CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-470

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	November 24, 2009
From	Andrea Leonard-Segal, M.D., M.S Director, Division of Nonprescription Clinical Evaluation (DNCE)
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 22-470
Applicant Name	Novartis Consumer Health, Inc.
Date of Submission	January 23, 2009
PDUFA Goal Date	November 26, 2009
Proprietary Name / **Established (USAN) Name**	Nexcede / Ketoprofen
Dosage Forms / Strength	Oral soluble film / 12.5 mg
Proposed Indication(s)	1. Temporarily relieves minor aches and pains due to • Headache • Toothache • Backache • Minor pain or arthritis • The common cold • Muscular aches • Menstrual cramps 2. Temporarily reduces fever
Action/Recommended Action	Approval • PMR for the pediatric studies to comply with PREA • PMC to study CPK values in consumers on Nexcede compared with a placebo population

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
DNCE Clinical Review 9/25/09, 11/24/09	Priscilla Callahan-Lyon, M.D. , Lesley Anne Furlong, M.D.
ONDQA Biopharmaceutics Review 08/31/09	Tien Mien Chen, Ph.D. and Patrick J. Marroum, Ph.D.
Pharmacology Toxicology Review 08/27/09	Cindy Li, Ph.D, Wafa Harrouk, Ph.D., and Paul Brown, Ph.D.
CMC Review/OBP Reviews 09/15/09, 11/16/09	Jane Chang, Ph.D. and Moo Jhong Rhee, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review 09/03/09, 09/30/09, 11/20/09	Suresh B. Naraharisetti, Ph.D. and Suresh Doddapaneni, Ph.D.
CDTL Review 11/06/09	Lesley-Anne Furlong, M.D.
DSI 09/11/09, 09/30/09, 11/19/09	Arindam Dasgupta Ph.D., and C.T. Viswanathan, Ph.D.
DMEPA Trade Name Reviews 04/24/09, 05/13/09, 08/28/09	Zachary Oleszczuk, PharmD, Kellie Taylor, PharmD, Denise Toyer, PharmD, Carol Holquist RPh
DNRD Labeling Reviews 8/27/09, 10/2/09, 11/9/09, 11/17/09	Michael L. Koenig, Ph.D., Matthew R. Holman, Ph.D.
Consult from Pediatric and Maternal Health Staff 05/12/09	Felicia Collins, M.D., M.P.H., Lisa Mathis, M.D.

1. Introduction

Novartis Consumer Healthcare, Inc. (NCH) submitted a 505(b)(2) application, NDA 22-470, for a new OTC formulation of ketoprofen. Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) of the proprionic acid class. The new formulation is a 12.5 mg oral soluble film which disintegrates in the mouth in seconds. The proposed indications, target population (adults and children at least 16 years of age), and dosing are identical to those of the ketoprofen OTC oral tablets 12.5 mg, Orudis® KT (NDA 20-429) and Actron® (NDA 20-499) which were both approved for OTC marketing on October 6, 1995. ANDA 75-364 was approved in 2002 for ketoprofen OTC oral tablets.

Currently, ketoprofen is marketed without a prescription in six other countries and the amount per dose for those nonprescription products ranges from 25 mg to 50 mg. Only in Finland is ketoprofen labeled for children < 16 years old; the dosing there is 25 mg up to three times a day for children ages 12 years and older.

2. Background

Ketoprofen was first approved for prescription marketing in the United States 1986 for the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis. The prescription products are available as immediate release and extended release formulations and range in strength from 25 mg to 200 mg per capsule. The recommended prescription maximum daily dose is 300 mg per day. The prescription labeling states that the safety and effectiveness in pediatric patients below the age of 18 years of age has not been established. Ketoprofen was available internationally for over a decade before it was approved in the United States.

The ketoprofen oral tablets approved for OTC use in 1995 (NDAs 20-429 and 20-499) are no longer marketed, but were not withdrawn for reasons of safety or efficacy. Likewise, the ANDA product is currently not marketed.

The approved OTC indications for ketoprofen are:

- The temporary relief of minor aches and pains due to: headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pain of arthritis
- Temporarily reduces fever

The target population for the OTC product is adults and children 16 years of age and older. The dosing regimen is 12.5 mg every 4 – 6 hours with an initial dose of either 12.5 mg or 25 mg and a maximum daily dose of 75 mg. Ketoprofen may be used up to three days to reduce fever and up to ten days to relieve pain.

