

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-294

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-470	Submission Date: 01/26/09
Submission Type; Code:	505 (b) (2)
Brand/Code Name:	Nexede
Generic Name:	Ketoprofen
Formulation; Strength(s):	Oral Soluble Film, 12.5 mg
Primary Reviewer:	Suresh B Narahariseti, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Nonprescription Clinical Evaluation
Sponsor:	Novartis Consumer Health, Inc
Proposed Indication:	For temporary relief of minor aches and pains due headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis; and reduction of fever
Proposed Dosage Regimen:	<ul style="list-style-type: none">• Adults and children 16 years and over: 1 film to dissolve on tongue every 4 to 6 hours. One more film may be taken, if pain or fever does not get better in 1 hour.• Films should not exceed more than 2 in any 4 to 6 hour period and 6 in any 24 hour period.• Children under age 16 should not be given oral (b) (4) films unless directed by a doctor

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY	2
1.1 RECOMMENDATION	2
1.2 PHASE 4 COMMITMENTS	2
1.3. SUMMARY OF CPB FINDINGS	3
2.0 QUESTION BASED REVIEW	4
2.1 GENERAL ATTRIBUTES OF THE DRUG	4
2.2 GENERAL CLINICAL PHARMACOLOGY	5
2.3 INTRINSIC FACTORS	8
2.4 EXTRINSIC FACTORS	8
2.5 GENERAL BIOPHARMACEUTICS	9
2.6 ANALYTICAL SECTION	14
3.0 LABELING COMMENTS	15
4.0 APPENDICES	15
4.1 SPONSOR’S PROPOSED LABEL	15
4.2 INDIVIDUAL STUDY REVIEWS	20
4.2.1 STUDY DESIGNS:	20
4.2.2 SUMMARY OF STUDIES	20
4.2.2.1 EDKT-PN-102-FOOD EFFECT STUDY	20
4.2.2.2 STUDY EDKT-PN-101:	22
4.2.2.2.1 PART I: PIVOTAL BE STUDY	22
4.2.2.2.2 PART II- DOSE PROPORTIONALITY AND BRIDGING BE STUDY:	24
4.3 COVER SHEET AND OCPB FILING/REVIEW FORM	27

1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the NDA 22-470. From a Clinical Pharmacology perspective, the submission is acceptable provided that (1) a satisfactory agreement is reached between Agency and Sponsor regarding the labeling language and (2) Report of audit of study EDKT-PN-101 by Division of Scientific Investigations does not uncover any significant issues that would preclude acceptance of data.

1.2 Phase 4 Commitments

None

1.3. Summary of CPB Findings

Novartis Consumer Health, Inc., has submitted NDA 22-470 under 505 (b) (2) regulations seeking the approval of 12.5 mg ketoprofen oral soluble film (KT-OSF) for OTC marketing. It should be noted that 12.5 mg dose of ketoprofen for OTC marketing for similar indications was previously approved under NDA 20-499 (Ketoprofen tablet under the trade name Actron by Bayer on October 6, 1995), NDA 20-429 (ketoprofen tablet under the trade name Orudis KT by Wyeth Consumer Health Care on October 6, 1995), and ANDA 75-364 (ketoprofen tablet on February 7, 2002). All these three products are discontinued from marketing at present. However, for Orudis KT Orange Book has the notation 'Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons'. To support the approval in accordance with 505(b) (2) regulations, the sponsor is relying on the previous findings of safety and efficacy of 12.5 mg Orudis KT tablets (NDA 20-429) and has demonstrated bioequivalence (BE) of the KT-OSF with Orudis KT tablets.

Since the approval is based on the demonstration of bioequivalence of what is essentially a new dosage form (but otherwise similar in all aspects) to a previously approved product, new safety and efficacy studies were not required for this NDA. Two Clinical Pharmacology and Biopharmaceutics studies EDKT-PN-101 and EDKT-PN-102 were conducted to acquire the data required to support the NDA. Findings from study EDKT-PN-101 supported the bioequivalence between KT-OSF and Orudis KT products, bioequivalence of KT-OSF with and without water, dose-proportionality of one and two KT-OSF tablets and bioequivalence between clinical service form (CSF) and Final Marketing Image (FMI) while study EDKT-PN-102 assessed the effect of food.

Administration of 12.5 mg KT-OSF with and without water is bioequivalent to the reference, 12.5 mg Orudis KT IR tablet administered with water. Under fed conditions, C_{max} of KT-OSF was 40% relative to that under fasted conditions; however the total BA ($AUC_{(0-t)}$, and $AUC_{(0-inf)}$) was comparable between fasted and fed conditions. The effect of food on C_{max} was similar to that observed with KT Orudis IR tablets. One and two 12.5 mg KT-OSF administered without water under fasting conditions demonstrated dose proportionality. During the development of KT-OSF, two formulations were used. The CSF was used in the pivotal BE study. The FMI was used in assessing the other aspects following demonstration of bioequivalence between the CSF and FMI. The FMI formulation contains the same amount of the active pharmaceutical ingredient (12.5 mg ketoprofen) as the CSF but has an increased film weight of 70 mg (versus 60 mg of the CSF).

At this time, report of the audit of study EDKT-PN-101 (assessing the BE between KT-OSF and Orudis KT tablets) by Division of Scientific Investigations (DSI) is pending. Apart from the pending DSI report, the submitted information is acceptable from a clinical pharmacology perspective.

2.0 Question Based Review

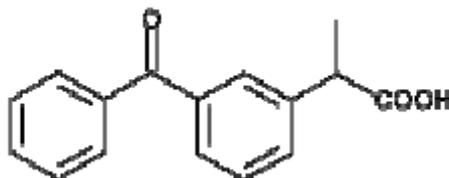
2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Drug substance

Chemical Name: N 2-(3-benzoylphenyl)-propionic acid.

Structural formula



Molecular Weight of the Free Base: 254.29

Physicochemical Properties: Ketoprofen is a white or off-white, odorless, non-hygroscopic, and fine to granular powder with a melting point of 95 ° C. At 20°C, it is freely soluble in ethanol, chloroform, acetone, and ether, soluble in benzene and strong alkali, and practically insoluble in water.

Drug product

Active ingredient(s): Ketoprofen

Inactive Ingredients: Water, Sodium Phosphate Dibasic, Sodium Hydroxide, Acetone, Hypromellose, FD&C Blue, Sucralose, Acesulfame Potassium, Xylitol, Maltodextrin, PEG 400, Peppermint Flavor, White Imprinting Ink

The commercial to-be marketed formulation is the not the same used for assessing BE between KT-OSF and the reference product. During the development of KT-OSF, two formulations were used. The Clinical Service Form was used BE between KT-OSF and Orudis KT. The Final Market Image was used in assessing other aspects following demonstration of bioequivalence between the CSF and FMI. The FMI formulation contains the same amount of the active pharmaceutical ingredient (12.5 mg ketoprofen) as the CSF but has an increased film weight of 70 mg (versus 60 mg of the CSF).

Table 1 Comparison of CSF and FMI formulas

Ingredient	mg per strip, CSF	mg per strip, FMI
Hypromellose (b) (4)	(b) (4)	(b) (4)
Hypromellose (b) (4)	(b) (4)	(b) (4)
Sodium Phosphate Dibasic (b) (4)	(b) (4)	(b) (4)
Total weight	60	70

2.1.2 What are the proposed mechanism of action and therapeutic indication(s)?

Mechanism of action

The exact mechanism of action of NSAIDs is unknown. NSAIDs are known to inhibit the biosynthesis of prostaglandins and thromboxanes from arachidonic acid through the inhibition of the enzyme cyclo-oxygenase (COX). The expression of the two isoenzymes of COX, COX-1 and COX-2, is differentially regulated. COX-1 is expressed constitutively at various levels, depending on tissue context: maintenance of gastric mucosal integrity, renal homeostasis and platelet aggregation. In contrast, COX-2 levels are undetectable and it is selectively up-regulated in response to inflammatory cytokines or trauma.

The indications for Ketoprofen-OSF as along other OTC analgesics include the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, minor pain of arthritis and menstrual cramps as well as the temporary reduction of fever.

2.1.3 What are the proposed dosage and route of administration?

The proposed dosage for this new formulation has not changed from the Orudis KT Tablets NDA (12.5 mg, OTC strength). The recommended dosing regimen is 12.5 mg every 4 to 6 hours while the initial dose may be 12.5 mg or 25 mg if needed. The maximum total daily dose should not exceed 75 mg. The new formulation is an oral (b) (4) film.

