

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-470**

**PHARMACOLOGY REVIEW(S)**



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: **22-470**  
SERIAL NUMBER: **000**  
DATE RECEIVED BY CENTER: **Jan 23, 2009**  
PRODUCT: **Ketoprofen oral soluble film<sup>1</sup>, 12.5mg**  
INTENDED CLINICAL POPULATION: **Temporarily relieve minor aches and pains due to headache, the common cold, toothache, muscular aches, backache, menstrual cramps and minor pain of arthritis; temporarily reduces fever**

APPLICANT: **Novartis Consumer Health, Inc**  
DOCUMENTS REVIEWED: **Nonclinical**  
REVIEW DIVISION: **Division of Nonprescription Clinical Evaluation (HFD-560)**  
PHARM/TOX REVIEWER: **Cindy Li, Ph.D.**  
PHARM/TOX SECONDARY REVIEWERS: **Wafa Harrouk, Ph.D.**  
**Paul Brown, Ph.D.**  
DIVISION DIRECTOR: **Andrea Leonard-Segal, M.D.**  
PROJECT MANAGER: **Neel Patel, RPM**

Date of review submission to DARRTS: August 27, 2009

1: Previously named "Ketoprofen oral [REDACTED] (b) (4)

## ***EXECUTIVE SUMMARY***

A. Recommendation on approvability

Approvable from the standpoint of pharmacology/toxicology.

B. Recommendation for nonclinical studies

There are no outstanding pharmacology/toxicology issues.

C. Recommendations on labeling: None

**PHARMACOLOGY/TOXICOLOGY REVIEW****NDA number:** 22-470**Review number:** 1**Sequence number/date/type of submission:** SN000/ 01/23/2009/NDA**Information to sponsor:** Yes ( ) No (x)**Sponsor and/or agent:** Novartis Consumer Health, Inc.**Reviewer name:** Cindy Li, Ph.D.**Division name:** DNCE, Office of Nonprescription Products (ONP)**HFD #:** 560**Review completion date:** 8/25/2009**Drug:** Ketoprofen oral soluble films, 12.5mg**Drug class:** non-steroidal anti-inflammatory drug**Intended clinical population:** Temporarily relieve minor aches and pains due to headache, the common cold, toothache, muscular aches, backache, menstrual cramps and minor pain of arthritis; temporarily reduces fever**Route of administration:** oral soluble films**Proposed clinical protocol:** None**Drug:**

Trade name: Nexcede

Generic name: Ketoprofen oral soluble films, 12.5mg

Synonyms: 3-Benzoyl- $\alpha$ -methylbenzeneacetic acid (USP name)

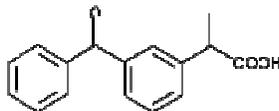
Chemical name: Ketoprofen

CAS registry number: [22071-15-4]

Molecular formula: C<sub>16</sub>H<sub>14</sub>O<sub>3</sub>

Molecular weight: 254.28

Structure:

**Relevant INDs/NDAs/DMFs:**

IND: 74,282 for ketoprofen oral (b) (4) 12.5mg

NDA: 18-754 (Orudis, prescription strength ketoprofen)

20-429 (Orudis KT, 12.5 mg, OTC strength)

(b) (4)

**Data reliance:** Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-470 are owned by Novartis Consumer Health, Inc. or are data for which Novartis Consumer Health, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 22-470 that Novartis Consumer Health, Inc. 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 Novartis Consumer Health, Inc. 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 22-470.

**Background:**

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) belonging to the arylpropionic acid group and used as an anti-inflammatory, analgesic and antipyretic agent. It has been approved in the United States for the management of osteoarthritis and rheumatoid arthritis since 1986 in NDA 18-754. It has also been approved for over-the-counter (OTC) use in 1995 in NDA 20-429 and NDA 20-499.

Ketoprofen is currently marketed in oral, topical and suppository formulations and is available in the US in both immediate release and extended release oral formulations. The recommended maximum daily prescription use is 300 mg. This NDA presents a new formulation - an orally soluble film containing 12.5 mg ketoprofen which disintegrates in the mouth within approximately 10 to 15 seconds. The maximum dose is 75 mg at the proposed dosing regimen of 12.5 mg every 4 to 6 hours for a maximum recommended treatment duration of 3 days for fever and 10 days for pain.

The inactive ingredients are sodium phosphate dibasic, sodium hydroxide, FD&C blue No. 1 (in Peppermint flavor strip), FD&C Red No. 40 (b) (4) (in Cinnamon flavor strip), hypromellose, sucralose, acesulfame potassium, xylitol, maltodextrin, PEG 400 and Peppermint flavor (b) (4) or Cinnamon flavor (b) (4) white imprint ink. (b) (4)

The impurity and degradation specifications for Ketoprofen oral soluble film conform to the limits set for ketoprofen in the U.S. Pharmacopoeia. No novel impurities or degradation products of ketoprofen are detected in the product.

