

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-470

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	5-Nov-2009
From	Lesley-Anne Furlong
NDA/BLA #	22-470
Applicant	Novartis Consumer Health, Inc.
Date of Submission	23-Jan-2009
PDUFA Goal Date	26-Nov-2009
Proprietary Name / Established (USAN) names	Nexcede/ketoprofen
Dosage forms / Strength	Oral soluble films/12.5 mg
Proposed Indication(s)	<ol style="list-style-type: none"> 1. temporary relieves minor aches and pains due to <ul style="list-style-type: none"> • headache • toothache • backache • minor pain of arthritis • the common cold • muscular aches • menstrual cramps 2. temporarily reduces fever
Recommended:	<p>Approval pending</p> <ul style="list-style-type: none"> • Resolution of the DSI issue related to incurred sample reproducibility • Satisfactory inspection of the manufacturing site

1. Introduction

This submission proposes a new formulation and new dosing directions for ketoprofen for over-the-counter (OTC) use. Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) that the Agency first approved in the United States in 1986 for prescription use, and then approved in 1995 for over-the-counter (OTC) use.

In the United States, the prescription (Rx) indications for ketoprofen include management of pain, treatment of primary dysmenorrhea, and management of the signs and symptoms of rheumatoid arthritis and osteoarthritis. The recommended maximum daily dose for the Rx indications is ketoprofen 300 mg/day, and available Rx single dosage strengths range from 25 to 200 mg. Rx pediatric labeling states that the “safety and effectiveness in pediatric patients

below the age of 18 have not been established.” In contrast, the OTC indications are temporary relief of minor aches and pains and temporary reduction of fever; the maximum OTC daily dose is ketoprofen 75 mg/day; and pediatric labeling supports use by children 16 years of age and older.

The new formulation consists of orally dissolving, sweetened films in cinnamon (red) or peppermint (blue) flavors. The new dosing directions allow for use without a glass of water.

To support the application, the applicant has performed one preclinical study in hamsters and three clinical pharmacokinetic (PK) studies. The applicant also referred to FDA’s previous findings of safety and efficacy for ketoprofen. Additionally, the applicant supplied postmarketing data and articles from the literature, with a focused discussion of photosensitivity reactions.

A potential safety concern related to the changes in the dosing instructions was effect on the oral mucosa. Therefore, safety of the oral mucosa was evaluated in the preclinical study (a buccal mucosal tolerability study in hamsters), and was part of the safety evaluation in all three clinical PK studies.

The proposed indications are the approved indications for ketoprofen OTC tablets. In addition, the proposed dose (12.5 mg), dosing frequency (one film every 4 to 6 hours), and dosing duration (for no more than 10 days) are the same as the approved dosing regimen for ketoprofen OTC tablets. Dosing instructions allow for taking two films or two tablets with the first dose. (“With experience, some people may find they need 2 films for the first dose.”) Finally, the proposed population, consumers 16 years of age and older, is the approved population for ketoprofen OTC tablets.

2. Background

Ketoprofen was first approved in the United States in 1986 for prescription use as ketoprofen capsules (50 mg and 75 mg). In September 1993, capsules containing up to 200 mg ketoprofen were approved, also for prescription use. Ketoprofen 12.5 mg tablets were approved for OTC use in 1995. Numerous generic prescription capsules in strengths ranging from 50 mg to 200 mg are currently listed in the FDA’s Orange Book. The OTC strength is not currently marketed in the United States. Although Orudis KT is not currently marketed, FDA has determined that Orudis KT was “not withdrawn from sale for reasons of safety or effectiveness.”¹

Novartis Consumer Healthcare (referred to as the applicant or NCH in this review) submitted a 505(b)(2) application that references FDA’s previous finding of safety and efficacy for ketoprofen (NDA 18-754 and NDA 20-429). NDA 18-754 is a prescription formulation of ketoprofen (brand name Orudis), and NDA 20-429 is an OTC formulation of ketoprofen (brand name Orudis KT).