2.1.4 What is KT-OSF to-be-marketed formulation?

The KT-OSF is rectangular, 7.04 cm² in area, having the approximate dimensions of 22 mm x 32 mm and light blue in color. The Active Pharmaceutical Ingredient is 12.5 mg Ketoprofen. Individual dose units are packaged in a foil laminate pouch.

2.1.5 What are the core studies submitted in this NDA?

Two Clinical Pharmacology and Biopharmaceutics studies EDKT-PN-101 and EDKT-PN-102 were conducted to acquire the data required to support the NDA. Findings from study EDKT-PN-101 supported the bioequivalence between KT-OSF and Orudis KT products, bioequivalence of KT-OSF with and without water, dose-proportionality of one and two KT-OSF tablets and bioequivalence between clinical service form (CSF) and Final Marketing Image (FMI) while study EDKT-PN-102 assessed the effect of food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The PK-BE approach is the main basis for the clinical pharmacology studies to support the dosing for this NDA.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Ketoprofen was measured in plasma to assess the PK parameters.

2.2.3 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA. All data in this NDA were presented as comparative pharmacokinetics.

2.2.4 Exposure Response

Sponsor is relying on the efficacy data submitted for the Actron (NDA 20-499) and Orudis KT (NDA 20-429). No additional exposure-response evaluation was conducted in the investigational program of this NDA.

2.2.4.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

No formal PK/PD studies were conducted in this NDA to establish the relationship between exposure and response/efficacy.

2.2.4.2 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety.

2.2.4.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of ketoprofen on QTc.

2.2.5 What are the PK characteristics of the drug?

After oral administration, ketoprofen is rapidly absorbed, metabolized and secreted. Ketoprofen is a racemate with only the S enantiomer possessing pharmacological activity. The enantiomers have similar concentration-time curves and do not appear to interact with one another.

Following oral administration of IR preparations, ketoprofen is rapidly absorbed into the systemic circulation with T_{max} occurring within 0.5 to 2.0 h. Food intake concurrent with Orudis® capsules reduces C_{max} by approximately 50% and increases T_{max} from 1.2 h for fasting subjects to 2.0 h for fed subjects. The systemic availability of ketoprofen, when oral formulation is compared with IV administration is approximately 90% in humans. Once absorbed, ketoprofen is >99% bound to plasma proteins, mainly to albumin.

Ketoprofen is extensively metabolized in the liver to the unstable acyl-glucuronide conjugates by hepatic microsomal enzymes with up to 80% of the administered dose recovered in the form of the acyl-glucuronide conjugate. The unstable acyl-glucuronide conjugates are excreted from the body in the urine. Other metabolic pathways such as hydroxylation have also been reported. There are no known active metabolites of ketoprofen. Ketoprofen has been shown not to induce drug-metabolizing enzymes.

The $t_{1/2}$ of ketoprofen has been reported at approximately 2h following its administration in healthy young volunteers while in the elderly, glucuronide conjugation and renal excretion are delayed resulting in the increase in $t_{1/2}$ to 3-5 h. Enterohepatic recirculation of the drug has never been confirmed.

2.2.5.1 Is the PK of KT-OSF dose-proportional?

Yes

In study EDKT-PN-101 Part II the dose proportionality was demonstrated between one and two 12.5 mg KT-OSF following single oral dose administration. The geometric mean ratios for dose-normalized C_{max} , $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ are within the 80 to 125% bioequivalence window (Table 2.2.5.1.1) demonstrating the dose-proportionality.

Table 2.2.5.1.1: Dose proportionality between one (B1) and two (B2) 12.5 mg KT-OSF FMI

Parameter ¹ /Statistic	B1 (N=38)	B2* (N=38)
C_{max} (ng/mL)		
Geometric mean	1935.0	1771.9
Test/Reference Ratio (%) (Reference =B1)	-	91.57
90% Confidence interval (Reference =B1)	-	(83.11, 100.89)
AUC_{0-t} (ng*h/mL)		
Geometric mean	2913.9	2830.9
Test/Reference Ratio (%) (Reference =B1)	-	97.15
90% Confidence interval (Reference =B1)	-	(92.02, 102.57)
AUC_{0-inf} (ng*h/mL)		
Geometric mean	2967.7	2887.7
Test/Reference Ratio (%) (Reference =B1)	-	97.30
90% Confidence interval (Reference =B1)	-	(92.11, 102.79)

¹ Ln-transformed data are displayed

* values displayed are normalized by dose

B1: One ketoprofen 12.5 mg orally- (b) (4)-MI ;

B2: Two ketoprofen 12.5 mg orally- (b) (4)-FMI.

N: Number of subjects in the PK dose proportionality population

2.3 Intrinsic Factors

2.3.1 Does weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal studies were conducted in special populations in this NDA.

2.3.1.1 Pediatrics

Sponsor has requested a full waiver for the safety and efficacy studies for KT-OSF in pediatric subpopulations.

Ketoprofen is not indicated for use in pediatric patients. The prescribing information for prescription strength Orudis (NDA 18-754) includes the statement “ketoprofen is not recommended for use in pediatric patients”. Orudis KT (NDA 20-429) was not indicated for use in children under 16.

The directions for use of 12.5 mg KT-OSF in the proposed labeling were similar to that of Orudis KT labeling and included a statement that the product is not for use in children under 16.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, smoking and alcohol on KT-OSF use were not evaluated. The sponsor conducted a specific study to investigate the effect of food on the PK of KT-OSF. This is discussed in the next section below.

2.5 General Biopharmaceutics

The sponsor has demonstrated the bioequivalence of KT-OSF by employing the Orudis KT IR tables as a reference in study EDKT-PN-101 Part I. The details of the study are as under.

Objectives: The objective this study was

- To evaluate the BE between 12.5 mg KT-OSF administered with and without water to 12.5 mg Orudis KT IR tablets
- To evaluate the potential effects of water on the PK profile of 12.5 mg KT-OSF

Dosing

The peppermint flavored 12.5 mg KT-OSF is administered to the each subject orally with 150 mL water (one treatment) or without water (a second treatment). The reference 12.5 mg Orudis® KT- IR tablet was administered orally with 150 mL of water.

Study Results:

A total number of 82 subjects completed the study procedures for each of the 3 study periods. Administrating 12.5 mg KT- OSF with and without water, is BE to the reference 12.5 mg Orudis KT IR tablet (Fig. 4.2.2.2.1) CIs for each PK parameter are within the required limits of 80 to 125%. The PK parameters summarized in the Table 4.2.2.2

Table 4.2.2.2. Summary statistics of KT-OSF PK parameters of administered with and without water Vs. Orudis® KT- IR tablet.

Parameter/Statistic	A 1 (N=82)	A 2 (N=82)	R (N=82)	p-value
C_{max} (ng/mL)				
Geometric mean	1940.1	1793.0	1873.4	
Test/Reference Ratio (%) (Reference =R)	103.56	95.71	-	
90% Confidence interval (Reference =R)	(96.53 – 111.10)	(89.22 – 102.67)	-	0.1798
Test/Reference Ratio (%) (Reference = A1)	-	92.42	96.56	
90% Confidence interval (Reference =A1)	-	(86.15 – 99.14)	(99.01 – 103.60)	0.1798
AUC_{0-t} (ng*h/mL)				
Geometric mean	2891.5	2912.9	2940.4	
Test/Reference Ratio (%) (Reference =R)	98.34	99.06	-	
90% Confidence interval (Reference =R)	(93.23 – 103.72)	(93.93 – 104.48)	-	0.8732
Test/Reference Ratio (%) (Reference = A1)	-	100.74	101.69	
90% Confidence interval (Reference =A1)	-	(95.52 – 106.25)	(96.41 – 107.26)	0.8732
AUC_{0-inf} (ng*h/mL)				
Geometric mean	2941.3	2963.7	2991.6	
Test/Reference Ratio (%) (Reference =R)	98.32	99.07	-	
90% Confidence interval (Reference =R)	(93.20 – 103.73)	(93.91 – 104.51)	-	0.8719
Test/Reference Ratio (%) (Reference = A1)	-	100.76	101.71	
90% Confidence interval (Reference =A1)	-	(95.52 – 106.29)	(96.41 – 107.30)	0.8719

