

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201803Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 201803

Supporting Documents: S025
Resubmission to complete response letter

Applicant's letter date: 12/16/2011

CDER stamp date: 12/16/2011

Product: Ibuprofen sodium 256 mg, (ibuprofen 200 mg)

Indication: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular pain, backache, minor pains of arthritis, menstrual cramps, and for the reduction of fever.

Applicant: Pfizer Consumer Healthcare

Review Division: Division of Nonprescription Clinical Evaluation

Reviewer: Cindy Li, Ph.D.

Secondary Reviewers: Paul Brown, Ph.D., ODE IV Associate Director for Pharmacology/Toxicology, OND

Division Director: Andrea Leonard-Segal, M.D.

Project Manager: James Lee, Pharm. D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA 201803) are owned by Pfizer Consumer Healthcare or are data for which Pfizer Consumer Healthcare has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that Pfizer Consumer Healthcare 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 reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

1 Executive Summary

1.1 Introduction

New Drug Application (NDA) 201803 for ibuprofen sodium 256mg was originally submitted by Pfizer Consumer Healthcare (PCH) on July 01, 2010. During the inspection of the manufacturer facility of the finished drug product, FDA field investigator indentified several serious cGMP deviations. A Complete Response letter was sent to the applicant on April 29, 2011 outlining the information needed to resolve these deficiencies. On December 16, 2011, Pfizer submitted the response to the listed deficiencies. The applicant stated that the manufacturer facility of the finished drug product has satisfactory resolved the deficiencies. In support of the applicant's claim, the recommendation filed in the Establishment Evaluation System (EES) is "acceptable".

1.2 Brief Discussion of Nonclinical Findings

The nonclinical information for the present NDA refers to the nonclinical data for Ibuprofen in NDA18989 (Advil®) which is held by Wyeth Consumer Healthcare (now known as Pfizer Consumer Health). A single oral dose rat toxicology comparison study with ibuprofen sodium and Ibuprofen was included in the application submitted in 2010. No nonclinical information was included in the present resubmission. The safety data submitted here were an update to the clinical safety information included in the original NDA submission and included post-marketing clinical data.

The original review of the nonclinical information for this NDA was conducted and completed on February 28, 2011. During the present review, no new nonclinical issues were identified.

1.3 Recommendations

1.3.1 Approvability

There are no approvability issues identified during the present review and **APPROVAL** is recommended for this NDA from the nonclinical perspective.

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/s/

XINGUANG LI
05/03/2012

PAUL C BROWN
05/03/2012

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 201803
Supporting Documents: S001
Applicant's letter date: 06/30/2010
CDER stamp date: 07/01/2010
Product: Advil® (b) (4) tablets and caplets, sodium
ibuprofen dihydrate 256 mg (ibuprofen 200 mg)
Indication: For the temporary relief of minor aches and
pains associated with the common cold,
headache, toothache, muscular pain, backache,
minor pains of arthritis, menstrual cramps, and
for the reduction of fever.
Applicant: Pfizer Consumer Healthcare
Review Division: Division of Nonprescription Clinical Evaluation
Reviewer: Cindy Li, Ph.D.
Secondary Reviewers: Wafa Harrouk, Ph.D., DNCE
Paul Brown, Ph.D., ODE IV Associate Director
for Pharmacology/Toxicology, OND
Division Director: Andrea Leonard-Segal, M.D.
Project Manager: James Lee, Pharm. D.

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1 Executive Summary

1.1 Introduction

Ibuprofen was developed in 1960 by “Laboratoires Boots” for the primary pharmacodynamic properties generally consistent with other non-steroidal anti-inflammatory drugs (NSAIDs): analgesic, antipyretic and anti-inflammatory effects. The present New Drug Application (NDA) was submitted for sodium ibuprofen dehydrate (Na IBU) 256 mg, a fast-acting formulation of Ibuprofen under the trade name Advil® (b) (4) tablets and caplets. Each Na IBU tablet/caplet provides 200 mg of IBU free acid, which is consistent with the currently marketed IBU tablets in the United States.

