC counts. Coagulation parameters were also not affected by the treatment.

Clinical chemistry: No treatment related change in the clinical chemistry parameters was noted in male and female dogs.

Urinalysis: Group 5 male dogs showed 0.15/L protein in the urine at terminal sacrifice. However, it was not treatment related because one control male dog also showed a similar level of protein in the urine. Blood cells were also present in the control and treated male dogs at terminal sacrifice.

A similar data were reported for female dogs. Based on the data, it was concluded that there was no treatment related change in the urine chemistry in the male and female dogs.

Gross pathology: Dark foci in the GI tract in control and treated animals were observed. The injection site inflammation was also observed in the control and groups 2-4 dogs.

Organ weights (specify organs weighed if not in histopath table):

Some of the organ weight data are shown below.

Organ, Sex	Gr 1	Gr 2	Gr 3	Gr 4	Gr 5
Liver (g), M	280	291	314	303	327
Spleen (g), M	82	49.4	74.0	51	55
Thymus, M	2.6	4.3	5.4	3.1	7.1
Thyroid (g), M	1.0	1.0	0.84	0.97	0.63
Liver (g), F	275	255	264	256	279
Spleen (g), F	43.7	80	53	42	63.7
Thymus (g), F	4.0	7.8	7.7	4.0	7
Thyroid (g), F	0.65	0.74	0.53	0.7	0.9

Histopathology: Adequate Battery: yes (x), no ()—explain
Peer review: yes (), no (x)

Some of the histopathology changes are shown in the table below.

Male dogs:

Lesion	Control, M	15 mg/kg/day, M	30 mg/kg/day, M	45 mg/kg/day, M	45 mg/kg/day/po, M
*Injection site, left cephalic, inflammation, intimal proliferation and thrombosis	6	6	4	4	0
*Injection site, left saphenous, inflammation, intimal proliferation and thrombosis	5	4	4	5	0
*Injection site, right cephalic, inflammation, intimal proliferation and thrombosis	5	8	5	4	0
*Injection site, right saphenous, inflammation, intimal proliferation and thrombosis	5	5	5	5	0
Kidney, glomerular and interstitial inflammation	0	0	1	2	0
Kidney, tubular necrosis	0	1	0	0	0
Lymph node, pancreatic, hemorrhage	0	0	2	2	2
Stomach, ulcer, necrosis	0	0	0	0	1
Thymus lymphoid atrophy	0	0	0	1	0

*= total incidences

Based on the data, injection site inflammation was related to the procedure and did not reflect the drug toxicity in male dogs. Kidney glomerular and interstitial inflammation was noted at 30 and 45 mg/kg/day/IV. One animal at 15 mg/kg/day/IV showed necrosis in the kidney. However, no GI toxicity was noted up to 45 mg/kg/day/IV. The oral dose of 45 mg/kg/day showed necrosis of stomach.

Female dogs:

Lesion	Control, F	15 mg/kg/day/IV, F	30 mg/kg/day/IV, F	45 mg/kg/day/IV, F	45 mg/kg/day/IV, F
*Injection site, left cephalic, inflammation and thrombosis	6	4	6	5	0
*Injection site, left saphenous, Inflammation and thrombosis	3	4	5	6	0
*Injection site, right cephalic, inflammation and thrombosis	4	3	4	6	0
*Injection site, right saphenous vein, inflammation and thrombosis	7	6	4	4	0
Kidney, tubular dilatation	0	0	1	2	1
Stomach, erosion, ulceration	0	0	0	1	0

*= total incidences

Data suggest that like male dogs, female dogs showed injection site inflammation that could be due to the procedure as similar findings were noted in the control animals.

Stomach erosion was noted at 45 mg/kg/day/IV due to NSAID toxicity. Kidney tubular dilatation was observed at 30 and 45 mg/kg/day/IV and 45 kg/day/oral.

Toxicokinetics:

Table 1. Mean (SD) Ibuprofen Toxicokinetic Parameters after Multiple Ibuprofen Doses of 15, 30, and 45 mg/kg/day (Groups 2, 3, and 4, Respectively, i.v.), and 45 mg/kg/day (Group 5, p.o.) were Administered and Divided into Three Daily Doses.