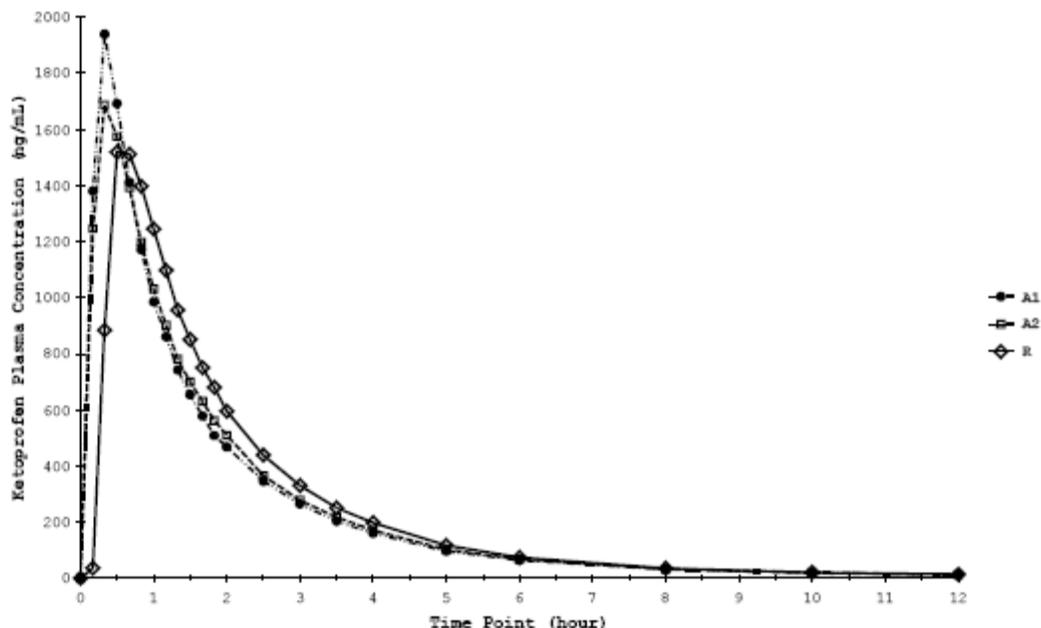
A1: One ketoprofen 12.5 mg orally; (b) (4) administered with 150 mL of water;

A2: One ketoprofen 12.5 mg orally; (b) (4) administered without water;

R: One Orudis KT 12.5 mg tablet administered with 150 mL of water.

N: Number of subjects in the PK analysis population; p-value is based on analysis of variance (ANOVA) with treatment, sequence, period and subject x treatment interaction as factors; Geometric means are obtained by exponentiating the least square means of log-transformed values from the ANOVA model

Fig 4.2.2.2.1 Mean plasma concentration-time profiles (linear scale) for KT-OSF with or without water Vs. Orudis® KT- IR tablet.



A1: One ketoprofen 12.5 mg orally- (b) (4) administered with 150 mL of water;
 A2: One ketoprofen 12.5 mg orally- (b) (4) administered without water;
 R: One Orudis® KT 12.5 mg tablet administered with 150 mL of water.

Conclusion: *KT- OSF with and without water is bioequivalent to the reference Orudis KT IR tablet*

The DSI inspection report is pending at this time. An addendum to this review will be written once DSI report is available.

2.5.1 What is the BCS Class classification for ketoprofen?

Not Applicable.

2.5.2 What is the effect of food on the BA of ketoprofen-OSF?

The sponsor evaluated the effect of FDA recommended high fat (approximately 50% of the total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) food on the BA of 12.5 mg KT-OSF administered without water in study EDKT-PN-102 .

This study was evaluated in 40 subjects. The mean C_{max} for KT-OSF under fed conditions was 40% relative to the fasted conditions; however the total BA (90% CIs for $AUC_{(0-t)}$, and $AUC_{(0-inf)}$) are within BE limits of 80-125% between fasted and fed conditions (Fig 2.5.2.1) The summary statistics of food effects on KT-OSF is shown in the Table 2.5.2.1. T_{max} increased from a mean of 0.43 h under fasting conditions to a mean of 0.70 h under fed conditions. Similar, decrease in rate of absorption (approximately 50% lower C_{max} and increase in T_{max} from 1 h to 2.1 h) and unaltered BA was reported with food for Orudis KT tablets. This magnitude of food effect seems to be

attributable to the ketoprofen drug substance and independent of the formulation. The package insert of Orudis 25 mg, 50 mg, and 75 mg capsules states that food resulted in reduction of C_{max} by approximately one-half with an increase in T_{max} from 1.2 h to 2.0 h. Both Orudis KT tablets and Orudis capsules labels do not contain any restriction with respect to concomitant food intake. Rather, the two products allow taking the drug product with food or milk if GI side effects are observed. It appears that in most of the clinical trials, ketoprofen was taken with food or milk.

Fig 2.5.2.1 Mean plasma concentration-time profiles (linear scale) for KT-OSF (12.5 mg X 2) administered without water to healthy volunteers under fed and fasted conditions. C_{max} is ~ 40 % lower and T_{max} is similar in the fasted subjects as compared to the fed.

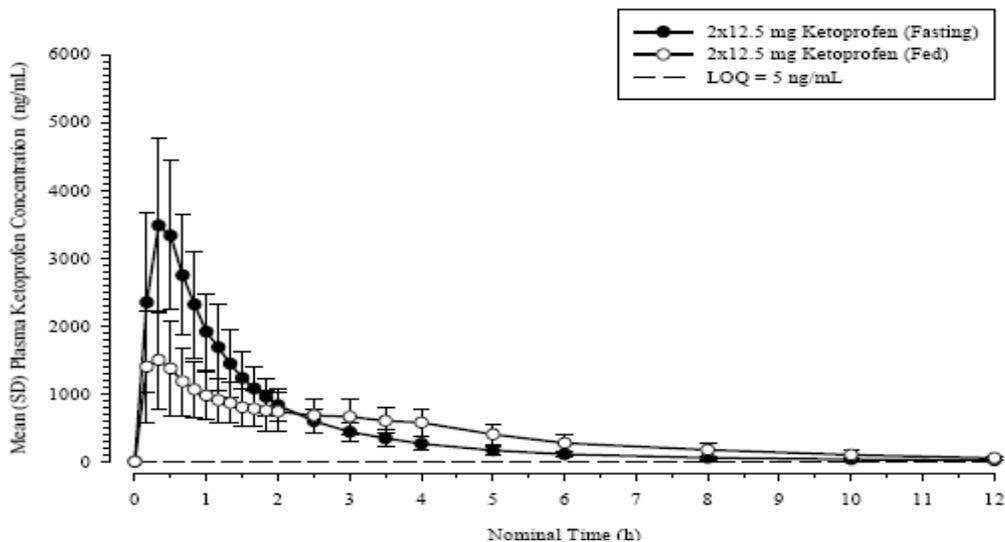


Table 2.5.2.1. Summary of ketoprofen PK parameters of KT-OSF (12.5 mg X 2) administered without water to healthy volunteers under fed and fasted conditions.

Parameter (Units)/ Statistic	Treatment groups	
	Fasting (N=40)	Fed (N=40)
C_{max} (ng/mL)	n=40	n=40
Geometric mean	3782.2	1511.3
Test/Reference Ratio (%)	-	39.96
90% Confidence Interval	-	(34.70, 46.02)
AUC_{0-t} (ng*h/mL)	n=40	n=40
Geometric mean	5247.1	4882.9
Test/Reference Ratio (%)	-	93.06
90% Confidence Interval	-	(85.22, 101.62)
AUC_{0-inf} (ng*h/mL)	n=39	n=40
Geometric mean	5345.1	5073.7
Test/Reference Ratio (%)	-	94.92
90% Confidence Interval	-	(86.82, 103.79)

Fasting serves as reference treatment

Reviewer comments: *The food effect study is acceptable. To address the food effect, the sponsor in the proposed labeling draft for KT-OSF indicated that “if taken with food this product may take longer to work”.*

2.5.3 Was the to-be-marketed formulation used in the PK/Clinical trials?

During the development of KT-OSF, two formulations were used. The Clinical Service Form (CSF) was used to assess BE between KT-OSF and Orudis KT tablets. The Final Market Image (FMI) was used in to assess other aspects following demonstration of bioequivalence between the CSF and FMI. The FMI formulation contains the same amount of the active pharmaceutical ingredient (12.5 mg ketoprofen) as the CSF but has an increased film weight of 70 mg (versus 60 mg of the CSF). Table 2.5.3.1 compares the differences between FMI was CSF.

Table 2.5.3.1 Comparison of CSF and FMI formulas

Ingredient	mg per strip, CSF	mg per strip, FMI
Hypromellose (b) (4)	(b) (4)	(b) (4)
Hypromellose (b) (4)	(b) (4)	(b) (4)
Sodium Phosphate Dibasic	(b) (4)	(b) (4)
Total weight	60	70

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

Two flavors of KT-OSF, peppermint and cinnamon are proposed for marketing in this NDA. The formulation compositions for both the flavors are shown in Table 2.5.4.1.