There is no nonclinical information on this form of ibuprofen except a single oral dose rat toxicology comparison study with Na IBU and Ibuprofen which was conducted for the applicant in support of a non-US regulatory agency. The nonclinical information for the present NDA refers to the nonclinical data for Ibuprofen in NDA18989 (Advil®) which is held by Wyeth Consumer Healthcare (now known as Pfizer Consumer Health).

1.2 Brief Discussion of Nonclinical Findings

In the single dose toxicity study, there were no significant differences in toxicity profiles between Ibuprofen and Na IBU. A No Observed Adverse Effect Level (NOAEL) of 200 mg/kg was established based on the severity, incidence and duration of the toxicity findings (body weight changes, clinical signs, mortalities and necropsy findings) seen among Na IBU-treated rats at 500 and 650 mg/kg when compared to Ibuprofen-treated rats.

1.3 Recommendations

1.3.1 Approvability

Based on the previous human use experience for Ibuprofen, the agency’s previous review of the nonclinical information on Ibuprofen, as well as the lack of novel significant toxicity findings for Na IBU during the current review, the present NDA can be approved from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

None

2 Drug Information

2.1 Drug

CAS Registry Numbers:
31121-93-4

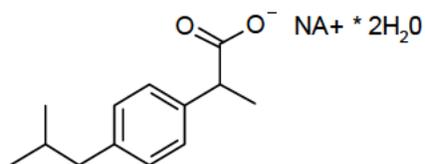
Generic Names:
Advil® (b) (4)

Code Names:
None

Chemical Names:
Sodium 2-(4-isobutylphenyl) propionate dihydrate

Molecular Formulae/Molecular Weights:
C₁₃H₂₁O₄Na /264.29

Structure



Pharmacologic Class
NSAID (non-steroidal anti-inflammatory drug)

2.2 Relevant INDs, NDAs, and DMFs

Motrin IB (NDA 19012), Advil Tablets, Caplets and Gel-Caplets (NDA 18989), Advil Liqui-Gels (NDA 20402), Children's Advil Suspension (NDA 20589 and NDA 19833), and Infant's Advil Drops (NDA 20812).

DMF (b) (4)

DMF (b) (4)

DMF (b) (4)

2.3 Drug Formulation

Advil® (b) (4) Tablets:

Table 1-1 summarizes the composition of Sodium Ibuprofen Tablets, 200 mg and the function of the excipients in the formulation.

Table 1-1: Composition of Sodium Ibuprofen Tablets, 200 mg Drug Product

Ingredient	Grade/Quality Standard	Unit Dose (mg/du)	Function
Sodium Ibuprofen Dihydrate	DMF	256.25	Active Ingredient
Colloidal Silicon Dioxide	NF, Ph. Eur.	(b) (4)	(b) (4)
Mannitol	USP, Ph. Eur.		
Microcrystalline Cellulose	NF, Ph. Eur.		
Sodium Lauryl Sulfate	NF, Ph. Eur.		
(b) (4)	DMF		
Acesulfame Potassium	NF, Ph. Eur.		
Sucralose	NF		
(b) (4)	DMF		
Carnauba Wax	NF, Ph. Eur.		
(b) (4)	DMF		
(b) (4)	USP, Ph. Eur.		
(b) (4)	USP, Ph. Eur.		
Total:			

a. Essentially removed during processing.

There are no excipients of human or animal origin. No novel excipients are used in manufacture of the drug product.

(b) (4)

2.4 Comments on Novel Excipients

The excipients used in the proposed product are either considered as Generally Recognized as Safe (GRAS) or listed in FDA's Inactive Ingredient Database, with the exception of the non-pharmacopeial excipients (b) (4) (b) (4) (b) (4)). Based on the chemist's review, the suppliers of the (b) (4) (b) (4) have provided documentation indicating that all components of these three excipients are approved for use per Food & Drug Administration's regulations or are listed as GRAS.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

The product is intended for temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular pain, backache, the minor pain of arthritis, the pain of menstrual cramps, and for reduction of fever. The recommended use of Na IBU for adults and children 12 years and older as over-the-counter (OTC) drug is 200 or 400 mg every 4 -6 hours with a maximum daily dose of 1200 mg/day.