Parameter*	Female Dogs		Male Dogs	
	Day 1	Day 27	Day 1	Day 27
Group 2				
T_{max} (h)	4.08 ± 0.00	4.08 ± 4.00	4.08 ± 0.00	4.08 ± 0.00
C_{max} (µg/mL)	49.910 ± 1.076	46.348 ± 1.974	44.363 ± 3.324	41.605 ± 5.130
$AUC_{0-\infty}$ (µg·h/mL)	332.4 ± 42.2	297.4 ± 16.6	283.4 ± 21.3	270.9 ± 39.3
$t_{1/2}$ (h)	2.7 ± 1.4	1.9 ± 0.9	2.6 ± 1.2	2.1 ± 1.2
Group 3				
T_{max} (h)	2.75 ± 2.31	2.75 ± 2.31	4.08 ± 0.00	4.08 ± 0.00
C_{max} (µg/mL)	83.429 ± 6.218	74.945 ± 12.940	79.604 ± 10.809	73.230 ± 4.738
$AUC_{0-\infty}$ (µg·h/mL)	589.6 ± 59.1	521.6 ± 107.6	562.4 ± 83.8	506.0 ± 52.7
$t_{1/2}$ (h)	3.2 ± 0.5	3.4 ± 0.4	3.1 ± 0.2	3.7 ± 0.7
Group 4				
T_{max} (h)	4.08 ± 0.00	4.08 ± 0.00	2.75 ± 2.31	4.08 ± 0.00
C_{max} (µg/mL)	102.101 ± 9.160	92.075 ± 6.529	94.801 ± 6.292	84.734 ± 17.044
$AUC_{0-\infty}$ (µg·h/mL)	848.0 ± 56.2	727.9 ± 19.0	717.4 ± 62.4	595.9 ± 124.9
$t_{1/2}$ (h)	4.2 ± 1.0	4.6 ± 1.9	3.1 ± 0.7	2.7 ± 0.8
Group 5				
T_{max} (h)	5.67 ± 3.51	4.33 ± 4.04	4.33 ± 4.04	4.33 ± 4.04
C_{max} (µg/mL)	43.316 ± 3.172	38.158 ± 2.358	48.723 ± 6.283	39.782 ± 9.577
$AUC_{0-\infty}$ (µg·h/mL)	539.4 ± 123.2	413.4 ± 51.2	565.5 ± 102.1	427.1 ± 49.4
$t_{1/2}$ (h)	4.7 ± 2.2	3.2 ± 0.6	3.9 ± 0.9	3.7 ± 0.8

* Time to reach maximum concentration (T_{max}), maximum observed concentration (C_{max}), and area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$) were calculated for the entire 24-hr sampling intervals on Days 1 and 27.

Note: Parameters were not estimated for Group 1 because those animals received normal saline as a vehicle control and none of the plasma samples had measurable ibuprofen concentrations.

Above data suggest that ibuprofen exposure was increased with doses and did not accumulate over the period of study. The exposure from the oral dose was less than that from the IV doses.

Summary of the study: Beagle dogs were injected with 15, 30 and 45 mg/kg/day/IV and 45 mg/kg/day/PO doses of ibuprofen for 28 days. Toxicity and PK parameters were evaluated. No mortality was noted. NOEL was not established in the study. The highest dose tolerated was 45 mg/kg. GI and kidney is target organ of toxicity. Liquid feces were observed in treated dogs. The toxicity profile observed in the study was common to NSAIDs. Injection site inflammation was noted in the control and treated animals. Data do not suggest that injection site reactions were due to ibuprofen itself.

Histopathology inventory (optional)

Study	28-day
Species	Beagle Dog
Adrenals*	x
Aorta	x
Bone Marrow smear	x
Bone (femur)	x
Brain*	x
Cecum	x
Cervix	
Colon	x
Duodenum	x
Epididymis	x
Esophagus	x
Eye	x
Fallopian tube	
Gall bladder	x
Gross lesions	x
Harderian gland	
Heart*	x
Ileum	x
Injection site	x
Jejunum	x
Kidneys*	x
Lachrymal gland	x
Larynx	
Liver*	x
Lungs*	x
Lymph nodes, inguinal	
Lymph nodes mandibular	x
Lymph nodes, mesenteric	x
Mammary Gland	x
Nasal cavity	
Optic nerves	x
Ovaries	x
Pancreas	x
Parathyroid	
Peripheral nerve	
Pharynx	
Pituitary*	x
Prostate*	x
Rectum	
Salivary gland	x
Sciatic nerve	x
Seminal vesicles	
Skeletal muscle	x
Skin	x
Spinal cord	x
Spleen*	x

Study	28-day
Sternum	x
Stomach	x
Testes	x
Thymus*	x
Thyroid*	x
Tongue	x
Trachea	x
Urinary bladder	x
Uterus*	x
Vagina	x
Zymbal gland	

X, histopathology performed

*, organ weight obtained

Study Title: A 28-day intravenous toxicity study in beagle dogs (Study # 2000-3042)

This study was reviewed under IND 62,605 on June 6, 2001 by Dr. Conrad Chen. The dose was 1, 5 and 15 mg/kg/day/IV and 15 mg/kg/day/oral in beagle dogs. Loose stool was noted at 5 and 15 mg/kg in the absence of GI and kidney lesions that were noted in the other toxicity study (2001-4932) reviewed above. The data suggest that 15 mg/kg/day/IV was tolerated with GI upset. However, NOEL was 1 mg/kg/Day/IV, corresponding C_{max} and AUC were 3.5 ug/mL and 20 ug.hr/mL, respectively as shown from the sponsor's table below.