It should be noted that either flavors are compositionally proportional in all ingredients with an exception to the amount of flavor which was (b) (4) mg in peppermint to (b) (4) in

cinnamon. To keep the weight of the film constant, hypromellose, amount was reduced in peppermint flavor as that of cinnamon (Table 2.5.4.1).

Ingredient	Amount (mg/film)		Function	Quality Standard
	Peppermint	Cinnamon		
Ketoprofen	12.5	12.5	active ingredient	USP/NF
Hypromellose (b) (4)	(b) (4)			USP/NF
Sucralose			USP/NF	
Polyethylene glycol 400			USP/NF	
Xylitol			USP/NF	
Maltodextrin			USP/NF	
Flavor (peppermint)			(b) (4)	
Flavor (cinnamon)			(b) (4)	
Sodium hydroxide			USP/NF	
Acesulfame potassium			USP/NF	
Sodium phosphate dibasic			USP/NF	
FD&C blue #1			(b) (4)	
FD&C red # 40			(b) (4)	
Water, purified ¹			USP/NF	
Acetone ²			USP/NF	
White imprint ink ³	(b) (4)			
Theoretical film weight ⁴	70.00	70.00		

(b) (4)

³ The quantity of imprint ink per film is negligible and not quantified.

⁴ Theoretical film weight absent process solvents.

2.6 Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

The plasma concentrations of ketoprofen were analyzed via using a validated HPLC- with MS/MS assay. The range of calibrators and QCs were

- Calibrators: 5, 10, 50, 100, 1000, 1500, 2000 and 2500 ng/ml
- Quality controls: 15, 900, 1800 ng/ml

The accuracy and precision for QCs were within the acceptable range of $100 \pm 15\%$. For the food effect and dose proportionality studies where 25 mg KT OSF was used, the observed plasma concentrations were above the range of calibrators (approx 4000 ng/ml). All these samples were diluted with blank human plasma

3.0 Labeling Comments

The labeling comments will be incorporated directly into the sponsor's proposed label after discussion with the review team.

In comparison with the reference drug Orudis KT tablets-monograph, in the proposed labeling draft for KT-OSF, the sponsor made the following changes:

- (b) (4) sentence has been removed
- "If taken with food, this product may take longer to act

Reviewer comments:

This proposed labeling is acceptable from the clinical pharmacology perspective.

4.0 Appendices

4.1 Sponsor's Proposed Label

4.2 Individual Study Reviews

4.2.1 Study Designs:

Study EDKT-PN-102-Food Effect Study: *A randomized, open-label, single-dose, two-period, crossover, single-center pharmacokinetic study in healthy volunteers to evaluate the effects of food on the bioavailability of 12.5 mg KT-OSF*

Study EDKT-PN-101: *A randomized, open-label, crossover, single-center, two part sequential pharmacokinetic studies in healthy volunteers under fasting condition:*

Part I –Pivotal BE: *To demonstrate BE between one 12.5 mg KT OSF with and without water to one mg 12.5 KT IR tablet in fasting conditions*

Part II- Dose Proportionality and Bridging BE: *To investigate dose proportionality properties between one and two 12.5 mg KT-OSF following single oral dose administration and to demonstrate BE between Clinical Service Form and Final Market image formulation following single oral dose*

4.2.2 Summary of studies

4.2.2.1 EDKT-PN-102-Food Effect Study

Objective: To evaluate the food effect on the bioavailability of 12.5 mg KT-OSF administered without water.

Dosing and Fasting/Fed procedure

Two peppermint flavor FMI of KT-OSF were used in this study. The first film was placed on the tongue of the subject by using forceps. The film was allowed to be dissolved and then swallowed. The second film was placed on the subject's tongue approximately 15 to 20 seconds after placement of the first film.

For the fasted treatment, all subjects underwent 10 hours of overnight fast prior to dosing. No liquid or food intake was allowed during the fasting period except water which was permitted up until 1 hour prior to study medication administration. Water was allowed 2 hours after dosing while meals were served at 4 hours and at approximately 11 hours after dosing.

For the fed arm treatment, a high fat (approximately 50% of the total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) breakfast was served 30 minutes prior to study medication administration. The subjects were required to consume the breakfast (test meal) in 30 minutes or less. The study medication was administered 30 minutes (\pm 1 minute) after the start of the breakfast. The test meal, containing approximately 150, 250 and 500-600 calories, respectively, from protein, carbohydrate and fat, was 2 eggs fried in butter, 2 films of bacon, 2 slices of toast with butter, 4 ounces (110 g) of hash brown potatoes and 8 fluid ounces (237 mL) of whole milk. The caloric content and components of the test meal were identical for all subjects for both treatment

periods. The caloric content and components of the test meal were identical for all subjects for both treatment periods.

Study Results:

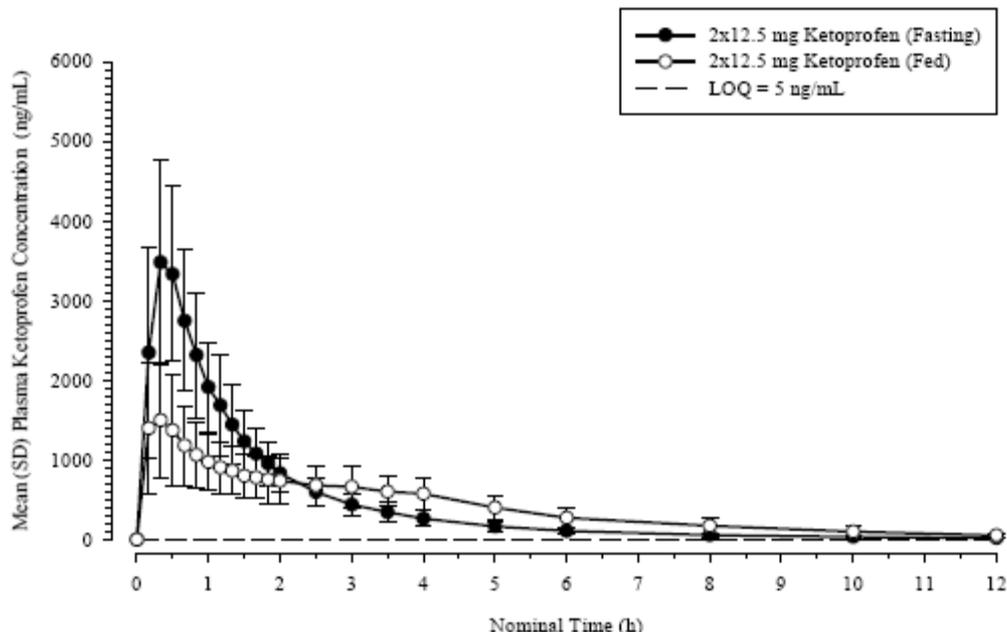
A total number of 40 subjects completed this study. For KT-OSF (25 mg), under fed conditions, the C_{max} was 39.96% relative to that under fasting condition with 90% CI of 34.70-46.02%; however the total BA ($AUC_{(0-t)}$, and $AUC_{(0-inf)}$) was comparable between fasted and fed conditions (Fig 4.2.2.1. and Table 4.2.2.1). T_{max} increased from a mean of 0.43 h under fasting conditions to a mean of 0.70 h under fed conditions. Similar, decrease in rate of absorption (approximately 50% lower C_{max}) and unaltered BA was reported with food for Orudis capsules (IR). The 90% CIs for $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ are within BE limits of 80-125 %.

Table 4.2.2.1. Summary of ketoprofen PK parameters of KT-OSF (12.5 mg X 2) administered without water to healthy volunteers under fed and fasted conditions.

Parameter (Units)/ Statistic	Treatment groups	
	Fasting (N=40)	Fed (N=40)
C_{max} (ng/mL)	n=40	n=40
Geometric mean	3782.2	1511.3
Test/Reference Ratio (%)	-	39.96
90% Confidence Interval	-	(34.70, 46.02)
AUC_{0-t} (ng*h/mL)	n=40	n=40
Geometric mean	5247.1	4882.9
Test/Reference Ratio (%)	-	93.06
90% Confidence Interval	-	(85.22, 101.62)
AUC_{0-inf} (ng*h/mL)	n=39	n=40
Geometric mean	5345.1	5073.7
Test/Reference Ratio (%)	-	94.92
90% Confidence Interval	-	(86.82, 103.79)

Fasting serves as reference treatment

Fig 4.2.2.1 Mean plasma concentration-time profiles (linear scale) for KT-OSF (12.5 mg X 2) administered without water to healthy volunteers under fed and fasted conditions. C_{max} is ~ 40 % lower and T_{max} is similar in the fasted subjects as compared to the fed.