Ketoprofen is extensively metabolized in the liver to the unstable acyl-glucuronide conjugates, which are excreted in the urine. Other metabolic pathways such as hydroxylation have also been reported. There are no know active metabolites and ketoprofen does not induce drug-metabolizing enzymes. Enterohepatic recirculation of the drug has never been confirmed. Once absorbed, ketoprofen is > 99% bound to plasma proteins, mainly to albumin.

The Tmax occurs in approximately 0.5 – 2 hours and the half life is approximately two hours. The half life increases in the elderly because of delayed glucuronide conjugation and renal excretion. Food is known to reduce the Cmax of ketoprofen by approximately 50% and to almost double the Tmax. Both Orudis KT tablets and Orudis prescription capsules labels do not contain any restriction regarding concomitant food intake. In fact, they allow for taking the medication with food or milk if GI side effects occur. The clinical pharmacology reviewers comment that it appears that, in most of the clinical trials, ketoprofen was taken with food or milk.

Ketoprofen has the inherent safety concerns associated with the other approved NSAIDS, but photosensitivity is an increased risk associated with arylproprionic acids, of which ketoprofen is one. Ketoprofen is known to decrease platelet adhesion and aggregation and thus can prolong bleeding time by approximately 3 to 4 minutes from baseline values.

This NCH 505(b)(2) NDA did not have right of reference to, but relied upon FDAs finding of safety and efficacy for, the prescription Orudis (ketoprofen) NDA 18-754 for preclinical and clinical safety and the OTC Orudis KT NDA 20-429 for clinical safety and efficacy. This NCH oral soluble film ketoprofen formulation is not yet approved for marketing internationally, so there is no postmarketing safety database on this formulation.

3. CMC/ Device

This ketoprofen formulation is a transparent, oral soluble film which is available in a peppermint flavor (aqua blue film) and a cinnamon flavor (light red film). The excipients in the cinnamon and peppermint products differ only with regard to the flavor and the colorant. The film dissolves in seconds in the mouth and is an immediate release product. It measures 22 mm X 32 mm. The primary packaging container is a single-use, multi-layer flexible laminated pouch. Multiple individual pouches are packaged together in a non-protective, standard folding carton as a secondary container.

An earlier peppermint formulation, Clinical Service Form (CSF), was used for the human PK studies (EDFT-PN-101, Parts I and II) and, subsequently, the commercial (to-be-marketed) peppermint formulation, otherwise known as the Final Marketing Image (FMI), was used in a bridging bioequivalence study and a food effect study (EDFT-PN-101 Part II and EDKT-PN-102). The sponsor submitted a biowaiver request and in vitro comparative dissolution data for the cinnamon flavor ketoprofen oral (b) (4) film formulation which was not tested in vivo. The biowaiver and in vitro comparative dissolution testing between the cinnamon and peppermint to-be-marketed formulations of ketoprofen oral (b) (4) films were reviewed by the ONDQA biopharmaceutical reviewers. They found that the biowaiver request for the cinnamon flavor film could be granted. However, they recommended that the proposed dissolution specification for the film be tightened from Q = (b) (4) in 30 minutes to Q = (b) (4) in 15 minutes. The ONDQA chemistry reviewers did not adopt this recommendation. (See pages 57 – 58 of Dr. Chang's review for the explanation.) The dissolution test acceptance criteria were updated to Q = (b) (4) at 30 minutes.

The drug substance complies with the USP monograph and the DMF was reviewed and found to be adequate to support the NDA. Specifications for the drug product, information related to

packaging and stability data were found to be acceptable. Stability data support an expiration dating period of 24 months when stored at 25° C (excursion 15° - 30°).

The chemists wrote an initial review for this NDA and then an amended review. The amended review addressed issues about labeling and the chemistry inspection that were not resolved at the time the first review was finalized. The reviewers concluded that the NDA provided sufficient information to assure identity, strength, purity, and quality of the drug product. The Office of Compliance made an "acceptable" site recommendation. The reviewers found that the labeling revisions, the last of which was provided on 11/02/09 by the sponsor, addressed their labeling concerns and thus the labeling was acceptable from the chemistry perspective. The chemists recommended approval and did not recommend any post-marketing commitments. Refer to the chemistry reviews for further details.