Table 1. Mean (SD for N>2) Ibuprofen Toxicokinetic Parameters After Multiple Ibuprofen Doses of 1, 5, and 15 mg/kg/day (Groups 2-4, Respectively) Administered Intravenously, and 15 mg/kg/day (Group 5) Administered Orally Divided in Three Daily Doses.

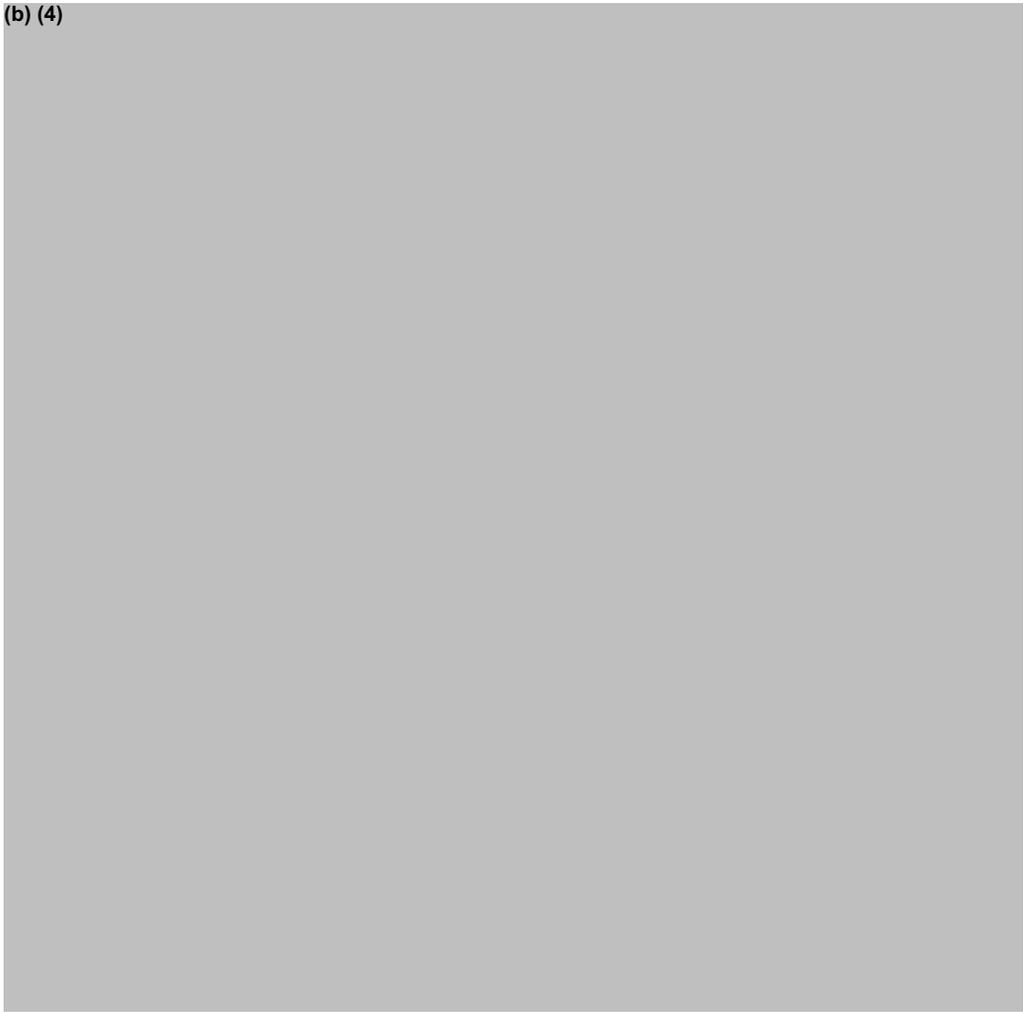
Parameter*	Female Dogs		Male Dogs	
	Day 1	Day 27	Day 1	Day 27
Group 2				
T _{max} (hr)	4.08 ± 0.00	4.09 ± 0.02	4.08 ± 0.00	4.09 ± 0.01
C _{max} (µg/mL)	4.040 ± 0.416	3.416 ± 0.438	3.896 ± 0.227	3.557 ± 0.472
AUC _{0-∞} (µg·hr/mL)	25.5 ± 0.9	20.0 ± 2.9	21.9 ± 1.3	20.0 ± 2.7
t _{1/2} (hr)	1.7 ± 0.3	1.3 ± 0.1	1.3 ± 0.1	1.1 ± 0.1
Group 3				
T _{max} (hr)	4.08 ± 0.00	4.08 ± 0.00	4.08 ± 0.00	4.08 ± 0.00
C _{max} (µg/mL)	19.127 ± 0.921	17.958 ± 0.217	18.324 ± 2.137	16.677 ± 1.761
AUC _{0-∞} (µg·hr/mL)	141.1 ± 23.8	121.9 ± 30.7	111.7 ± 5.8	102.2 ± 4.5
t _{1/2} (hr)	4.4 ± 2.1	2.4 ± 1.6	2.6 ± 1.7	1.2 ± 0.4
Group 4				
T _{max} (hr)	4.08 ± 0.00	5.42 ± 2.32	4.08 ± 0.00	2.08
C _{max} (µg/mL)	49.884 ± 3.936	43.301 ± 8.438	46.412 ± 0.85	51.646
AUC _{0-∞} (µg·hr/mL)	351.7 ± 16.4	335.9	352.3 ± 66.4	335.6
t _{1/2} (hr)	4.6 ± 1.0	4.0 ± 2.2	4.4 ± 1.5	3.5
Group 5				
T _{max} (hr)	7.00 ± 1.73	5.67 ± 3.51	4.67 ± 2.31	4.67 ± 2.31
C _{max} (µg/mL)	17.980 ± 4.055	17.445 ± 3.349	14.907 ± 2.097	19.358 ± 2.217
AUC _{0-∞} (µg·hr/mL)	167.6 ± 73.2	165.0 ± 51.0	172.7 ± 44.2	163.0 ± 23.8
t _{1/2} (hr)	3.3 ± 0.00	3.3 ± 0.5	4.5 ± 1.4	3.5 ± 1.0