Reviewer Comments:

- Food effect study is acceptable
- To address the food effect, the sponsor in the annotated labeling draft indicated that “if taken with food this product may take longer to work”

4.2.2.2 Study EDKT-PN-101:

4.2.2.2.1 Part I: Pivotal BE

Objectives: The objective this study was

- To evaluate the BE between 12.5 mg KT-OSF administered with and without water to 12.5 mg Orudis KT IR tablets
- To evaluate the potential effects of water on the PK profile of 12.5 mg KT-OSF

Dosing

The peppermint flavored 12.5 mg KT-OSF is administered to the each subject orally with 150 mL water (one treatment) or without water (a second treatment). The reference 12.5 mg Orudis® KT- IR tablet was administered orally with 150 mL of water.

Study Results:

A total number of 82 subjects completed the study procedures for each of the 3 study periods. Administrating 12.5 mg KT- OSF with and without water, is BE to the reference 12.5 mg Orudis KT IR tablet (Fig. 4.2.2.2.1) CIs for each PK parameter are within the required limits of 80 to 125%. The PK parameters summarized in the Table 4.2.2.2

Table 4.2.2.2. Summary statistics of KT-OSF PK parameters of administered with and without water Vs. Orudis® KT- IR tablet.

Parameter/Statistic	A 1 (N=82)	A 2 (N=82)	R (N=82)	p-value
C_{max} (ng/mL)				
Geometric mean	1940.1	1793.0	1873.4	
Test/Reference Ratio (%) (Reference =R)	103.56	95.71	-	
90% Confidence interval (Reference =R)	(96.53 – 111.10)	(89.22 – 102.67)	-	0.1798
Test/Reference Ratio (%) (Reference = A1)	-	92.42	96.56	
90% Confidence interval (Reference =A1)	-	(86.15 – 99.14)	(99.01 – 103.60)	0.1798
AUC_{0-t} (ng*h/mL)				
Geometric mean	2891.5	2912.9	2940.4	
Test/Reference Ratio (%) (Reference =R)	98.34	99.06	-	
90% Confidence interval (Reference =R)	(93.23 – 103.72)	(93.93 – 104.48)	-	0.8732
Test/Reference Ratio (%) (Reference = A1)	-	100.74	101.69	
90% Confidence interval (Reference =A1)	-	(95.52 – 106.25)	(96.41 – 107.26)	0.8732
AUC_{0-inf} (ng*h/mL)				
Geometric mean	2941.3	2963.7	2991.6	
Test/Reference Ratio (%) (Reference =R)	98.32	99.07	-	
90% Confidence interval (Reference =R)	(93.20 – 103.73)	(93.91 – 104.51)	-	0.8719
Test/Reference Ratio (%) (Reference = A1)	-	100.76	101.71	
90% Confidence interval (Reference =A1)	-	(95.52 – 106.29)	(96.41 – 107.30)	0.8719

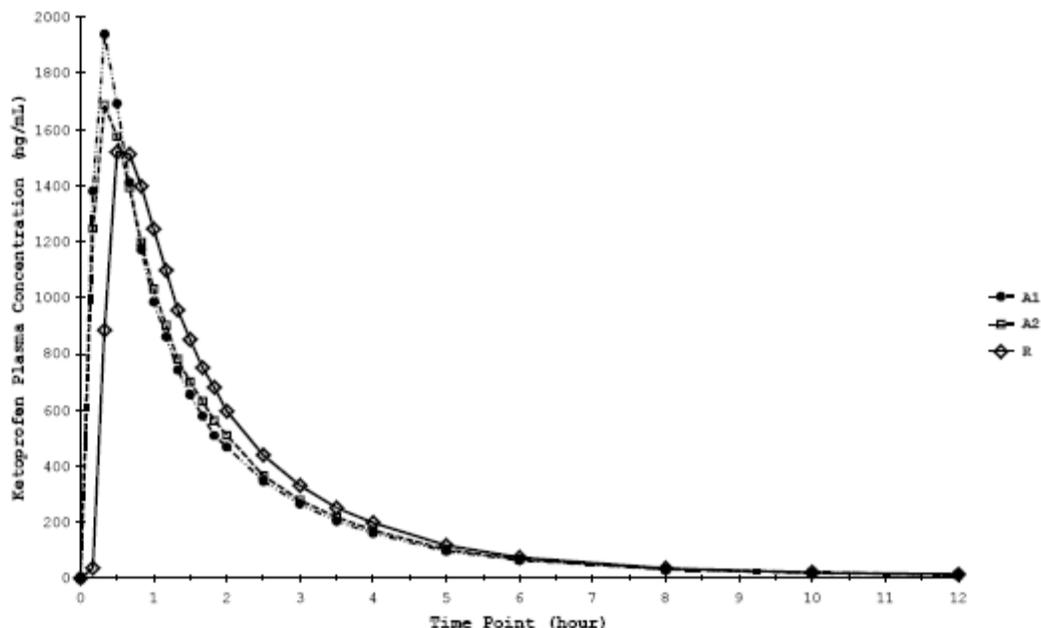
A1: One ketoprofen 12.5 mg orally- (b) (4) administered with 150 mL of water;

A2: One ketoprofen 12.5 mg orally- (b) (4) administered without water;

R: One Orudis KT 12.5 mg tablet administered with 150 mL of water.

N: Number of subjects in the PK analysis population; p-value is based on analysis of variance (ANOVA) with treatment, sequence, period and subject x treatment interaction as factors; Geometric means are obtained by exponentiating the least square means of log-transformed values from the ANOVA model

Fig 4.2.2.2.1 Mean plasma concentration-time profiles (linear scale) for KT-OSF with or without water Vs. Orudis® KT- IR tablet.



A1: One ketoprofen 12.5 mg orally- (b) (4) administered with 150 mL of water;
A2: One ketoprofen 12.5 mg orally- (b) (4) administered without water;
R: One Orudis® KT 12.5 mg tablet administered with 150 mL of water.

Conclusion: *KT- OSF with and without water is bioequivalent to the reference Orudis KT IR tablet*

4.2.2.2.2 Part II- Dose Proportionality and Bridging BE:

Objectives: The objective of this study was to investigate dose proportionality between one and two 12.5 mg KT-OSF and to demonstrate BE between Clinical Service Form (used in pivotal BE study) and Final Market image formulation.

Dosing

This study consisted of 3 treatment periods of approximately 24 hours in duration separated by a washout period of 72 hours in length. All the 3 treatment groups received peppermint flavor and were:

- One 12.5 mg KT-OSF FMI administered without water
- Two 12.5 mg KT-OSF FMI administered without water
- One 12.5 mg KT-OSF CSF administered without water.

Note: The FMI formulation contains the same amount of KT as in the CSF but has an increased film weight of 70 mg (versus 60 mg of the CSF).

The first film was placed on the tongue of the subject by using forceps. The film was allowed to be dissolved and then swallowed. The second film was placed on the subject's tongue approximately 15 to 20 seconds after placement of the first film.

Study Results:

A total of 42 subjects were exposed to at least one dose of study medication. The total number of subjects' completed each treatment is listed in the tables 4.2.2.2.2.1 and 4.2.2.2.2.2

The FMI (treatment B1) and CSF formulations (treatment B3) are BE to each other based upon the CIs for C_{max} , AUC_{0-t} and AUC_{0-inf} falling within 80 to 125%. For the dose proportionality study, one (treatment B1) and two (treatment B2) 12.5 mg KT-OSF administered without water under fasting conditions demonstrated dose proportionality. The geometric mean, ratios of geometric means and CIs for the treatments, B1, B2 and B3 are shown in the Table 4.2.2.2.2.1 and 4.2.2.2.2. The mean plasma concentration-time profiles (linear scale) for this study is represented figure 4.2.2.2.2.1.

Table 4.2.2.2.2.1: PK parameters for Bridging BE study between FMI (B1) and CSF (B3).

Parameter/Statistic	B1 (N=39)	B3 (N=39)
C_{max} (ng/mL)		
Geometric mean	1949.6	1858.0
Test/Reference Ratio (%) (Reference =B3)	104.93	-
90% Confidence interval (Reference =B3)	(97.79, 112.58)	-
AUC_{0-t} (ng*h/mL)		
Geometric mean	2903.1	2848.2
Test/Reference Ratio (%) (Reference =B3)	101.93	-
90% Confidence interval (Reference =B3)	(99.41, 104.50)	-
AUC_{0-inf} (ng*h/mL)		
Geometric mean	2948.6	2891.5
Test/Reference Ratio (%) (Reference =B3)	101.98	-
90% Confidence interval (Reference =B3)	(99.39, 104.63)	-

B1: One ketoprofen 12.5 mg orally- (b) (4) FMI;

B3: One ketoprofen 12.5 mg orally- (b) (4) CSF (Reference).