¹ Federal Register Vol 72, No. 156, p.45434, 14-Aug-2007

The applicant requested only one meeting with the FDA during product development. At the preIND meeting held on February 6, 2007 under IND #74,282, FDA provided general guidance about the 505(b)(2) route to market approval. At the meeting, NCH received the following advice pertinent to the clinical review

- The NDA should provide available data regarding phototoxicity and photoallergenicity of ketoprofen.
- Safety on the oral mucosa should be addressed, but FDA stated that “the concern is local toxicity and that safety studies would not be requested unless the data provided in the NDA submission is not adequate to support the safety of the product”
- Worldwide marketing and safety data should be provided

The proposed product is a new formulation that has not been marketed elsewhere.

3. CMC/Device

According to the chemistry review team, the applicant “has provided sufficient information to assure identity, strength, purity, and quality of the drug product.” The chemistry review team has recommended approval of the NDA when labeling is satisfactorily negotiated and when the clinical site issues identified by the Office of Compliance are resolved. The manufacturing site inspection was still pending at the time this review was finalized.

The drug product is a rapidly dissolving, immediate release, thin film measuring 22 mm x 32 mm. Two flavors are proposed: a transparent peppermint-flavored film and a light red, cinnamon-flavored film. The CMC review team has recommended that the dosage form be called “oral soluble film.”

Bioequivalence studies were performed using the peppermint-flavored film and the applicant requested a biowaiver for the cinnamon-flavored film. The biopharmaceutics reviewer recommended granting the biowaiver based on the similar compositions and similar dissolution profiles of the flavored films.

Specifications for the drug product, information related to packaging, and stability data were all deemed acceptable. Stability data support a proposed expiration dating period of 24 months when stored at 25° C, with excursion permitted to 15° to 30° C. The drug substance complies with the USP monograph.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team had no outstanding issues, and recommended approval from a nonclinical perspective.

The only preclinical study in the application was a local buccal tolerability study in hamsters. The buccal tolerability involved exposure of hamsters to ketoprofen soluble films for 14 consecutive days, at six applications per day, and no buccal irritation was detected.

The applicant also submitted a review on photosensitization potential of ketoprofen in the nonclinical section. According to the review team, “Ketoprofen phototoxicity has not been confirmed in standardized (guinea pig) studies, but it is clearly photoallergenic.” However, “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 irradiations) 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.”

5. Clinical Pharmacology/Biopharmaceutics

The pharmacokinetic studies achieved their endpoints by showing that

- The soluble film was bioequivalent to the approved tablet
- Taking the film with or without water did not change the AUC or Cmax
- There was food effect, noted as a 40% decrease in Cmax under fed conditions, as expected based on historical data for the tablet formulation. Tmax was delayed from about 0.4 hours in the fasting state to 0.7 hours in the fed state.

The clinical pharmacology team found the applicant’s submission approvable pending agreement on labeling and pending an acceptable audit of Study EDKT-PN-101 by FDA’s Division of Scientific Investigations (DSI).

The clinical pharmacology team also found NCH’s proposed labeling acceptable. NCH made the following changes compared with the label of the approved product, based on the PK data:

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

The clinical pharmacology team agreed that both changes were supported by the pharmacokinetic data in the submission.

In response to DSI concerns about data from eight subjects, the clinical pharmacology team re-analyzed the pharmacokinetic data from study 101, Part I, removing the data from eight subjects. The re-analysis also demonstrated bioequivalence. Additional information about the PK studies follows in Section 7 of this review.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Efficacy was demonstrated through bioequivalence of the new formulation to an approved tablet (Orudis KT) that has the same indications. The change in dosing instructions (without water) was supported by demonstrating that the pharmacokinetics of the new formulation were the same with or without water ingestion.

The features of the three pharmacokinetic studies are summarized in Table 1, and their endpoints are reviewed in detail in the clinical pharmacology review. A summary is provided here.