The only new nonclinical study that has been submitted in this NDA application is a buccal mucosal tolerability study in hamsters. The applicant also submitted publications of nonclinical studies of relevance to the safety and mechanism of action of ketoprofen, a list of the studies from NDA 18-754 and the safety findings of the agency from NDA 18-754 and NDA 20-429. The applicant does not have a right of reference from the holders of these other applications. However, the applicant conducted a human bioequivalence study comparing the oral film to the 12.5 mg Orudis KT tablet. This NDA was submitted under section 505(b)(2) of the FD&C Act.

**Pharmacology/Toxicology Review:**

## 1. Buccal mucosal tolerability study

**Study title:** Assessment of local tolerance and general tolerance by repeated application on the hamster cheek pouch

**Key study findings:** There were no test article-related changes in mortality, observed clinical signs, body weight, body weight changes, food consumption, local reaction and histopathologic changes in cheek pouch and esophagus with treatment of ketoprofen (b) (4) (b) (4) after 6 applications per day for 14 days in hamsters. An increase in mean drink intake was observed in test article-treated females during Days 2-3 by 97.4% when compared to the control group.

**Study no.:** MJ-PH-07/0087

**Volume # and page #:** 1/31

**Conducting laboratory and location:** (b) (4)

(b) (4)

**Date of study initiation:** April 3, 2007

**GLP compliance:** Yes (OECD)

**QA report:** yes (X) no ( )

**Drug, lot #, and % purity:** (b) (4) (Ketoprofen oral soluble film, 12.5mg);  
Batch # 6850041, 100%

## METHODS

Doses: 12.5mg/film (One Ketoprofen oral soluble film cut to size of 5 mm diameter was applied to a cheek pouch of each hamster.)  
Species/strain: Hamsters / Golden Syrian  
Number/sex/group or time point (main study): 5/sex/group  
Route, formulation, volume, and infusion rate: buccal; soluble film; NA; NA  
Satellite groups used for toxicokinetics or recovery: no  
Age: NA  
Weight: male: 87-95g; female: 65-75g  
Sampling times: daily for mortality and clinical examinations; Day 3, 7 and 14 for body weight and food/drink consumption; 24 hours after last treatment for histopathological processing and examination  
Unique study design or methodology (if any): buccal mucosal study (The films used in hamsters in the present study were the same as in human; The hamsters were treated 6 times per day with 1 hour between

applications for 14 consecutive days.)

### **Observations and times:**

Mortality, clinical observations, body weights, body weight change, food and drink consumption, macroscopic and microscopic anatomic pathology were evaluated in this study. TK and Recovery groups were not included.

Mortality: daily

Clinical Observations: daily, including local irritation, test item expulsion, general clinical examination, behavioral abnormalities, and alteration of neuro-vegetative reactions.

Ophthalmic Examinations: not conducted

Body Weights: Day 3, 7, 14

Food and Drink Consumption: Day 3, 7, 14

Clinical Pathology: not conducted

EKG: not conducted

Urinalysis: not conducted

Gross pathology: On the day of terminal sacrifice

Organ weights: not conducted

Histopathology: After terminal sacrifice

## **RESULTS**

Mortality: No unscheduled deaths during the study.

Clinical signs: No clinical signs related to the administration of the test item.

Body weights (BW): The mean body weight changes in treated animals were comparable to the changes in control groups.

Food consumption (FC):

1. The food intake was similar between the treated and control animals for the period of Days 2-3, 6-7, and 13-14 in both male and females.
2. The water intake was similar between the treated and control animals for the period of Days 2-3, 6-7, and 13-14 in males, and for the period of Days 6-7 and 13-14 in females.
3. An increase of 97.4% in mean water intake was observed in test article-treated female hamsters on Days 2-3 when compared to the control group, though the range of individual animal water intake in the treated group was not significantly different from the range in control animals. It is possible that the test article may have caused this increase. The biological significance of the increase is considered to be minimal because there were no significant body weight changes in the treated group compared to that in controls.

Gross pathology: No macroscopic reactions (erythema) were observed at the treated areas.

Histopathology: Adequate Battery: yes (x), no ()—explain: This is a local irritation study, so the sponsor only examined buccal related areas – cheek pouch and esophagus.

Peer review: yes ( ), no (x)-an independent pathologist examined the histopathologic tissue samples

Summary of the findings:

- No relevant histopathologic changes related to local tolerance or general tolerance were noted in cheek pouch or esophagus examined.