* Time to reach maximum concentration (T_{max}), maximum observed concentration (C_{max}), and area under the concentration-time curve extrapolated to infinity (AUC_{0-∞}) were calculated for the entire 24-hr sampling interval.

Note: No parameters were estimated for Group 1 because those animals received normal saline as a control and none of the dogs had measurable ibuprofen concentrations.

The certificate of analysis from the sponsor's submission is shown below.

(b) (4)



2.6.6.4 Genetic toxicology

The sponsor did not conduct any new genotoxicity studies. However, the summary indicated publications by Oldham 1986 and Philipose 1997 that ibuprofen was not positive in the Ames assay in the absence or presence of hepatic metabolic activation. Sister chromatid exchange (SCE) study showed a positive response at 50, 100 mg/kg/ip or 270 mg/po.

2.6.6.5 Carcinogenicity

The sponsor did not conduct any carcinogenicity studies for ibuprofen. However, the sponsor referenced the work of Adams 1970 up to 300-100 mg/kg/oral for a total of 80 weeks in mice. Rats were treated up to 180-60 mg/kg/oral for 2 years. No treatment carcinogenicity was reported.

The application is for 505(b)(2) and referenced already approved NDAs for ibuprofen. Based on that fact, the information from approved package inserts as referenced would be used for the label of the product.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

The sponsor did not conduct any reproductive and developmental toxicity studies for the NDA. However, they summarized several literature findings that suggested ibuprofen contributed to still births and dystocia in pregnant rats. No teratogenicity was observed in rats and rabbits. The effect of ibuprofen in pregnancy was due to the inhibition of PG synthesis. A standard language for NSAIDs for reproductive safety would be provided as a warning to the use of ibuprofen injections in pregnant women.

Embryofetal development

No new study for ibuprofen injection was submitted in the NDA.

Prenatal and postnatal development

No new study for ibuprofen injection was submitted in the NDA.

2.6.6.7 Local tolerance:

Study title: Rabbit vein irritation study

Key study findings: Necrosis at the injection site at 20 mg/kg and higher doses was observed. Ibuprofen was tolerated with erythema and edema at the injection site in rabbits after a single injection. Arginine vehicle contributed to the irritancy. Therefore, the product has irritancy potential.

Study no.: 0452LC65.001

Volume #M4, and page #: 1

Conducting laboratory and location: (b) (4)

Date of study initiation: July 11, 2001

GLP compliance: Yes

QA reports: yes (x) no ()

Drug: Ibuprofen, lot # LPL-7247, and % purity: On file, not provided in the report. Since the tolerability to the injection was examined in the clinical study and the repeat dose dog study, lack of this information is not critical to the approval of the product.

Formulation/vehicle: Ibuprofen was dissolved into arginine HCl solution. Ibuprofen solutions were prepared at 1.6 mg/mL, 4.0 mg/mL, and 100 mg/mL. Solutions showed

96.84 to 100.03% of the label claim with respect to the concentration. The sponsor did not provide the arginine concentration.

Methods

Doses: See table below.

Study design: Male New Zealand white rabbits (HM:NZW, fBR) were used in the study. Rabbits weighed 2.2 to 2.8 kg and 13 weeks old. There were 5 groups in the study. The study design is from the sponsor's table below.