Table 1. Clinical Pharmacology Studies in the Submission

Study Name	Design	Goals	N (randomized)
101 Part I	Randomized Open-label Crossover Single-center Fasting Used Clinical Service Formulation (CSF)	<ul style="list-style-type: none"> • Show BE between film and Orudis KT • Show BE of film with and without water 	90
101 Part II	Randomized Open-label Crossover Single-center Used CSF and FMI (“final marketing image” = to-be-marketed formulation)	<ul style="list-style-type: none"> • Investigate dose proportionality of one and two films • Show BE between clinical study formulation (CSF) and to-be-marketed formulation (FMI) 	42
102	Randomized Open-label Crossover Single-center Used FMI	<ul style="list-style-type: none"> • Evaluate food effect 	40

Source: Section 2.5 Clinical Overview, Table 3-1, page 11

The three studies achieved their goals. Briefly,

- Study 101 Part I showed bioequivalence between a prototype of the new formulation (called CSF, for clinical service formulation) and Orudis KT.
- Study 101 Part 1 also showed that taking the film with or without water did not affect systemic exposure to ketoprofen.
- Study 101 Part II showed bioequivalence between the CSF and the to-be-marketed formulation (called FMI, for final marketing image). Dose proportionality was also demonstrated.

- Study 102 evaluated the food effect and found that, under fed conditions, the C_{max} of ketoprofen was 40% relative to that under fasted conditions; however, the overall bioavailability measured by AUC was similar under fed and fasted conditions. The clinical pharmacology reviewer noted that the magnitude of the food effect seems to be attributable to the drug substance and is independent of formulation because comparable effects have been noted with other formulations.

The PK parameters demonstrating bioequivalence, with and without water, are shown in Table 2.

Table 2. Summary Statistics of PK Parameters Comparing Film (with and without water) to Orudis KT 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

Source: FDA clinical pharmacology review, p. 10

During the review, the Agency's Division of Scientific Investigations notified the review team of deficiencies related the data for eight subjects in Study 101, Part 1. The clinical pharmacology reviewer re-analyzed the data after removing the data contributed by those eight subjects. Bioequivalence was maintained. Table 3 compares the BE analysis with the BE re-analysis and shows that the PK parameters relevant to bioequivalence, AUC and C_{max}, remained within the required limits of 80 to 125%.

Table 3. BE Re-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

Source: addendum to FDA clinical pharmacology review, p.2

8. Safety

The development program adequately supported the safety of ketoprofen soluble films.

The general safety of ketoprofen films was primarily supported by the demonstration of bioequivalence to an approved product, Orudis KT. In addition, data related to adverse events, examinations (including examinations of the oral cavity), and laboratory evaluations were collected during the PK studies.

The applicant paid particular attention to mucosal safety because, unlike the tablet, the film dissolves completely in the mouth and will be dosed without water. Therefore, oral mucosa safety was evaluated in the clinical pharmacology studies listed in Table 1, as well as the hamster study described in Section 4 of this review.

In addition, the applicant provided a summary of postmarketing data and literature.

Summary of safety from the PK studies

A total of 172 healthy subjects between 18 and 65 years old participated in the clinical pharmacology studies. Because of the crossover designs, some subjects received two exposures to the films. Dosing was one or two ketoprofen 12.5 films. There were a total of 368 exposures to the films among 172 subjects.

There were no deaths or serious adverse events. There were two discontinuations for adverse events. Both discontinuations occurred in subjects who received only Orudis KT. One subject withdrew due to oral mucosal eruption noted at a Period II predose oral examination, and the second subject withdrew due to moderate upper lip swelling accompanied by a mild rash. The lip swelling resolved in one day and the rash resolved in 10 days.

The percentage of subjects reporting adverse events in any study arm ranged from 2.5% (2 of 41) to 10% (4 of 40). The oral (b)(4) film had a safety profile that was comparable to the safety profile of the tablets. The most common adverse events were headaches (12 reports in 11 subjects). None of the headaches were severe or serious. Other adverse events reported

more than once included nausea (2), oral mucosa eruption (2), vomiting (3), and blood creatinine phosphokinase (CPK) increased (3). All were reported as mild in severity. As noted, above, one episode of oral mucosal eruption occurred in a subject who received only Orudis KT and this subject discontinued the study; the other episode occurred in a subject who received the soluble film. For the subject who received the soluble film, the oral mucosal eruption was described as a 2-mm, asymptomatic papule on the right cheek noted four hours after administration of study drug. The papule resolved by 12 hours post dose.

Mean hemoglobin decreased about 1 g/dL, as expected for the amount of blood drawn (270-400 mL) for these PK studies. The elevated CPKs were evaluated by the applicant and the primary clinical reviewer and were not felt to be significant. I have reviewed their analyses and concur. All three subjects were young (21, 22, and 23 years old) and reported no adverse events. Furthermore, the applicant reported that elevated CPK was a common finding at screening and postulated that the finding could be related to exercise in these young adults. Of note, CPK elevation does not appear on labeling for ketoprofen.