2.7 Regulatory Background

Ibuprofen was first introduced as a prescription product in the United Kingdom UK in 1966 and in the United States (US) in 1974. Ibuprofen was the first NSAID licensed for over-the-counter (OTC) use in the UK in 1983 and in the US the following year. The proposed product in this NDA, Na IBU, is a fast-acting formulation of Ibuprofen. There is no nonclinical information on this form of ibuprofen except a single oral dose rat toxicology comparison study with Ibuprofen which was conducted for the applicant in support of a non-US regulatory agency. The nonclinical information for the present NDA refers to the nonclinical data for Ibuprofen in NDA18989 (Advil®) which is held by Wyeth Consumer Healthcare (now known as Pfizer Consumer Health).

3 Studies Submitted

3.1 Studies Reviewed

No new nonclinical studies were required for the approval of Na IBU. The applicant submitted a single dose rat toxicology study (b) (4) which was conducted using Ibuprofen and Na IBU in support of an application to a non-US regulatory agency. The purpose of the single dose study was to compare the acute oral toxicity potential of a reference Ibuprofen to Na IBU, and evaluate the differences in toxicity and mortality between the two compounds. Groups of 5 male and 5 female rats were administered a single oral dose (200, 500 and 650 mg/kg) of either the reference Ibuprofen product or Na IBU and followed for observation for 14 days after dosing. No toxicokinetics, clinical chemistry or histopathology evaluation was performed. Therefore the study provided limited information on the toxicities of Na IBU.

In terms of toxicities, no significant toxic effects were noted for both Ibuprofen and Na IBU-treated rats at 200 mg/kg. A dose-related increase in toxicity was noted at 500 mg/kg and 650 mg/kg, which was distinct and more pronounced among animals treated with Na IBU compared to those treated with ibuprofen. Details of the study observations are shown as follows:

Mortalities: No mortalities were seen among rats treated with 200 mg/kg from either treatment group. Among rats treated with the reference Ibuprofen at 500 mg/kg and 650 mg/kg, 3 animals died or were severely moribund and had to be terminated. Among rats treated with Na IBU at 500 mg/kg and 650 mg/kg, 2 rats died and 7 rats were severely moribund and had to be terminated (as shown in the following table).

Treatment Groups (N=5 rats/sex/dose group)		Dose Level (mg/kg)	Found Dead	Sacrificed ¹
Ibuprofen USP (Reference)	1 (NOAEL)	200	0	0
	2 (LOAEL)	500	2F	1F
	3 (LD ₁₆)	650	2M	1F
Ibuprofen Sodium Dihydrate (Test)	4 (NOAEL)	200	0	0
	5 (LOAEL)	500	1M	1M
	6 (LD ₁₆)	650	3M + 2F	2F

M = Males

F = Females

¹ *Animals sacrificed in deteriorating health, for the ethical reasons.*

Clinical Signs:

Animals treated with 200 mg/kg Ibuprofen and Na IBU had tarry feces on Day 1. There was no significant differences between the two compounds at 500 mg/kg.

Tarry feces, rough pelage, piloerection, hunched back, pot-bellied appearance, or pallor and dyspnea were observed at 500 and 650 mg/kg in both Ibuprofen and Na IBU treated groups. At 650 mg/kg, an increase in the incidence of altered clinical signs was observed among rats treated with Na IBU compared to those treated with Ibuprofen.

Body weights: There were no apparent differences in body weight gains among rats treated with Ibuprofen or Na IBU. Rats dosed with 500 mg/kg (males) Ibuprofen gained substantially more weight than rats dosed with Na IBU.

Necropsy Observations (Unscheduled): Bloated stomachs, intestines filled with fluid, sero-sanguineous fluid in the abdominal cavity, black colored intestinal contents, and stomach bleeding and micro-ulcers were observed in both Ibuprofen and Na IBU-treated groups dosed at 500 mg/kg and 650 mg/kg.