N: Number of subjects in the PK BE population

Table 4.2.2.2.2: Dose proportionality between one (B1) and two (B2) 12.5 mg KT-OSF FMI

Parameter ¹ /Statistic	B1 (N=38)	B2* (N=38)
C_{max} (ng/mL)		
Geometric mean	1935.0	1771.9
Test/Reference Ratio (%) (Reference =B1)	-	91.57
90% Confidence interval (Reference =B1)	-	(83.11, 100.89)
AUC_{0-t} (ng*h/mL)		
Geometric mean	2913.9	2830.9
Test/Reference Ratio (%) (Reference =B1)	-	97.15
90% Confidence interval (Reference =B1)	-	(92.02, 102.57)
AUC_{0-inf} (ng*h/mL)		
Geometric mean	2967.7	2887.7
Test/Reference Ratio (%) (Reference =B1)	-	97.30
90% Confidence interval (Reference =B1)	-	(92.11, 102.79)

¹ Ln-transformed data are displayed

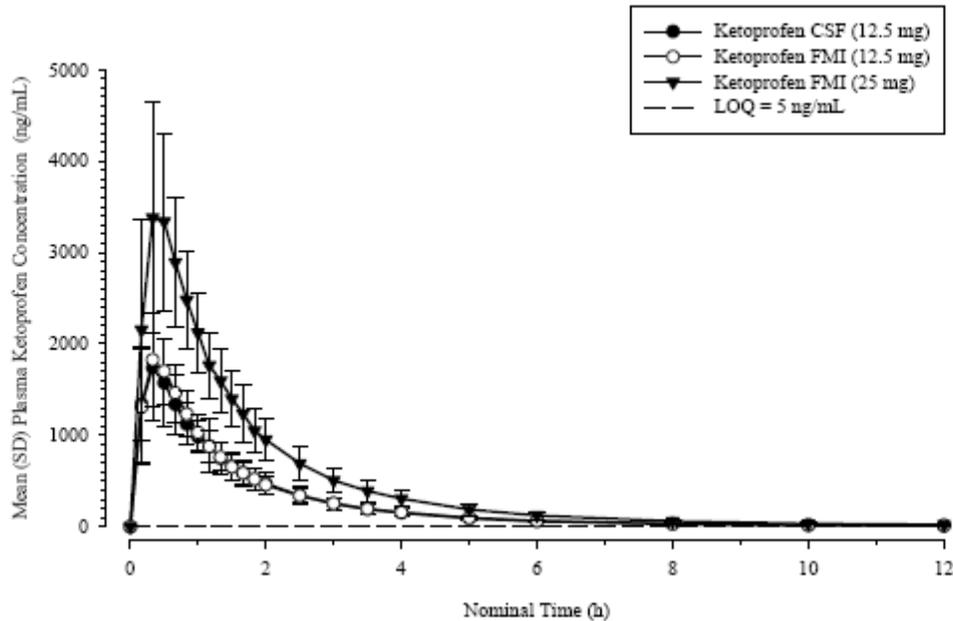
* values displayed are normalized by dose

B1: One ketoprofen 12.5 mg orally; (b) (4) FMI ;

B2: Two ketoprofen 12.5 mg orally; (b) (4) FMI.

N: Number of subjects in the PK dose proportionality population

Fig 4.2.2.2.1. The mean plasma concentration-time profiles (linear scale) for CSF and, one and two 12.5 mg KT-OSF FMI



Reviewer comments:

- The dose proportionality for KT-OSF has been demonstrated between one 12.5 mg film and two 12.5 mg films.
- Bridging BE study is acceptable

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	NDA-22-470		Brand Name	
OCP Division (I, II, III, IV, V)	II		Generic Name	Ketoprofen
Medical Division		Drug Class	Propionic acid derivative	
OCP Reviewer	Suresh B Narahariseti		Indication(s)	Temporary relief of minor aches and pains
OCP Team Leader	Suresh Doddapaneni		Dosage Form	Oral (b) (4) Film
Pharmacometrics Reviewer		Dosing Regimen	1 film every 4-6 h	
Date of Submission	January 26, 2009		Route of Administration	Oral
Estimated Due Date of OCP Review	June 24, 2009		Sponsor	Novartis Consumer Health, Inc.
Medical Division Due Date		Priority Classification		
PDUFA Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				

multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	3	

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22470

ORIG-1

NOVARTIS
CONSUMER
HEALTH INC

KETOPROFEN ORAL-ORAL
(b) (4)

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/s/

SURESH B NARAHARISSETTI
09/03/2009

SURESH DODDAPANENI
09/03/2009

Addendum to the Primary Clinical Pharmacology Review Dated September 03, 2009

NDA: 22-470	Submission Date: 01/26/09
Submission Type; Code:	505 (b) (2)
Brand/Code Name:	Nexede
Generic Name:	Ketoprofen
Formulation; Strength(s):	Oral Soluble Film, 12.5 mg
Primary Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Nonprescription Clinical Evaluation
Sponsor:	Novartis Consumer Health, Inc
Proposed Indication:	For temporary relief of minor aches and pains due headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis; and reduction of fever
Proposed Dosage Regimen:	<ul style="list-style-type: none">• Adults and children 16 years and over: 1 film to dissolve on tongue every 4 to 6 hours. One more film may be taken, if pain or fever does not get better in 1 hour.• Films should not exceed more than 2 in any 4 to 6 hour period and 6 in any 24 hour period.• Children under age 16 should not be given oral (b) (4) films unless directed by a doctor

This addendum to Primary Clinical Pharmacology review is to address the recommendations made by Division of Scientific Investigation (DSI) on the audited pivotal BE study, EDKT-PN-101. At the time of signing-off the primary Clinical Pharmacology review for NDA 22-470, DSI inspection-report for study EDKT-PN-101 was pending. Subsequently, DSI finalized their report on September 11, 2009 (see review by Dr. Dasgupta, Arindam, Ph.D. dated 09/11/2009 for details).

The recommendations from DSI were:

1. The accuracy of the pharmacokinetic data from the subjects 1016, 1020, 1023, 1025, 1053, 1054, 1071 and 1072 in study EDKT-PN-101 (Part -I) has not been assured, as the analytical runs for analysis of plasma samples from these subjects had two of three failed quality controls samples at 15 ng/ml (>15% deviation from the actual concentration). The data from these subjects should be excluded from the BE analysis. Except for these runs in the BE study, all other runs were acceptable.
2. The firm should investigate and provide the data to show that there is no Incurred Sample Reproducibility issue with LC/MS/MS method used in the study EDKT-PN-01

To address DSI recommendation 1, the BE data was reanalyzed by excluding the PK data from these 8 subjects. The reanalysis showed no significant differences between the

original and reanalyzed data (table 1) and consequently the conclusions made in the primary review dated September 03, 2009 regarding the outcome of this study stand.

Table 1. BE analysis results for study EDKT-PN-101 (Part-I)

PK parameter	Treatment	Original submission		After reanalysis	
		90 % CI	90 % CI	90 % CI	90 % CI
		lower limit	upper limit	lower limit	upper limit
C _{max}	With water	96.53	111.10	97.65	108.80
C _{max}	Without water	89.22	102.67	90.96	101.39
AUC _{last}	With water	93.23	103.72	96.38	99.53
AUC _{last}	Without water	93.93	104.48	97.53	100.74
AUC _{inf}	With water	93.20	103.73	96.38	99.54
AUC _{inf}	Without water	93.91	104.51	97.50	100.72

DSI will review the data pertaining to recommendation 2 when the data are submitted by the CRO, (b) (4)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22470

ORIG-1

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KETOPROFEN ORAL-ORAL
(b) (4)

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/s/

SURESH B NARAHARISSETTI
09/30/2009

SURESH DODDAPANENI
09/30/2009

Second Addendum to the Primary Clinical Pharmacology Review Dated 09/03/2009

NDA: 22-470	Submission Date: 01/26/09
Submission Type; Code:	505 (b) (2)
Brand/Code Name:	Nexede
Generic Name:	Ketoprofen
Formulation; Strength(s):	Oral Soluble Film, 12.5 mg
Primary Reviewer:	Suresh B Naraharisetti, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Nonprescription Clinical Evaluation
Sponsor:	Novartis Consumer Health, Inc
Proposed Indication:	For temporary relief of minor aches and pains due to headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis; and reduction of fever
Proposed Dosage Regimen:	<ul style="list-style-type: none">• Adults and children 16 years and over: 1 film to dissolve on tongue every 4 to 6 hours. One more film may be taken, if pain or fever does not get better in 1 hour.• Films should not exceed more than 2 in any 4 to 6 hour period and 6 in any 24 hour period.• Children under age 16 should not be given oral (b) (4) unless directed by a doctor