Published literature

The applicant performed several general MEDLINE searches on 10-Nov-2008 with no limitation in dates, using a variety of safety related terms, such as “safety,” “side effects,” “renal,” “cardiovascular,” “hematologic,” and “liver.” References related to prolonged use, extended release formulations, and pediatric subjects were excluded. The search did not identify any new AEs for the NSAID class.

The applicant also performed targeted searches for the photosensitivity potential of ketoprofen and related NSAIDS, and evaluated the postmarketing databases for photosensitivity reactions. Per the primary clinical reviewer, “Most of the photosensitization reactions were associated with topical ketoprofen formulation. Reports of photoallergic reactions with oral ketoprofen are rare.” Among 81 literature reports of photosensitization with ketoprofen, only one was associated with oral dosing. However, the subject had reacted with acute dermatitis during a previous summer to a topical formulation, suggesting that the induction of allergy occurred after topical administration. A total of 17 cases of photosensitivity were retrieved from AERS; 2 cases specified OTC oral doses.

Postmarketing data

According to the primary clinical reviewer, “the postmarketing information available for ketoprofen shows no evidence of unexpected adverse events.”

As ketoprofen soluble film is a new formulation that is not yet approved in any country, the postmarketing analysis relied on data from other Rx and OTC oral and topical formulations. The applicant reviewed data from the following databases

- FDA’s Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) (1969 to June 30, 2008)
- The World Health Organization’s (WHO) International Drug Monitoring Program (over 30 years until November 16, 2008)

- The New Drug Abuse Warning Network (New DAWN) (Jan 2003 to Nov 2008)

SRS/AERS provided 3740 cases, WHO provided 6608 cases, and the New DAWN database provided 73 cases. The most common adverse events were those expected for an NSAID, including gastrointestinal disorders, allergic phenomena, and renal disorders.

In the SRS/AERS database, of 3740 total cases, 188 involved reports of death. The most frequently reported preferred term associated with death was ‘renal failure acute,’ which accounted for 2% of all terms associated with death. According to the primary clinical review, “overall, for the data available from the FDA databases for ketoprofen, the side effect profile observed reflected known pharmacologic properties of the drug. Of the seven most commonly reported AE terms, ‘drug ineffective’ has the highest frequency, five of the seven terms were related to gastrointestinal disturbances, and the other term was ‘renal failure, acute.’ ”

In the WHO database, there were 117 deaths among exU.S. reports, primarily among adults older than 65 years of age. ‘Gastrointestinal haemorrhage’ appeared in 21 reports of death, and 19 of the 21 reports were for adults older than 65 years of age. ‘Hematemesis had 14 reports, and 9 were in the >65 year age range. According to the primary clinical reviewer, “no unexpected findings emerged from this analysis of the adverse event data for ketoprofen from the WHO drug safety database.”

The New DAWN data provided information for drug-related emergency department visits from a sample of U.S. emergency departments. Overall, there were 45,026 emergency department visits that reported use of the following NSAIDs: ketoprofen, fenoprofen, flubiprofen, ibuprofen, and naproxen. Ketoprofen use was documented in 73 of the 45,026 reports. No deaths were reported for ketoprofen. According to the primary clinical reviewer, “Considering the relatively small number of reports for ketoprofen (0.16% of the total), the profile of demographic and case characteristics for ketoprofen as reflected in the New DAWN database was, in general, similar to that of the selected NSAIDs taken as a group. The range and distribution of diagnoses applied by the DAWN methodology did not show any important differences between ketoprofen and the selected NSAIDs considered overall, except that ketoprofen was involved in relatively fewer suicide attempts.”

The applicant did not provide any estimate of drug exposure postmarketing, but FDA’s Office of Surveillance Epidemiology provided estimates of U.S. sales from IMS Health data from 2004 through 2008. Estimated yearly U.S. sales have ranged from [REDACTED] (b) (4) capsules of ketoprofen, with sales declining after 2005.