Group	Number/Group	Dose (mg/kg)*		Sacrifice Time (hr)**
		Left Ear	Right Ear	
1	6	Arginine HCl	0.9% NaCl	1, 24
2	3	1.6 (pH 7.4)	20 (pH 7.4)	1
2	3	1.6 (pH 7.4)	100 (pH 7.4)	24
3	4	1.6 (pH 7.6)	20 (pH 7.6)	1, 24(1)
3	2	1.6 (pH 7.6)	100 (pH 7.6)	24 (2)
4	6	1.6 (pH 7.8)	20 (pH 7.8)	1, 24
5	6	4 (pH 7.6)	4 (pH 7.8)	1, 24

* Dose volume was 1 ml/kg with the exception of the right ear of all 1 hr sacrifice animals in Groups 2 and 3, one 24 hr sacrifice animal in Group 3, and all animals in Group 4 which were dosed at a volume of 0.2 ml/kg.

** 3 rabbits sacrificed/group/timepoint, except as noted

Injections were given into the ear vein after removing hair adjacent to the vein. The injection site was evaluated macroscopically at 1, 4 and 24 hour post injections. The irritation was scored using Draize's score as shown below from the sponsor's table. Animals were sacrificed by lethal injections at the end of 1 or 24 hours post injections for evaluation of histopathological changes in the ear and permeability changes in the vessels in the ear. Rabbits were injected with Evan's blue dye and sacrificed 30 min late by IV injections of a barbiturate. Both ears were excised, veins were examined for the recording of intensity of dye retention using a 0-4 score (0= none, 4=marked). Injection site and adjacent area was fixed in 10% formalin for histopathology.

TABLE 2
Rabbit Vein Irritation Study
Ibuprofen
Study Number: 0452LC65.001
Cumberland Pharmaceuticals
Draize Evaluation of Dermal Irritation
Copyright Information



¹ Draize, J.H. 1959. The Appraisal of Chemicals in Foods, Drugs and Cosmetics, pp. 36-45. Association of Food and Drug Officials of the United States, Austin, Texas.

Results: Clinical observations in animals treated with ibuprofen in arginine or saline vehicle showed no change due to the injection site at 1, 4 and 24 hour post dose.

Group 2 animals that received 20 or 100 mg/kg at pH 7.4 showed mortality to # 3071 (100 mg/kg) immediately after the injection. Purple discoloration was noted at 20 mg/kg, pH 7.4 within one hour observation. However, at 100 mg/kg pH 7.4, ibuprofen injection showed purple discolors at 24 hour but not at 1 and 4 hour. Ibuprofen at 1.6 mg/kg/IV did not show purple discoloration in the clinical observation.

The group 3 animals showed purple discoloration at 20 or 100 mg/kg, pH 7.6 at 1 and 24 hour. Animal # 3077 was found dead at 100 mg/kg immediately after the injection. In the absence of untoward effects in any other animals, the death was considered unrelated to the treatment. Ibuprofen injection at 1.6 mg/kg/IV, pH 7.6 did not show purple coloration in the ear.

The effect of IV injections of ibuprofen at 20 mg/kg, pH 7.8 was similar to that when the pH was 7.4 or 7.6. Ibuprofen injections at 1.6 mg/kg, pH 7.8 did not show purple color at 1 and 24 hour post dose.

The sponsor tested 4 mg/kg ibuprofen solutions at pH 7.6 or pH 7.8. Data showed a slight purple mottling at 4 mg/kg of ibuprofen. NOEL for clinical observation was 1.6 mg/kg.

No other clinical sign was reported. The body weight was not affected by the treatment. Based on the data, it is concluded that ibuprofen injections at 20 or 100 mg/kg showed purple color in the ear irrespective of the pH. Ibuprofen at 1.6 mg/kg did not contribute to the clinical observation in ears. These observations were different from the irritancy scoring using Draize's scores.

A summary of the results for The Draize's test for irritancy reported as erythema and edema are shown below.

Group	Observation
1	Slight erythema and no edema were noted at one hour post dose when arginine was given. Saline injection showed a slight erythema at 1 hour and no edema.
2	20 or 100 mg/kg ibuprofen at pH 7.4 showed moderate erythema, slight to moderate edema at 1 and 24 hours post dose. Ibuprofen at 1.6 mg/kg showed a slight erythema immediately after the injection and did not show edema.
3	The observation at 20 or 100 mg/kg, pH 7.6 was similar to that for pH 7.4 with respect to erythema and edema. Ibuprofen at 1.6 mg/kg, pH 7.6 Showed a slight erythema and no edema.
4	Slightly higher severity of erythema was noted at 20 mg/kg at 1 and 24 hour post injection at pH 7.8. Ibuprofen at 1.6 mg/kg showed a slight erythema at 1 hour and no edema.
5	Ibuprofen at 4 mg/kg/IV and pH 7.8 also showed slight erythema and edema when compared to very slight erythema and edema at pH 7.6

The result of Draize test of irritation suggests that ibuprofen showed erythema and edema at 20 or 100 mg/kg at 1 hour post dose that lasted up to 24 hour. However, increase in the pH from 7.4 to 7.8 also increased the severity of erythema and edema. Based on the data from Draize's test it was concluded that 20 or 100 mg/mL solutions of ibuprofen was irritant to IV injections. The NOEL for Draize test was 1.6 mg/kg considering a slight erythema observed with the vehicle.