BACKGROUND:

At the time of signing-off the primary Clinical Pharmacology review for NDA 22-470 on 9/3/09, Division of Scientific Investigations (DSI) inspection report for pivotal BE study EDKT-PN-101 was pending. Subsequently, DSI finalized their report on September 11, 2009 (see review by Dr. Arindam Dasgupta, Ph.D. dated 09/11/2009 for details). First addendum to Primary Clinical Pharmacology review dated 9/30/09 addressed the recommendations made by Division of Scientific investigation (DSI) on the audited pivotal BE study, EDKT-PN-101. Of the two recommendations made by DSI, issue regarding BE analysis after omitting data from subjects where accuracy of such data could not be assured was satisfactorily resolved. However, issue regarding incurred sample reproducibility was not satisfactorily resolved at that time as sponsor did not provide new data on incurred sample reproducibility as advised by the Agency. On 11/17/09, additional data on incurred sample reproducibility was submitted and was reviewed by Dr. Arindam Dasgupta, Ph.D. on 11/19/09.

This 2nd addendum to Primary Clinical Pharmacology review addresses the recommendations made by Dr. Dasgupta in his review of 11/19/09. Essentially, DSI review found that ISR results demonstrate reproducibility and there are no stability issues and concluded that "The analytical portion of the study EDKT-PN-101 can be accepted for review".

RECOMMENDATION:

As all issues related to DSI inspection of pivotal BE study EDKT-PN-101 have been satisfactorily resolved, NDA 22-470 is acceptable from a Clinical Pharmacology perspective.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22470

ORIG-1

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KETOPROFEN ORAL-ORAL
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SURESH B NARAHARISSETTI
11/20/2009

SURESH DODDAPANENI
11/20/2009

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-470
Submission Date:	01/23/09
Brand Name:	(b) (4)
Generic Name:	Ketoprofen
Formulation:	Oral (b) (4)
Strength:	12.5 mg (b) (4) (with Peppermint or Cinnamon flavor)
Sponsor:	Novartis
Type of submission:	Biowaiver request for the strip with Cinnamon flavor, not tested in the <i>in vivo</i> bioequivalence study
Reviewer:	Tien-Mien Chen, Ph.D.

BACKGROUND

Ketoprofen drug products had been on the market as a prescription NSAID (non-steroidal anti-inflammatory drug). It is indicated as a pain reliever for temporarily relief of minor aches and pains due to: headache, the common cold, toothache, muscular aches, backache, menstrual cramps, minor pain of arthritis, or temporarily reduces fever.

On 01/23/09, Novartis submitted NDA 22-470 for (b) (4) (ketoprofen 12.5 mg) oral (b) (4) with peppermint or cinnamon flavor for OTC (over-the-counter) use. The to-be-marketed (TBM) formulation (No. 1588-02) with peppermint flavor has been tested in an *in vivo* bridging, bioequivalence (BE) study (No. EDKT-PN-101) comparing the formulation No. 1588-02 (Batch No. Z214871A) with Orudis KT 12.5 mg tablet. The sponsor reported that the results show BE between the tested articles.

The sponsor also submitted a biowaiver request and *in vitro* comparative dissolution data for another ketoprofen oral (b) (4) formulation (No. 1589-01) with cinnamon flavor which was not tested *in vivo*. The biowaiver and *in vitro* comparative dissolution testing between the two TBM formulations (Nos. 1588-02 and 1589-01) of ketoprofen oral (b) (4) are therefore, reviewed here. Please see Appendix for individual dissolution data for details.

FORMULATION COMPARISONS

The composition of TBM formulations of (b) (4) (Ketoprofen 12.5 mg) oral (b) (4) (b) (4) is shown below:

Table 1. Composition of (b) (4) (Ketoprofen 12.5 mg) Oral (b) (4) With Peppermint Flavor

Ingredient	Amount (mg) (b) (4)	Function	Reference to quality standards ¹
Ketoprofen	12.50	active ingredient	USP/NF
Hypromellose (b) (4)	(b) (4)	(b) (4)	USP/NF
Sucralose	(b) (4)	(b) (4)	USP/NF
Polyethylene glycol 400	(b) (4)	(b) (4)	USP/NF
Xylitol	(b) (4)	(b) (4)	USP/NF
Maltodextrin	(b) (4)	(b) (4)	USP/NF
Peppermint flavor	(b) (4)	(b) (4)	(b) (4)
Sodium hydroxide	(b) (4)	(b) (4)	USP/NF
Acesulfame potassium	(b) (4)	(b) (4)	USP/NF
Sodium phosphate dibasic	(b) (4)	(b) (4)	USP/NF
FD&C blue #1	(b) (4)	(b) (4)	(b) (4)
Water, purified ³	---	(b) (4)	USP/NF
Acetone ⁴	---	(b) (4)	USP/NF
White imprint ink ⁵	---	(b) (4)	(b) (4)
Total strip weight	70.00		

¹ Current edition

² In-house specification of (b) (4)

(b) (4)

⁵ The quantity of imprint ink per strip is negligible.

⁶ In-house specifications of (b) (4)

Table 2. Composition of (b) (4) (Ketoprofen 12.5 mg) Oral (b) (4) With Cinnamon Flavor

Ingredient	Amount (mg) (b) (4)	Function	Reference to quality standards ¹
Ketoprofen	12.50	active ingredient	USP/NF
Hypromellose (2910, 4-6 centipoise)	(b) (4)	(b) (4)	USP/NF
Sucralose	(b) (4)	(b) (4)	USP/NF
Polyethylene glycol 400	(b) (4)	(b) (4)	USP/NF
Xylitol	(b) (4)	(b) (4)	USP/NF
Maltodextrin	(b) (4)	(b) (4)	USP/NF
Sodium hydroxide	(b) (4)	(b) (4)	USP/NF
Acesulfame potassium	(b) (4)	(b) (4)	USP/NF
Cinnamon flavor	(b) (4)	(b) (4)	HSE ²
Sodium phosphate dibasic	(b) (4)	(b) (4)	USP/NF
FD&C red #40	(b) (4)	(b) (4)	21CFR74.1340
Water, purified ³	(b) (4)	(b) (4)	USP/NF
Acetone ⁴	(b) (4)	(b) (4)	USP/NF
White imprint ink ⁵	(b) (4)	(b) (4)	(b) (4)
Total strip weight	70.00		

¹ Current edition

² In-house specification of (b) (4)

(b) (4)

⁵ The quantity of imprint ink per strip is negligible.

⁶ In-house specifications of (b) (4)

The above two formulations are compositionally the same and proportional similar except for difference in flavor (and amount) and in a film-forming polymer, Hypromellose (b) (4). The Agency agreed that the changes were considered having no impact on the bioavailability of various flavors of the finished products. Please see 02/06/07 Pre-IND meeting minutes for details.

DISSOLUTION COMPARISONS

The comparative dissolution data was submitted, however, incomplete. An IR (information request) was sent out due to 1) the biobatch (No. Z214871A) was not used for dissolution comparison and 2) data generated only with 6 strips/batch. On 08/25/09, the sponsor responded to Agency's IR. The additional data is therefore reviewed and presented here. The batches used in the comparative dissolution testing are shown below.

Table 1. Batch Information on the Ketoprofen Oral (b) (4)

Product	Sample ID	Batch number	Batch type
Ketoprofen oral (b) (4) 12.5 mg, peppermint, 70 mg (b) (4) (1588-02)	1588-2859, 17	Z214871A	Biobatch
Ketoprofen oral (b) (4) 12.5 mg, cinnamon, 70 mg (b) (4) (1589-01)*	1589-2796, 48	Z214923A	Stability

* - same data as previously provided in the original report

Twelve (b) (4) two buffered dissolution media (pH 7.2 and 5.8) and multiple pull times (5, 10, 15, 30, 45 and 60 mins) were employed. A pH lower than 5.8 was reportedly not evaluated because of the low solubility of ketoprofen at low pH. The mean dissolution results [mean and SD (standard deviation) of 12 strips] for the two formulations at pH 5.8 and pH 7.2 are provided below.