CDTL comment: To put the postmarketing reports in context, some understanding of exposure is helpful. The postmarketing data comes from U.S. and exU.S. databases, covers capsule and non-capsule formulations, and covers approximately 30 years of marketing. Although we do not have exposure data encompassing all global exposure to all formulations, it is reassuring that the U.S. exposure, based on Rx capsule sales only, is substantial over the past four years. The number of deaths reported postmarketing does not appear excessive for a product with a 30-year postmarketing history.

Other safety information

At the time of this review, FDA was not tracking any safety issues for ketoprofen. The applicant submitted a 120-day safety update that included a literature search from 11 Nov 2008 to 23 March 2008. Seven clinical articles were retrieved; according to the primary clinical reviewer, "This review did not identify any evidence to suggest new risks to the safety profile of oral ketoprofen." The primary reviewer did an independent search of FDA's AERS database and did not detect any unexpected findings.

9. Advisory Committee Meeting

N/A

10. Pediatrics

The applicant has submitted a pediatric plan of limited scope; the Agency has recommended a broader plan; the applicant "respectfully declines" to perform the recommended studies. ^{(b) (4)}

However, FDA must inform the applicant of the nature and scope of their PREA postmarketing requirements in the approval letter.

Initially, the applicant requested a waiver of pediatric studies for children less than 16 years of age because "the drug product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients." The clinical team did not agree. Although there are approved pain relievers/fever reducers for children (e.g. ibuprofen for children 6 months and older, acetaminophen for children 2 years and older, aspirin and naproxen for children 12 years and older), the proposed ketoprofen formulation seemed particularly "child friendly." The clinical team requested a pediatric consult to help determine what pediatric studies were necessary.

The pediatric consultants concluded that the applicant should conduct a pediatric assessment for children aged 6 month to < 17 years old for the pain reliever indication. The consult further stated that the applicant will need to conduct pediatric PK and safety studies, but extrapolation of efficacy may be justifiable. For the fever indication, the consult agreed with a full waiver of pediatric studies because "ketoprofen does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients." A regulatory letter conveying this advice was sent to the applicant on June 11, 2009.

On June 19, 2009, the applicant submitted a pediatric plan. The plan consisted of a single PK study with safety supplemented with "data pooled from published manuscripts." The proposed PK study was a single dose, open-label study involving a total of 16 children, with 4 children

in each of 4 age ranges (6 months to < 2 years, 2 years to <6 years, 6 years to <12 years, and 12 years to < 16 years). The groups would be dosed in a sequential fashion proceeding from the oldest to the youngest groups. The applicant proposed to enroll healthy subjects because adult experience suggested that risk was minimal, and sick children would likely require re-dosing of rescue medication during the period of 12 hours.

The applicant anticipated that it would take at least three years to have the study report completed. The three-year estimate included 12-15 months to develop a pediatric formulation of appropriate strength and flavor prior to starting pediatric studies. Additionally, the applicant claimed a need to develop new analytic methods for pharmacokinetic testing because of the need to test sample volumes as low as 1 to 2 ml.

CDTL comments: The review team felt that a total of 16 children in the pediatric plan was inadequate to address safety and would not provide an adequate pharmacokinetic profile. The likelihood that literature alone could adequately support pediatric safety seemed small as safety is not the usual focus of study reports that appear in the literature. In addition, a three-year completion time seemed too generous, particularly as the proposed studies are single dose PK studies that should take days to complete. Furthermore, the applicant's claim that new analytic methods for PK testing must be developed because of small sample volumes may be incorrect as the problem has apparently been solved by investigators who performed published studies. (The primary reviewer found five ketoprofen PK and efficacy studies in children down to six months of age in the literature; the studies were done primarily in Finland and used higher dose, Rx formulations of ketoprofen.)

Currently, there are six countries marketing OTC ketoprofen, including China, Finland, France, Italy, Korea, and the Netherlands. The OTC dose contained in a single tablet is higher than in the United States for all six countries, ranging from 25 to 50 mg. Only in Finland is OTC ketoprofen labeled for children less than 16 years of age. In Finland, OTC labeling supports use in children 12 years old and older at a dose (25 mg up to three times daily) that is similar to the U.S.-approved dose (12.5 mg every 4 to 6 hours, with two doses allowed for the first dose).