The dye accumulation in the ear was examined visually under a dissecting microscope. Evan's blue dye binds to albumin and the complex accumulated in the extra-vascular space due to capillary permeability change. The intensity of dye accumulation reflects capillary permeability change. Following observations were made with respect to the intensity of the dye at necropsy.

Group	Observation
1	Arginine injection showed mild to moderate dye accumulation up to 1 hour post dose and the dye accumulation became minimal at the end of 24 hour

Group	Observation
	post dose. Saline injection did not show dye accumulation.
2	Ibuprofen injection at 1.6 mg/kg/IV, pH 7.4 showed marked dye accumulation at 1 hour post dose and no dye accumulation was noted at 24 hour post dose. Ibuprofen injection at 100 mg/kg/IV, pH 7.4 also showed a moderate to marked dye accumulation at 24 hour post dose. Ibuprofen at 20 mg/kg/IV did not show any dye accumulation at 1 hour post dose.
3	Ibuprofen 1.6 mg/kg/IV at pH 7.6 showed moderate dye accumulation at 1 hour post dose and reduced to minimal at the end of 24 hour. Ibuprofen at 20 mg/kg/IV, pH 7.6 showed a minimal dye accumulation at 1 and 24 hour post dose. However, ibuprofen at 100 mg/kg/IV, pH 7.6 showed marked dye accumulation at 24 hour post dose.
4	Ibuprofen at 1.6 mg/kg/IV, pH 7.8 showed minimal to moderate dye accumulation that was persistent at 1 and 24 hour post dose. Ibuprofen at 20 mg/kg/IV and pH 7.8 showed minimal to mild dye accumulation at 24 hour post injection.
5	Ibuprofen at 4 mg/kg/IV at pH 7.8 showed no dye accumulation at 1 and 24 hour post dose. However, minimal to mild intensity of dye accumulation was noted at 4 mg/kg, pH 7.6

Above data for dye accumulation into the ear suggested that arginine contributed to dye accumulation within one hour post injection. The intensity and duration of dye accumulation was increased at 100 mg/kg. Considering the effect of arginine in this experiment, it was considered that up to 20 mg/kg/IV did not increase the dye accumulation.

Therefore, IV injections of ibuprofen would induce permeability change to the vascular bed at 100 mg/kg/IV.

Histopathology:

Procedure related changes e.g. acute hemorrhage and congestion was noted in saline, arginine and ibuprofen injected ears. However, regional necrosis of the ear was noted at 1 and 24 hour post injections of ibuprofen at 20 and 100 mg/kg, pH 7.4 and 7.6. Regional necrosis of the ear was not present at 4 mg/kg/IV ibuprofen.

It was concluded that necrosis of the injection site was noted in rabbits following a single dose at 20 or 100 mg/kg of ibuprofen in the vein irritation study. A slight erythema and edema would be expected up to 4 mg/kg that contributed due to irritancy of ibuprofen and arginine vehicle.

2.6.6.8 Special toxicology studies

Study Title: Evaluation of a test article to induce hemolysis in human blood (study # 0725XC65.001)

The study was conducted at ^{(b) (4)} according to GLP.

Hemolytic potential of ibuprofen injections was determined at 1.6, 4.0 and 100 mg/mL. One mL of the test article, saline or water was mixed with one mL of the blood collected from healthy volunteers and incubated for 45 min at 37°C. The mixture was centrifuged and hemoglobin content of the supernatant was determined by spectrophotometric analysis at 540 nM as a probe to hemolysis.

Data showed that almost a complete hemolysis occurred at 100 mg/mL. No hemolysis was observed at 1.6 or 4.0 mg/mL at pH 7.4 to 7.6. Deionized water also showed 100% hemolysis.

It was concluded that ibuprofen injections at 100 mg/mL, pH 7.4 was not compatible with the whole blood and resulted hemolysis. Data from the sponsor's table are shown below.

TABLE 1**Hemolysis Assay in Human Blood**

Treatment	Concentration	OD ₅₄₀ without Blood	OD ₅₄₀ with Blood	% Hemolysis
Saline	0.9%	-	0.283	0
De-ionized Water	-	-	2.496	100
Ibuprofen Injection	100 mg/ml, pH 7.4	0.057	2.496	97.4
Ibuprofen Injection	1.6 mg/ml, pH 7.4	0.057	0.250	-4.1
Ibuprofen Injection	4.0 mg/ml, pH 7.6	0.057	0.305	-1.6

The sponsor did not use the vehicle of ibuprofen solution as the control. However, absence of hemolysis at lower concentrations suggests that the vehicle did not have any hemolytic effect.

Conclusion: Ibuprofen 100 mg/mL solution induced hemolysis of blood cells in vitro.