Necropsy inventory:

Study	14 days			
Species	Hamster			
Adrenals	x			
Cecum	x			
Colon	x			
Duodenum	x			
Epididymis				
Esophagus	x			
Gall bladder	x			
Heart	x			
Ileum	x			
Jejunum	x			
Kidneys	x			
Liver	x			
Lungs	x			
Ovaries	x			
Pancreas	x			
Rectum	x			
Spleen	x			
Trachea	x			
Urinary bladder	x			
Uterus	x			

X, gross necropsy performed

Conclusions: Exposure of hamsters to ketoprofen (b) (4) at six applications per day for 14 consecutive days did not result in any buccal irritation.

2. Other information

Photosensitivity: A review of the publications on photosensitization potential of ketoprofen has been included in the nonclinical section. Ketoprofen phototoxicity has not been confirmed in standardized (guinea pig) studies, but it is clearly photoallergenic, and shows photocross reactivity to a variety of related structures, including suprofen, tiaprofenic acid and benzophenone. The photoallergenicity is unlikely to be a major safety issue with the ketoprofen 12.5 mg oral soluble film because photoallergy requires a sufficiently high skin concentration (and sufficient UV irradiation) for both induction and expression. There is no UV exposure in the mouth, and the skin concentrations after dosing with 12.5 mg oral soluble film are relatively low.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Based on the risk-benefit analysis of the existing nonclinical information, the submitted nonclinical study and agency's previous findings, NDA 22-470 can be approved from the nonclinical perspective for the indication and duration proposed.

On overview of the NDA application: there are no outstanding pharmacology/toxicology issues.

Unresolved toxicology issues (if any): None

Recommendations: NDA22-470 can be approved from the nonclinical perspective.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22470	----- ORIG 1	----- NOVARTIS CONSUMER HEALTH INC	----- KETOPROFEN ORAL-ORAL <small>(b) (4)</small>

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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XINGUANG LI  
08/27/2009

Wafa HARROUK  
08/27/2009

PAUL C BROWN  
08/27/2009

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

**NDA/BLA Number:** 22,470      **Applicant:** Novartis Consumer Health Inc.      **Stamp Date:** 01/23/2009

**Drug Name:** Ketoprofen oral      **NDA/BLA Type:** 505(b)(2)  
(b) (4) 12.5mg  
(b) (4) or Nexcede)

## Background:

The proposed drug product contains the active drug substance, ketoprofen, a propionic acid derivative which acts as a nonsteroidal anti-inflammatory, analgesic and antipyretic agent. The chemical name of the drug substance is 2-(3-benzoylphenyl)-propionic acid. The proposed indication for ketoprofen in this NDA is to "temporarily relieve minor aches and pains due to headache, the common cold, toothache, muscular aches, backache, menstrual cramps and minor pain of arthritis; temporarily reduces fever". The recommended maximum daily prescription use is 300 mg, while the maximum OTC dose is 75 mg at a proposed dosing regimen of 12.5 mg every 4 to 6 hours for a maximum recommended treatment duration of 3 days for fever and 10 days for pain.

Ketoprofen is currently marketed in oral, topical and suppository formulations. It has been approved in the US since 1986 for the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis under NDA 18-754. It has also been approved for over-the-counter (OTC) use since 1995 under NDAs 20-429 and 20-499. Ketoprofen is currently available in the US in immediate release and extended release oral formulations.

This NDA presents a new formulation - an orally (b) (4) containing 12.5 mg ketoprofen which disintegrates in the mouth within approximately 10 to 15 seconds. The inactive ingredients are sodium phosphate dibasic, sodium hydroxide, FD&C blue No. 1 (in Peppermint flavor strip), FD&C Red No. 40, (b) (4) (in Cinnamon flavor strip), hypromellose, sucralose, acesulfame potassium, xylitol, maltodextrin, PEG 400 and Peppermint flavor (b) (4) or Cinnamon flavor (b) (4). Water (b) (4)  
(b) (4).

The applicant has submitted a non-clinical local buccal tolerability study of the ketoprofen oral (b) (4). In addition, the applicant is referring to the Agency's finding of safety for Orudis NDA 18-754 (prescription strength ketoprofen), and the Agency's finding of efficacy for Orudis KT NDA 20-429 (12.5 mg, OTC strength). The applicant does not have a right of reference from the holders of these other applications.

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

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

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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		This is a 505(b)(2) application.
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. The applicant is referencing the Agency's finding of safety for NDA 18-754 (without a right of reference from the application holders). The applicant submitted a local tolerability study.
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		
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			N/A

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

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	with 201.57?			
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?		X	
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 and need to be forwarded in 74-day letter.

Cindy Li, PhD

3/5/2009

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Reviewing Pharmacologist

Date

Paul Brown, PhD

3/5/2009

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Team Leader/Supervisor

Date

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

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Xinguang Li  
4/14/2009 03:56:33 PM  
INTERDISCIPLINARY

Paul Brown  
4/14/2009 05:23:39 PM  
PHARMACOLOGIST