The review team presented the applicant's proposal to the Pediatric Review Committee (PeRC) committee on July 8, 2009. The PeRC advised the review team that

- A waiver could be granted for children from 0 to 6 months old because, for the pain indication, the disease condition did not occur, and for the fever indication, the product did not offer a meaningful therapeutic benefit.
- A safety trial in a sizable population of symptomatic children conditions is necessary for children ages 6 months to less than 16 years of age.
- The applicant had not adequately justified the extrapolation of efficacy from adults to children less than 16 years of age for the pain indication. PeRC committee noted that the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) had not previously allowed extrapolation of efficacy for a pain indication to children. On the other hand, PeRC noted that if adequate data on efficacy were available in children, it might be unethical to do another study. However, the applicant did not provide adequate data.

The review team met with DAARP to present available clinical efficacy data for ketoprofen in children. The primary clinical reviewer had retrieved five literature studies that demonstrated efficacy for ketoprofen in children; all five studies involved preoperative administration of intravenous ketoprofen. DAARP informed the review team that the data were not adequate to extrapolate efficacy for the pain indication in children. DAARP explained an internal policy not to allow extrapolation for the pain indication, but also indicated that sponsors were having difficulty enrolling children in placebo controlled trials for the pain indication. The issue of extrapolation of the pain indication from adults to children is to be revisited at a public workshop in December 2009. At the time of this review, however, it is DAARP policy not to extrapolate efficacy for the pain indication to children. Clinical efficacy data are required.

On 21-Sep-2009, FDA sent a letter to the applicant in response to the pediatric plan with the following recommendations:

“1. You will need to provide efficacy data for children less than 16 years of age for the pain indication. The data provided in your submission are not sufficient for extrapolation of efficacy in children for the pain indication. You will need to conduct adequate and well-controlled superiority trials demonstrating efficacy for children ages 6 months to 15 years. These trials should be conducted using a pain model or models suitable for an over-the-counter population.

2. It is reasonable to conduct the pharmacokinetic trial prior to studying efficacy. However, the proposed single dose pharmacokinetic trial is inadequate. The PK trial should be done in children who may benefit from the drug rather than in otherwise healthy pediatric volunteers. Hence, we recommend conducting a single dose PK trial leading into a multiple dose PK trial that would evaluate the safety, tolerability, and pharmacokinetics of an appropriate dose of ketoprofen in children. We recommend recruitment of children in the following age groups, which have been known for differences in developmental physiology as it relates to drug clearance:

- 6 to < 12 months
- 12 to < 24 months
- 2 to < 6 years
- 6 to < 16 years

A minimum of 12 children are required per age group for traditional pharmacokinetic analysis in each of the age groups indicated above. Alternatively, you may consider population PK analysis by the sparse sampling approach. You should attempt to ensure that the distribution of pediatric patients across gender, age, and weight ranges is reasonably even. The number of children should be based on being able to estimate, for each age group, the mean apparent CL and apparent volume of distribution, with a standard error of 20% or less. The trial(s) may be conducted in a sequential fashion such that older children are exposed to the test product before younger children.

3. Your proposed safety plan is inadequate. Monitoring these subjects for safety will not provide sufficient data. You should conduct a safety trial on a sizable population of children ages 6 months to 15 years of age. This trial should include adequate

representation of the age groups and should be conducted in a symptomatic population under ‘actual use’ conditions.”

On 9-Oct-2009, the applicant replied in a letter that “NCH respectfully declines to perform the required pediatric clinical studies.” Novartis Consumer Healthcare (NCH) believes that the inability to extrapolate efficacy is unwarranted because it believes that the characteristics and mechanisms of pain and fever are generally the same in adults and children. NCH asked the Agency to reconsider the proposed pediatric plan outlines in the 19-Jun-2009 submission.

 (b) (4)
However, we must inform the applicant of the nature and scope of their PREA postmarketing requirements in the approval letter.