Study Title: Evaluation of a test article to induce flocculation in human plasma and serum (study # 0726XC65.001)

The study was conducted at ^{(b) (4)} according to GLP. One mL of ibuprofen injections at 1.6, 4 and 100 mg/mL was mixed with 1 mL of human plasma or serum and incubated for 30 min at room temperature.

The control samples were incubated with saline. Presence of precipitation or coagulation was examined microscopically. Also, samples were centrifuged to determine any precipitation. It was concluded that ibuprofen injections up to 100 mg/mL did not show any precipitation or coagulation of plasma proteins. The result is shown from the sponsor's table below.

TABLE 1**Flocculation Assay in Human Plasma and Serum**

Treatment	Dose (mg/ml)	Plasma			Serum			Saline		
		Macro	Micro	Pellet	Macro	Micro	Pellet	Macro	Micro	Pellet
Saline	-	-	-	-	-	-	-	-	-	-
Ibuprofen Injection	100 mg/ml, pH 7.4	-	-	-	-	-	-	-	-	-
Ibuprofen Injection	1.6 mg/ml, pH 7.4	-	-	-	-	-	-	-	-	-
Ibuprofen Injection	4 mg/ml, pH 7.6	-	-	-	-	-	-	-	-	-

+ = presence of precipitation/coagulation or a pellet
 - = absence of precipitation/coagulation or a pellet

Conclusion: Ibuprofen injections did not show flocculation of the blood proteins.

Study Title: Stopper extractables and leachables in ibuprofen for injection (study # LF-138-R-095-08)

The study was conducted by (b) (4) to analyze and compare extractables from the stopper using ibuprofen injections without stoppers and with stoppers. Extractables were generated under a harsh condition. Ibuprofen injection was manufactured by (b) (4). Each mL of the formulation contained 100 mg of ibuprofen and 78 mg of arginine. The total volume of the solution in each vial was 4 mL with one mL of dead space in the vial. The (b) (4) stoppers provided by (b) (4) were used.

The formulation batches are shown below.

Ibuprofen injection Lot #	Date of manufacturing
K029420	Aug 2000
L019420	Nov 2001
T019420XAA	March 2007

About 20 stoppers were added to 50 mL of ibuprofen solution and refluxed for 30 min. The control contained 20 stoppers in 50 mL of purified water refluxed for 30 min. Extractable and leachables were analyzed by HPLC using UV detectors at various wavelengths.

The sponsor stated that HPLC analysis did not show any peak common to both saline and the drug product under the same experimental conditions signifying that no leachable or extractable organic residues were present. However, [REDACTED] was present.

The sponsor indicated that results were obtained in 2008 from solutions prepared 7 years back. Therefore, results of the study indicated stability of stoppers in the solution for 7 years and lack of leachable/extractable organic substances.

In addition to above data (b) (4) [REDACTED] provided data on (b) (4) [REDACTED] extractables from stoppers using a USP method for cytotoxicity, intracutaneous toxicity and acute systemic toxicity.

Acute systemic toxicity was conducted at (b) (4) [REDACTED]. Following (b) (4) [REDACTED] extraction from stoppers for 72 hours at 50°C. Extracts were injected by in mice by IP and IV routes at 50 mL/kg. All mice survived up to 3 days. The test article was considered to be non-toxic in the USP test. In another study intracutaneous administration in rabbits did not report any adverse reactions up to 72 hours when 0.2 mL of the extract was injected.

The cytotoxicity test was conducted at (b) (4) [REDACTED] using L929 cells in the culture. Extracts incubated in the culture did not show cytotoxicity by microscopic evaluation.

Based on the data from (b) (4) [REDACTED] stopper (b) (4) [REDACTED] extracts were non-toxic.

2.6.6.9 Discussion and Conclusions

The NDA was submitted for the reduction of fever and pain by the IV route of administration with ibuprofen by 100 mg/mL solution at 800 mg Q6 hour up to 3200 mg/day. The solution contains arginine to (b) (4) [REDACTED]. It will be diluted 1:25 with saline or 5% dextrose saline. There are no inactive ingredient safety concerns with the formulation.

General Toxicity: The sponsor submitted two 28-day IV toxicity studies in dogs. Beagle dogs were treated at 5, 10 and 15 mg/kg tid by intravenous injections equal to 15, 30 and 45 mg/kg/day. No treatment related mortality was noted. However, liquid feces and inflammation of the kidney were noted at all doses. GI erosions and ulcers were noted at 45 mg/kg/day. These toxicities are expected from NSAIDs. Since a NOEL was not

observed in the study, the sponsor provided results of a study at 1, 5 and 15 mg/kg/day/IV in beagle dogs. The NOEL was 1 mg/kg/day and NOAEL was 5 mg/kg/day in the second study. GI side effect was noted at 5 mg/kg/day and higher doses. Injection site inflammation and thrombosis was noted in control and treated animals that was related to the procedures. Local tolerance study in rabbit veins showed sign of irritancy, edema and erythema around the vein at 1.6, 20 and 100 mg/kg/IV single dose. The vehicle alone contributed to the local irritancy. Overall the formulation showed irritant effect at local injection sites.