Table 2. Percent of Ketoprofen (mean ± SD) Dissolved at Various Time Points (pH 5.8)

Flavor/Batch No.	5 min	10 min	15 min	30 min	45 min	60 min
Peppermint/Z214871A	67.1 ^a (± 24.3)	85.3 (± 12.5)	93.4 (± 6.0)	99.3 (± 0.9)	99.0 (± 1.0)	99.0 (± 1.0)
Cinnamon/Z214923A	71.6 (± 24.1)	85.8 (± 12.3)	93.2 (± 4.9)	97.4 (± 1.1)	97.5 (± 1.1)	97.5 (± 1.1)
f2 Value	73.7					

^a. Mean data in blue was used in f2 calculation.

Table 3. Percent of Ketoprofen (mean ± SD) Dissolved at Various Time Points (pH 7.2)

Flavor/Batch No.	5 min	10 min	15 min	30 min	45 min	60 min
Peppermint/Z214871A	57.4 ^a (± 17.0)	80.2 (± 9.5)	91.9 (± 4.3)	98.8 (± 0.8)	98.8 (± 0.8)	98.9 (± 0.7)
Cinnamon/Z214923A	64.5 (± 19.0)	84.0 (± 9.6)	92.7 (± 4.3)	97.3 (± 1.2)	97.4 (± 1.2)	97.5 (± 1.1)
f2 Value	66.0					

^a. Mean data in blue was used in f2 calculation.

The comparative dissolution profiles are shown below in pHs 5.8 and 7.2, respectively.

Figure 1. Comparative Dissolution Profiles in pH 5.8 Medium

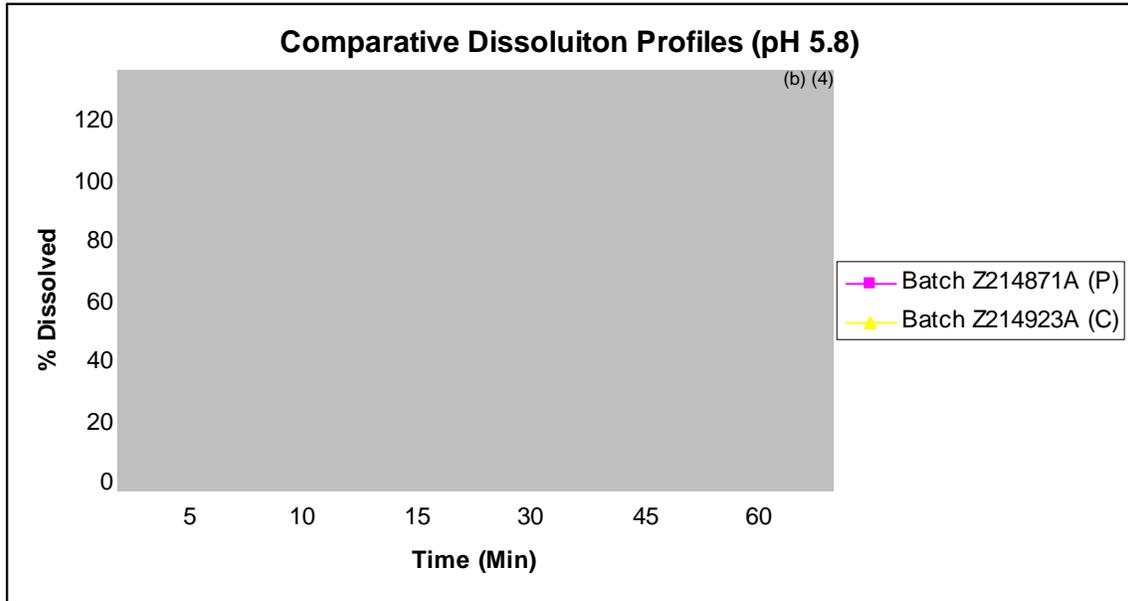
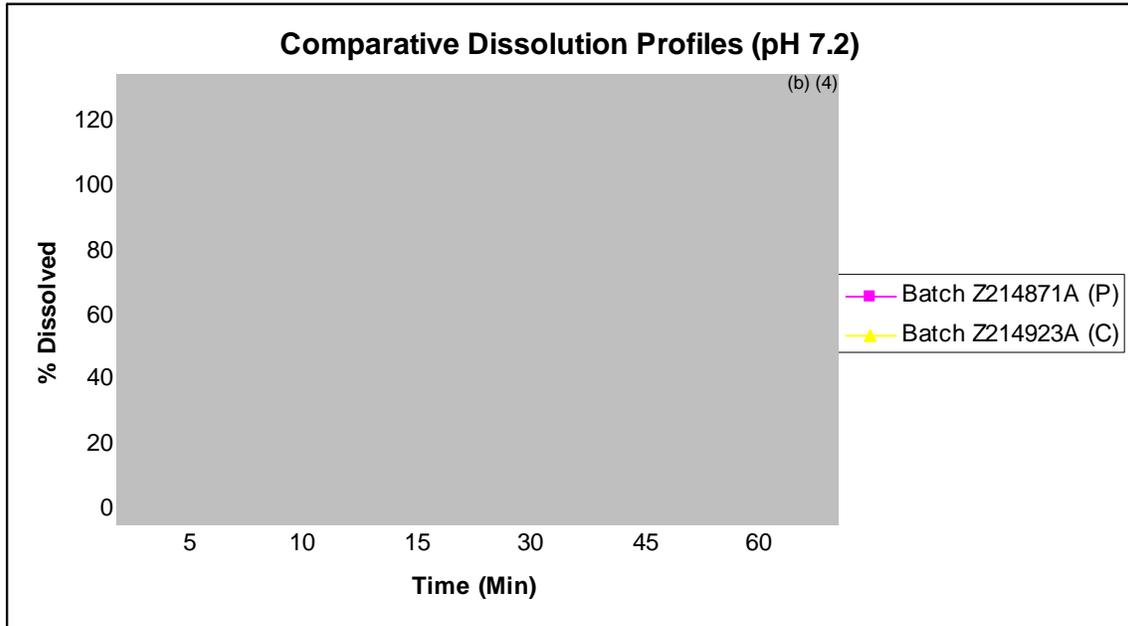


Figure 2. Comparative Dissolution Profiles in pH 7.2 Medium



Please see individual dissolution data in Appendix for details. The proposed dissolution methodology and specifications are shown below:

- Apparatus:** USP Paddle (II) with 50 rpm
- Medium:** 900 mL Phosphate buffer (pH 7.2) at 37°C
- Specifications:** Q= (b) (4) in 30 min

Reviewer's Comments

1. The above f2 value was calculated by this reviewer using 2 points for pH 5.8 and 3 points for pH 7.2 media (mean data in blue in Tables 2 and 3). The f2 values are all within 50-100 indicating the two formulations (No. 158802 for peppermint flavor and No. 158901 for cinnamon flavor) are similar.
2. The time point at 5 min was included for f2 calculation, however, the guidance stated that the CV should not be >20%. If the mean data points at 5 min were excluded, this represents a case of difficulties in f2 calculation for there is only one time point left to use for pH 5.8 medium.
3. Large variation was found at initial dissolution in both pH media, however, it was not considered in the current f2 calculation. The CV% ranged from 29.5 to 36.2% (at 5 min) and 11.5 to 14.6% (at 10 min). The sponsor provided a rationale that it is typical of most dosage forms at they disintegrate and release the drug substance for dissolution. However, the sponsor's conclusion could not be verified by this reviewer, since the disintegration time is reported to be <0.5 min.
4. The proposed dissolution specs. should be tightened as follows.

From: Q= (b) (4) in 30 min to: Q= (b) (4) in 15 min

RECOMMENDATION

Novartis submitted NDA 22-470 on 01/23/09 for Ketoprofen oral (b) (4) 12.5 mg for OTC use. The biowaiver request and results of *in vitro* comparative dissolution are reviewed.

From the Biopharmaceutics perspective, the biowaiver request for Ketoprofen oral (b) (4) with Cinnamon flavor is granted. However, the proposed dissolution specifications for this oral (b) (4) product should be tightened to Q (b) (4) in 15 min.

COMMENT: (needs to be conveyed to the sponsor)

The proposed dissolution specifications for Ketoprofen oral (b) (4) should be tightened as follows:

From: Q= (b) (4) in 30 min to: Q (b) (4) in 15 min

_____	08/28/09
Tien-Mien Chen, Ph.D.	Date
Reviewer	
ONDQA Biopharmaceutics	
_____	08/28/09
Patrick Marroum, Ph.D.	Date
ONDQA Biopharmaceutics	

CC: NDA, Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

NDA 22-470 for Ketoprofen Oral (b) (4)
(b) (4) 12.5 mg (Peppermint or Cinnamon Flavor)

Appendix

Individual Dissolution Data

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

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

/s/

TIEN MIEN CHEN
08/31/2009

PATRICK J MARROUM
08/31/2009