CDTL comments: It is unclear to me that the applicant must submit efficacy data for children if the applicant does an acceptable PK study. The PK study outlined in the Agency letter summarized above may provide acceptable support for efficacy because the Agency allows extrapolation of efficacy for other populations, such as adults with liver disease or kidney disease, supported only by PK data, and because, in internal discussions of the issue, no one has brought forth a reason to think that the pathophysiology of pain is different in children compared with adults. Furthermore, FDA has decided that ibuprofen, a structurally similar drug in the same class as ketoprofen, is effective in children down to the age of six months. Finally, the primary clinical reviewer found five randomized and controlled trials reported in the literature supporting efficacy of ketoprofen, albeit not OTC ketoprofen, for pain in children. Approximately 300 children were exposed to intravenous ketoprofen in these published studies.

Therefore, I am willing to extrapolate efficacy for pain in children if the applicant provides acceptable PK data. However, the decision about efficacy is the responsibility of DARRP, and current policy in DARRP is not to extrapolate for the pain indication. This policy will be revisited in a public workshop in December. If DARRP policy changes as a result of the workshop, developing a pediatric plan that is acceptable both to the Agency and to the applicant should be possible.

Similarly, it is unclear to me that the applicant must submit data from a large safety study in children if the applicant does an acceptable PK study. The PK study outlined in the Agency letter summarized above may be acceptable because the Agency allows extrapolation of safety to other populations, such as adults with liver or kidney disease, supported only by PK data. Furthermore, there appears to be no reason to expect that NSAIDs have unique safety issues in children. As noted above, FDA has decided that a structurally similar NSAID, ibuprofen, is safe for children down to six months of age. OTC ibuprofen has been approved for children in the United States for over 10 years, and FDA has no open safety issues for ibuprofen specific to its use in children. Furthermore, the applicant could provide information supporting ketoprofen safety in children from the literature and postmarketing data. As noted above, the

primary clinical reviewer was able to find five randomized, double-blind, controlled studies of ketoprofen used in over children. The applicant could use these studies and a review of postmarketing usage and adverse event data to supplement a robust single and multiple dose PK study. Whether the data would be adequate to support labeling would be a review issue.

For the fever indication, the FDA pediatric consultants agreed with a full waiver of pediatric studies because “ketoprofen does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients.” However, if the applicant develops a pediatric formulation and successfully supports safety and efficacy of ketoprofen in children for the pain indication, the issue of labeling for the fever indication should be carefully considered. If NSAIDs continue to have a fever indication in adults, if ibuprofen continues to have a fever indication in children, and if data support pediatric labeling for the pain indication, it seems reasonable to extrapolate the fever indication in children to ketoprofen. There is a risk of consumer confusion and potential concomitant use of two NSAIDs if one NSAID is labeled for fever and another is not.

11. Other Relevant Regulatory Issues

At the time this review was finalized, a deficiency in the analytical method for Study 101 was unresolved and results of the manufacturing site inspection were not yet available. The deficiency was one of three detected by the FDA’s Division of Scientific Investigations (DSI) during an audit of the analytical portion of Study 101. The three deficiencies and the responses to the deficiencies were:

- 1) “Analytical batches were accepted even when > 50% of the low QC samples (15 ng/ml) failed.” The lab responded that there would be little impact on study data. DSI recommended that data from 8 subjects in Part I of Study 101 be excluded from evaluation. FDA’s clinical pharmacology team reanalyzed the data excluding the 8 subjects; the bioequivalence determination was upheld in the reanalysis.
- 2) “Failure to conduct Incurred Sample Reproducibility (ISR) experiment for Study 101.” The lab responded that, at the time the study was performed, the ISR method was being implemented in response to a new requirement, but that they did not use the method for this particular study (reason not provided). On 7-Oct-2009, FDA informed the applicant in a letter that the lab would need to conduct an ISR assessment to confirm the reproducibility of their method. At the time this review was finalized, this deficiency had not been resolved.
- 3) “Failure to provide proper criteria to analyst for selection of initial integrations parameters used in all analytical runs.” The firm implemented corrective action and the response was acceptable to DSI.

There are no other outstanding regulatory issues. The applicant does not appear on FDA’s Application Integrity Policy list. The regulatory project manager has detected no exclusivity or patent issues, although his review was not finalized at the time of this review. The financial

disclosures were acceptable. All studies were performed by the same investigator. On FDA Form 3454, the applicant certified that

- there were no financial arrangements with the clinical investigator whereby compensation could be affected by the outcome of the studies
- the clinical investigator did not disclose any proprietary interest in the product and the clinical investigator did not receive any significant payments of other sorts as defined in 21 CFR 54.2(f).