Ibuprofen solution up to 100 mg/mL did not show blood protein flocculation in vitro at 1:1 ratio between the drug product and plasma or serum obtained from humans. A similar study with human whole blood showed hemolysis of red blood cells at 100 mg/mL solutions. However, ibuprofen solution if diluted up to 1:25 or greater (as suggested in the package insert) would not pose hemolysis risks because no hemolysis of red blood cells was detected at 4 mg/mL. One mL of 100 mg/mL solution of ibuprofen is intended to be diluted with 100 mL saline for injection or 5% dextrose-saline for use in patients according to the treatment procedures indicated in the package insert. Irritancy to the solution at the site of injections and inflammation due to the procedure is expected from the clinical uses of ibuprofen injection. Local erythema and edema was observed in the Draize's test that could be due to arginine also.

Drug Substance and Drug Product Impurities: The maximum daily dose of ibuprofen in this drug product 3200 mg. Therefore, as per ICH guidelines Q3A(R) the qualification threshold for drug substance impurities is 0.05% and, as per ICH Q3B(R) the qualification threshold for drug product impurities 0.15%.

The test methods and specifications for the drug product has been recently reviewed by Chemist dated Feb 2, 2009. The chemistry review indicated that (b) (4) was present about (b) (4) or less and needs to be either reduced or qualified according to ICH Q3B (R2) guidelines. It should be noted that such requirements were also discussed in the Pre-NDA meeting dated May 29, 2008. During the review cycle, the Sponsor agreed to lower the impurity specification for the drug product to NMT (b) (4) and therefore have now met the ICH Q3B guidelines for the drug product with a maximum daily dose of >2 grams.

The total maximal clinical dose of ibuprofen would be 3200 mg daily. Considering (b) (4) (b) (4) in the drug substance, the total daily intake of (b) (4) would be (b) (4). However, considering 0.15% impurity limit as set in the ICH guidelines for the drug product and the current drug product in the application, (b) (4) level per day would be (b) (4) in patients.

During the review cycle, the Division reiterated their concern with the drug substance specifications that exceeded ICH Q3A qualification thresholds, stating, "if higher than 0.05% limits are required for any specific identified impurity, submit qualification data." The sponsor provided a response on April 20, 2009. The sponsor stated that the drug product meets the current ICH guidelines, the drug product is used over 30 years and they

intend to work with the manufacturer of the drug substance (b) (4) to limit the impurity to (b) (4) instead of (b) (4). Considering (b) (4) limit for the (b) (4) its maximum daily dose would be (b) (4) in patients (b) (4).

The sponsor conducted a 28-day toxicity study in which the maximum dose was (b) (4). The impurity level was (b) (4), a 10 kg dog was treated at (b) (4) dose of (b) (4). According to the ICH guidelines for the drug product, up to 0.15% of (b) (4) in ibuprofen injection or (b) (4) of (b) (4) would be allowed e.g. 3 x higher than the dose used in dogs could be used. In other words, the existing dog toxicology study did not provide adequate coverage to justify the safety of this impurity at the proposed specification. However, these levels of drug substance (b) (4) do not pose a toxicity risks due to following reasons:

1. Repeat dose toxicity study in dogs did not show any toxicity other than that expected from a NSAID.
2. Lack of any functional groups in (b) (4) that poses a structural alert for mutagenicity.
3. The sponsor indicated that they intend to reduce the spec of (b) (4) to match closely to that in the dog study.

Data for leachables and extractables did not show unusual extractables from the stoppers from batches of drug products made 1 to 7 years before the test.

Based on observations in non-clinical data, the reviewer recommends that CALDOLOR (ibuprofen injection) to be safe for the indication in the parenteral formulation. However, injection site irritation is expected from the formulation.

2.6.6.10 Tables and Figures: None

2.6.7 TOXICOLOGY TABULATED SUMMARY

See review above

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The toxicity profile of the injection in GI, kidney as well as the site of injection was noted in a 4-week intravenous toxicity study in dogs. These toxicities are expected from NSAIDs. The highest dose tolerated was 45 mg/kg/day that was equivalent of 1350 mg/day in humans for a 60 kg subject at equal body surface area between dogs and humans. However, the maximum proposed dose per day is 3200 mg. Therefore, both acute GI and kidney inflammation is expected from the treatment. The label should state the hemolytic potential of the product if used without further dilution as stated in the proposed package insert. This NDA may be approved on the basis of non-clinical toxicity data.

Reviewer: Asoke Mukherjee, Ph.D.

NDA No. 22-348

Unresolved toxicology issues (if any): Nil

Recommendations: From a nonclinical pharmacology toxicology perspective, the NDA may be approved.

APPENDIX/ATTACHMENTS: NIL

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/s/

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