4. Nonclinical Pharmacology/Toxicology

Refer to Dr. Li's review. The nonclinical reviewers recommend that from their perspective this NDA can be approved.

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

Because this oral soluble film disintegrates in the mouth and could be taken without water, the sponsor submitted a buccal mucosal tolerability study in hamsters. This study assessed local tolerance and general tolerance via six applications daily of the soluble film to the hamster cheek pouch for fourteen days. There were no relevant histopathologic changes related to local or general tolerance. There was no buccal irritation.

NCH also submitted publications relevant to the safety and mechanism of action of ketoprofen, a list of studies from NDA 18-754 and the safety findings of the agency from NDA 18-754 and NDA 20-429. The applicant does not have right of reference from the holders of these other applications.

A review of the publications on photosensitization potential of ketoprofen showed that phototoxicity has not been confirmed in standardized (guinea pig) studies. However, ketoprofen is clearly photoallergenic and shows photo cross-reactivity to a variety of related chemical structures. The reviewers comment that "photoallergenicity is unlikely to be a major safety issue with the ketoprofen 12.5 mg oral soluble film because photoallergy requires a sufficiently high skin concentration and sufficient UV irradiation for both induction and expression. There is no UV exposure in the mouth and the skin concentrations after dosing with 12.5 mg are relatively low."

There were no carcinogenicity studies conducted for this NDA, but previously conducted studies on ketoprofen have not indicated a carcinogenic potential. Previous teratology studies on ketoprofen show embryo toxicity in rabbits, but not teratogenicity. There have been no adequate and well controlled studies in pregnant women and ketoprofen is listed as a Pregnancy Category C drug. It is not known if ketoprofen is excreted in human milk but it is

excreted in the milk of lactating dogs. Studies in rats on ketoprofen demonstrate that it prolongs pregnancy when administered prior to the onset of labor.

5. Clinical Pharmacology/Biopharmaceutics

Approach to the Clinical Pharmacology Review:

The clinical pharmacology reviewers wrote a review on 09/03/09 and then an addendum to their review on 09/30/09. Refer to these two reviews for the details of the clinical pharmacology studies in the submission.

In the first review, written before the DSI inspection results were known, the reviewers recommended that this ketoprofen film could be approved providing that a satisfactory agreement was reached between FDA and NCH regarding labeling language and providing that the Division of Scientific Investigations (DSI) report of audit of study EDKT-PN-101 did not uncover any significant issues that would preclude acceptance of data.

The addendum to the clinical pharmacology review addressed the recommendations made by DSI after they finalized their report on study EDKT-PN-101. The DSI found deficiencies during an audit of the analytical portion of study EDKT-PN-101. The audit of the clinical and analytical portions of the study was conducted at (b) (4) and at (b) (4) The DSI report stated that:

1. The accuracy of the pharmacokinetic data from 8 specific subjects in study EDKT-PN-101 (Part I) has not been assured, as the analytical runs for analysis of plasma samples from these subjects has 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 (ISR) issue with the LC/MS/MS method used in study EDKT-PN-101.
3. There was failure to provide proper criteria to the analyst for selection of initial integration parameters used in all analytical runs.

In the addendum to the clinical pharmacology review, the reviewers reanalyzed the data excluding the eight subjects mentioned as the first deficiency. Regarding the second deficiency, FDA informed the applicant in a letter on 10/07/09 that the laboratory would need to conduct an ISR assessment to confirm the reproducibility of their method. The sponsor did this and, in a review dated 11/19/09, DSI concluded that the analytical portion of the study EDKT-PN-101 could be accepted for review. Regarding the third deficiency, the firm implemented corrective action and the response was acceptable to DSI. The clinical pharmacology reviewers wrote a second addendum to their review on 11/20/09 stating that all issues related to the DSI inspection were satisfactorily resolved and that NDA 22-470 is acceptable from the clinical pharmacology perspective.

Study Design:
To support approval of the NDA, NCH is relying upon the previous findings of safety and efficacy of 12.5 mg Orudis KT tablets and has demonstrated bioequivalence of the oral soluble film with Orudis KT. Two clinical pharmacology studies were conducted. (See **Table 1**.)