12. Labeling

The review team negotiated acceptable labeling with NCH.

The first proprietary name, (b) (4) proposed by the applicant was not acceptable to the review team because it was thought to be vulnerable to name confusion and because it was promotional in nature. The second proposed proprietary name, “Nexcede,” was acceptable to the review team. In particular, the Division of Medication Error Prevention and Analysis (DMEPA) found “Nexcede” acceptable if

- approval of the NDA was not delayed beyond 90 days from the date of DMEPA’s review (8/28/2009)
- the proposed product characteristics were not altered

DMEPA’s review also noted that the Division of Drug Marketing, Advertising, and Communications (DDMAC) did not object to the proposed name from a promotional perspective. The rest of the review team also had no objection to “Nexcede.”

The Division of Nonprescription Regulation Development (DNRD) provided the primary review of remaining labeling in consultation with the other members of the review team. The DNRD reviewer noted that the labeling has been updated from the approved Orudis KT labeling to conform to changes in class labeling for NSAIDs. Formatting changes and the change from (b) (4) to “oral soluble film,” as recommended by FDA’s chemistry team, were negotiated. The review team asked the applicant to remove the promotional statement (b) (4) (written in a font size as large as “Nexcede”) because of concerns about consumer confusion. The applicant countered with the addition of a small box, remote from the promotional statement, stating in small font that the product does not contain any of the active ingredients found in Excedrin products. The review team did not agree and reiterated their request that the applicant remove the promotional statement. NCH agreed to remove the promotional statement.

The applicant made the following additional changes compared with the label of Orudis KT:

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

The review team agreed that both statements were adequately supported by the PK data. Furthermore, the second statement appears on the labeling for the NSAID naproxen (NDA 21-920), also supported by PK data.

Proposed labeling carries the same pregnancy warnings as other NSAIDS, and this is acceptable. NSAIDs, including ketoprofen, should be avoided during late pregnancy because they may cause premature closure of the ductus arteriosus in the fetus.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I recommend approval if the following issues are resolved:

- Resolution of the DSI issue related to incurred sample reproducibility
- Satisfactory inspection of the manufacturing sites

Risk Benefit Assessment

The proposed product has a favorable risk benefit profile. The demonstration of an acceptable risk benefit profile was supported by the demonstration of bioequivalence between the new soluble film and the approved tablet. Mucosal safety, an issue raised by the difference in the dosing directions for the new soluble film, was satisfactorily addressed with a preclinical study in hamsters and three clinical studies. A review of postmarketing safety did not detect any safety issues beyond those expected for an NSAID.

Recommendation for Postmarketing Risk Management Activities

I recommend routine postmarketing surveillance.

Recommendation for other Postmarketing Study Commitments

The company should address PREA by providing adequate pharmacokinetic, efficacy, and safety data in a timely fashion. A reasonable timeline for the pharmacokinetic study would be two years.

Recommended Comments to Applicant

As noted in this review, I have reservations about the need to require efficacy and safety studies in children if the applicant develops appropriate formulations for children and performs an acceptable PK study. However, at the time of this review, the requirement to show pain relief in children is the policy of DARRP, the FDA division responsible for reviewing efficacy for the pain indication. The policy will be the subject of a public workshop in December. If any policy changes emerge from the workshop, the changes can be conveyed to the applicant post-approval.

In the interim, I recommend that the PREA section of the approval letter grant a waiver in children up to 6 months of age and a deferral for children ages 6 month to 15 years. The approval letter should also refer to the advice given in the Agency letter dated 21-Sep-2009, as the letter provides current FDA advice.

In addition, the sponsor should be encouraged to start pharmacokinetic studies in children without delay because the flavored soluble film formulation is an attractive formulation for children, and the film will likely be used off-label in children. Data on appropriate dosing is therefore a public health need. The applicant's proposal to take three years to complete formulation development and a single dose PK study seems excessive to me. I recommend that the time to provide a final study report for the PK study described in the Agency letter dated 21-Sep-2009 be set at two years from the date of approval.

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/

LESLEYANNE A FURLONG

11/06/2009