Necropsy Observations (Scheduled): At 200 mg/kg, no treatment-related findings were observed for either ibuprofen or Na IBU. At 500mg/kg, there were no necropsy findings in Ibuprofen-treated animals but in Na IBU treated animals, the following observations were made: dark colored intestinal contents, serosanguineous fluid in abdominal cavity, thickening of small intestinal wall, abscesses on mesenteric lymph nodes, duodenal-jejunal adhesion and white infiltration on Peyers patches. At 650 mg/kg, intestinal contents darker in color and white color infiltration in spleen were observed in Ibuprofen treated animals and thickening of intestinal wall, duodenal-jejunal adhesion and white infiltration on Peyers patches were observed in Na IBU treated animals.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

See previous nonclinical reviews for Motrin IB (NDA 19-012), Advil Tablets, Caplets and Gel-Caplets (NDA 18-989), Advil Liqui-Gels (NDA 20-402), Children's Advil Suspension (NDA 20-589 and NDA 19-833), and Infant's Advil Drops (NDA 20812).

4 Integrated Summary and Safety Evaluation

Ibuprofen, an arylpropionic acid derivative, was introduced in the US in 1974 and has been available as an OTC drug since 1983. Commercially available Ibuprofen is an equimolar mixture of the (R)- and (S)+ isomers. Only the (S)+ isomer is pharmacologically active, but chiral inversion occurs in vivo. The mode of action of Ibuprofen is believed to involve the reversible inhibition of the enzyme cyclooxygenase (COX) which is responsible for the biosynthesis of prostaglandins (PGs) from arachidonic acid in the cellular membrane. The inhibitory action of Ibuprofen on PG synthesis is the most probable cause of gastrointestinal side effects, gastric micro ulcers and bleeding. PGs play an important role for synthesis of protective alkaline secretions in gastric mucosa cells. The inhibition of PG synthesis can lead to a reduced protection of gastric mucosa and may cause abdominal pain, gastric and duodenal ulcers and gastro-intestinal bleeding.

The present NDA submission is for a fast-acting formulation of Ibuprofen, Na IBU. The applicant is referring to the Agency's assessment of nonclinical information submitted under Advil® (NDA 18989) for Ibuprofen to support the safe use of Na IBU. NDA18989 was approved in 1984 where the nonclinical information on Ibuprofen was reviewed and found to be sufficient if used within the dosage limits and in the dosage forms established. The applicant also conducted an online search of the published literature for Ibuprofen (Medline/PubMed, Ovid, Embase and Toxnet/Toxline) from 1966 through January 2006. The search did not produce any nonclinical citations of significant relevance to suggest modification of previous regulatory findings on the safety of ibuprofen for its use in adults or children.

No nonclinical information is currently available on the proposed form of Na IBU except for a single oral dose rat toxicology study which the applicant had conducted in support of an application for a non-US regulatory agency. Based on severity, incidence and duration of clinical signs, mortalities and necropsy findings, there were no significant toxic effects at 200 mg/kg for both currently-marketed Ibuprofen and the proposed product, Na IBU. The dose of 200 mg/kg is approximately 30 times higher than the maximum single human dose of Na IBU at 400 mg (6.7mg/kg), and 10 times higher than the maximum daily human dose of Na IBU at 1200 mg (20 mg/kg). Higher dose levels of Na IBU (500 & 600 mg/kg) caused a more pronounced toxicity profile when compared to the currently available Ibuprofen. The observed toxicity was primarily in the gastrointestinal tract as expected. The increased toxicity findings observed with Na IBU may be related to the higher solubility of Na IBU which results in faster absorption and higher bioavailability compared to Ibuprofen.

In conclusion, based on the previous human use experience for Ibuprofen, the agency's previous review of the nonclinical information on ibuprofen, as well as the lack of novel significant issues during the current review of Na IBU, the present NDA can be approved from the nonclinical perspective.