Table 1. Clinical Pharmacology Studies

Study Name	**Design**	**Objectives**	**N (randomized)**
EDKT-PN-101 Part I	Randomized Open-label Crossover Single-center Fasting CSF*	• Show BE between film and Orudis KT • Show BE of film with and without water	90
EDKT-PN-101 Part II	Randomized Open-label Crossover Single-center Used CSF and FMI**	• Investigate dose proportionality of one and two films • Demonstrate BE between CSF and FMI formulations	42
EDKT-PN-102	Randomized Open-label Crossover Single-center Used FMI	• Evaluate food effect	40

* CSF = Clinical Service Formulation **FMI = Final Marketing Imaging Formulation

Study EDKT-PN-101 Part I had three periods. The three treatment groups (one per subject per period) were:
1) One ketoprofen 12.5 mg film with water
2) One ketoprofen 12.5 mg film without water
3) One Orudis KT 12.5 mg tablet with water

Study EDKT-PN-101 Part II had two periods. The 2 treatment groups were:
1) One ketoprofen 12.5 mg film
2) Two ketoprofen 12.5 mg films

No drug-drug interaction studies were performed for the ketoprofen oral soluble film. However, drug interaction information for ketoprofen is described on the prescription ketoprofen labeling and is addressed in consumer-friendly language in the "Ask a doctor or pharmacist before use if you are…." section of the OTC labeling.

Results:
Study EDKT-PN-101:

- Part I: This study demonstrated bioequivalence between the soluble film and the Orudis KT tablets when the film was administered with 150 mL of water and without

water and the Orudis KT was administered with 150 mL of water. Bioequivalence was established both in the initial analysis and in the re-analysis that was performed after the DSI report. The study used the CSF of the ketoprofen oral soluble film. There were 90 randomized subjects in this study. Refer to Table 4.2.2.2, and Fig 4.2.2.2.1 in the primary clinical pharmacology review and to Table 1 in the addendum to that review for the numeric study results. Because the data demonstrated bioequivalence with and without water, the data supported not including the Orudis KT direction (b) (4) (b) (4) on the soluble film label.

- Part II: This study demonstrated dose proportionality and also bioequivalence between the CSF and FMI formulations. (The Final Marketing Imaging formulation is the final to-be-marketed formulation and is not the same as the CSF formulation used for assessing bioequivalence between the soluble film and the reference tablet.) There were 42 subjects randomized in this study. Refer to Table 4.2.2.2.2.1 and Table 4.2.2.2.2.2 and Fig 4.2.2.2.2.1 in the clinical pharmacology review for numeric study results.

Study EDKT-PN-102:
This study demonstrated that the food effect appears to be attributable to the ketoprofen drug substance and independent of the formulation. There were 40 subjects randomized in this study. Refer to Fig 4.2.2.1 and Table 4.2.2.1 (pages 21-22) in the clinical pharmacology review for the numeric study results. The Cmax of the soluble film formulation was 39.96% relative to that under fasting conditions; however, the total bioavailability was comparable between fasted and fed conditions. The Tmax increased from a mean of 0.43 hours under fasting conditions to a mean of 0.70 hours under fed conditions. Similar findings were seen in the past with the Orudis® capsules. The reviewers found the food effect study acceptable and commented that the sponsor suggested labeling that states, "if taken with food this product may take longer to work." FDA included that statement in the ***Directions*** section of the ***Drug Facts*** label.

6. Clinical Microbiology
There were no clinical microbiology data submitted with this application because of lack of relevancy.

7. Clinical/Statistical – Efficacy
The bioequivalence studies demonstrated bioequivalence to the reference drug, Orudis® KT. This is the mechanism by which the efficacy of the new oral soluble film was established. There was no need for clinical efficacy studies to demonstrate efficacy of the new formulation.

8. Safety
Overview:
The bioequivalence studies demonstrated bioequivalence to the reference drug, Orudis® KT. Because of this, new clinical safety studies were not required to support the safety of the new oral soluble film formulation. However, because of the nature of the new formulation, which dissolves in the mouth and could be used without water, the impact of the safety of the new soluble film on the oral mucosa was assessed nonclinically in the hamster buccal mucosa study

described above and clinically via the assessment of the oral mucosa of the 172 study participants enrolled in the PK studies.

In addition to safety data from the clinical pharmacology studies, safety data were provided from clinical trials conducted on Orudis® KT and Actron®, the published medical literature and postmarketing adverse events for ketoprofen. The ketoprofen 12.5 mg oral soluble film is not marketed anywhere in the world, so no postmarketing data is available on this specific formulation.

Safety Results from the Clinical Pharmacology Studies:
General safety information was assessed during the Clinical Pharmacology Studies by means of physical examination including vital signs, pregnancy testing, blood work (chemistry, hematology) and urinalysis. The safety population consisted of all randomized subjects who participated in at least one study period and received at least one dose of study drug. According to Table 14 on page 32 of Dr. Callahan-Lyon's review, exposure to drug during these studies was as follows:

- Clinical Service Form: 125 subjects of whom 84 received 2 doses of 12.5 mg
- Final Marketed Imaging Form: 119 subjects of whom 40 received two 25 mg doses and of whom 39 received one 25 mg dose.
- Orudis KT: 88 subjects received 12.5 mg

Dosing was one or two ketoprofen films and some subjects received two exposures because of the crossover designs. There were no deaths or serious adverse events. Two subjects withdrew from study EDKT-PN-101 Part I who took Orudis® KT, one because of an oral mucosal eruption noticed at a pre-dose oral exam and the other because of lip swelling and a rash, which resolved over the next several days. No one who took the film withdrew. The safety profile of the tablet and film were comparable in these studies. The most common adverse event was mild headache, twelve instances among eleven subjects. Other frequent but mild adverse events were nausea, oral mucosa eruption, and vomiting in two subjects each. Treatment-related adverse events appear to have been epigastric pain, nausea, vomiting and hypersensitivity reaction (manifested by rash and lip swelling in the subject on Orudis® KT). The symptomatic adverse effects seen in the clinical pharmacology studies are consistent with those known to occur with NSAIDs, including ketoprofen. In study EDKT-PN-101 Part II, four subjects discontinued the study prematurely. Three of them withdrew consent and one was lost to follow-up.

One subject in the film arm of Study EDKT-PN-101 developed a 2 mm asymptomatic papule on the right cheek oral mucosa noted 4 hours following study drug and still evident until 12 hours post dose. Upon admission for Period II, however, the oral cavity finding was normal and the subject completed the study.

Creatine Phosphokinase Levels:
There was one laboratory finding of possible concern in the PK studies, elevated creatine phosphokinase (CPK) in several study participants in this healthy young population upon study completion. It was also noted that, commonly, potential study participants had elevated

CPKs during screening, one as high as 1002 U/L. In fact, eight potential participants failed screening because of their elevated CPK values. (See Table 1 in the addendum of Dr. Callahan-Lyon's review.)

In Dr. Callahan-Lyon's initial clinical review and Dr. Furlong's CDTL review they assessed the information that the sponsor had provided and also adverse event data to further elucidate any relationship between ketoprofen and elevated CPK. They noted that the prescription labeling is silent on this issue; it is not clear whether CPK was assessed or not in the studies for the prescription products.

Dr. Callahan-Lyon searched the FDA AERS database for reports of elevated CPK associated with ketoprofen use. A total of 10 reports were identified and 9 of them were reviewed. None showed a clear cause and effect relationship between elevated CPK and ketoprofen. Dr. Callahan-Lyon performed a PubMed search for similar reports and found none. An additional search in AERS for all reports related to ketoprofen revealed no unexpected findings.

Based upon the safety information sources available, the reviewers found that ketoprofen does not appear to be associated with CPK elevations. They attributed the elevated CPK elevations to exercise, a reasonable supposition to be sure, but supposition nonetheless.

After reading the Medical Officer initial review and the CDTL review, I was bothered that we were lacking specific details related to the study participants whose CPK rose during the study and that we did not have data on the number of people who were eliminated from study participation based upon CPK elevation at screening. In the initial submission, Novartis did not provide this specific information and therefore we requested it. We requested additional information from NCH on five specific study participants in whom the CPK values increased during the clinical pharmacology study. The most extreme elevation was in Study Patient #1034, a 32-year-old Hispanic woman who entered study EDKT-PN-101 with a normal CPK of (b) (4) and, upon study completion 4 weeks later (on the day of her last dose of the ketoprofen film) had a level of (b) (4) The investigator checked a box on the case report form that indicated that the elevation was drug-related. It is not clear why the investigator thought this, but that he checked that box cannot be ignored. The investigators for the other study participants with elevations of CPKs (ranging from in the 300s U/L to in the 800s U/L) at the end of the study indicated with their check marks that the elevations were not drug-related. Reasons why were not provided.