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/s/

XINGUANG LI
02/28/2011

WAFI HARROUK
03/01/2011

PAUL C BROWN
03/01/2011

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201803

Applicant: Pfizer Consumer
Healthcare

Stamp Date: 07/01/2010

Drug Name: Advil® (b)(4)
tablets and caplets, sodium
ibuprofen dihydrate 256 mg
(ibuprofen 200 mg)

NDA/BLA Type: 505(b)(2)

Background:

This New Drug Application (NDA) for Advil® (b)(4) tablets and caplets, sodium ibuprofen dihydrate 256 mg (ibuprofen 200 mg) is submitted by Pfizer Consumer Healthcare. The proposed drug product is a fast-acting formulation of Ibuprofen and is intended for temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular pain, backache, the minor pain of arthritis, the pain of menstrual cramps, and for reduction of fever. The recommended use for adults and children 12 years and older as OTC drug is 200 or 400 mg every 4 - 6 h (maximum daily dose of 1200 mg).

Ibuprofen, an arylpropionic acid derivative, was introduced in the US in 1974 and has been available as an Over The Counter (OTC) drug since 1983. Commercially available Ibuprofen is an equimolar mixture of the (R)- and (S)+ isomers. Only the (S)+ isomer is pharmacologically active, but chiral inversion occurs in vivo. In humans, orally administered ibuprofen is rapidly absorbed, with peak plasma concentrations at 30 min - 2 hour, depending on formulation characteristics. Bioavailability of orally administered ibuprofen is high (>80%) and >99% is bound to plasma proteins. Subsequent to oral ingestion, ibuprofen shows rapid uptake, high bioavailability (>80%) and very high (~99%) plasma protein binding. Absorbed ibuprofen is rapidly metabolized and excreted, with a plasma half-life of approximately 2 hours.

This application is a 505(b)(2) application where the sponsor is referring to the Agency's assessment of safety from nonclinical information submitted under NDA 18-989 (Advil®) by Wyeth Consumer Healthcare. While there is a substantial body of information available to support the clinical use for ibuprofen, there is no preclinical information available on the proposed form of Na ibuprofen dehydrate except for a 14 day single oral dose rat toxicology study which the sponsor had conducted in support of a non-US regulatory agency and which was submitted under this NDA for the Agency's review. The descriptions of the product formulations for the tablets and caplets are presented in the following tables:

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Advil® ^{(b) (4)} Tablets:

Table 1-1 summarizes the composition of Sodium Ibuprofen Tablets, 200 mg and the function of the excipients in the formulation.

Table 1-1: Composition of Sodium Ibuprofen Tablets, 200 mg Drug Product

Ingredient	Grade/Quality Standard	Unit Dose (mg/du)	Function		
Sodium Ibuprofen Dihydrate	DMF	256.25	Active Ingredient		
Colloidal Silicon Dioxide	NF, Ph. Eur.		(b) (4)		
Mannitol	USP, Ph. Eur.				
Microcrystalline Cellulose	NF, Ph. Eur.				
Sodium Lauryl Sulfate	NF, Ph. Eur.				
^{(b) (4)}	DMF				
Acesulfame Potassium	NF, Ph. Eur.				
Sucralose	NF				
^{(b) (4)}	DMF				
Carnauba Wax	NF, Ph. Eur.				
^{(b) (4)}	DMF				
	USP, Ph. Eur.				
	USP, Ph. Eur.				
Total:				446.2	

a. Essentially removed during processing.

There are no excipients of human or animal origin. No novel excipients are used in manufacture of the drug product.

Advil® ^{(b) (4)} Caplets:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Potential impurities for sodium ibuprofen dihydrate are controlled by a specification of Not More Than (NMT) ^{(b) (4)}% and total impurities by a specification of NMT ^{(b) (4)}%.

On initial overview of the NDA application: There are no outstanding pharmacology/toxicology issues identified at this time in the pharmacology/toxicology section.

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		This is a 505(b)(2) application where the sponsor is relying on agency's findings for NDA 18-989.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	Has the applicant addressed any abuse potential issues in the submission?			N/A.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

At present, no issues have been identified that need to be forwarded in the 74-day letter.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-201803

ORIG-1

PFIZER
CONSUMER
HEALTHCARE

Advil ^{(b) (4)} (256 mg sodium
ibuprofen dihydrate)

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/s/

XINGUANG LI
08/26/2010

PAUL C BROWN
08/30/2010