In response to our request for more information, Novartis submitted additional data on the CPKs in their study population. They also submitted three references from the published literature. Dr. Callahan-Lyon wrote an addendum to her review in which she reviewed the NCH submission and three more articles on CPK that she found by conducting an additional literature search. The three additional articles that she found demonstrate the wide variability of CPKs in the general population across race/ethnicity, gender, and age. The data submitted by Novartis and the literature reviewed conducted by Dr. Callahan-Lyon appear to bolster the likelihood that the CPK elevations in the subjects at the end of the study were not drug related, but, as she states in her review addendum, "residual uncertainty" remains. This is because the sponsor did not follow up the specific subjects involved to resolution and did not provide a

specific history of exercise or other exposures that could be responsible for the CPK elevations.

Teasing out what we do know from the case report forms, none of the five subjects had elevated alcohol levels or appeared to have other significant drug exposures based upon medical history and other laboratory data. They had normal physical examinations at study entry and completion. This, plus the study exclusion criteria, should have eliminated participants with inflammatory connective tissue disorders and metabolic disorders that could elevate CPK and should have provided information about major injuries. In essence, to explain the CPK elevations we are left with study drug or exercise.

First, let us consider whether study drug is likely to be the culprit. Many things argue against this. Ketoprofen is an old drug that has been approved for decades both in the U.S. and internationally as prescription (at higher doses than were studied for this NDA) and OTC products. The drug has never been associated with CPK elevations. CPK elevations are not a finding associated with NSAIDs as a drug class. The study participants did not have much drug exposure during the course of the study and there were washout periods in between. To further elucidate any drug relationship I discussed with Dr. Li (the pharmacology/toxicology reviewer) whether the data submitted for the pharmacology/toxicology portion of the NDA was helpful to us in enhancing our understanding of the elevated CPKs in the human data. (See e-mail exchange in Appendix 1.) It was not, because CPKs were not drawn on the hamsters, the muscles were not examined, and there were no excipients of concern either in the CSF or the FMI formulations of the film used in the Clinical Pharmacology Studies.

Thinking about physical activity as the likely cause, the literature provided by NCH and the additional articles found by Dr. Callahan-Lyon demonstrate that:

- CPK elevations are common
- There are diurnal variations in CPK
- Exercise, depending upon the vigor associated, can be responsible for marked increases in CPK
- CPK levels vary widely in the general healthy population related to gender, race/ethnicity and age

Physical activity is the most reasonable explanation for CPK elevations in this study population. Logically, the likelihood that drug was responsible for rises in CPK in the study population seems quite remote, but without more information on the individual study participants, we cannot absolutely say for sure. Because the sponsor did not provide definitive history and follow-up on the involved study participants, doubts linger.

<u>Summary of safety data from clinical trials for Orudis® KT and Actron®:</u>
The sponsor provided pooled safety data for Actron® from twenty-two clinical trials, sixteen of which were single-dose studies. They also provided pooled safety data for Orudis® KT from twenty clinical trials, seventeen of which were single-dose studies. Doses in the other studies were as high as 300 mg/day for three days, 150 mg/day for seven days, and 75 mg/day for ten days. Among all of the trials, 7090 study participants received ketoprofen. Most adverse events were mild to moderate in severity and nonserious. There was one death in a

patient who had melanoma that was metastatic to the brain. There was one report of ketoprofen related esophagitis and one case of melena. There were no reports of peptic ulcer disease, GI perforation, renal insufficiency or anaphylaxis. There were 32 participants who withdrew from the studies, none for serious adverse effects. The majority of these withdrew for GI symptoms (e.g., dyspepsia, nausea, diarrhea, abdominal pain). CNS symptoms such as dizziness and somnolence also led to withdrawal in study participants.

Published literature:
The literature searches using such terms as "safety," "side effects," "renal," "cardiovascular," "hematologic," and "liver" did not identify new adverse events. Among eighty-one literature reports of ketoprofen-associated photosensitization, the majority concerned topical formulations; one was associated with oral dosing, but in this patient, the induction of photoallergy may have been associated with use of a topical formulation the previous summer. The literature and the postmarketing data indicate that photoallergy associated with oral dosing is rare and the reviewers think that this is unlikely to be a safety issue of concern with the ketoprofen 12.5 mg film. This is because physiologically, photosensitization response requires a sufficiently high skin concentration of drug and sufficient UV irradiation for induction and expression. I agree with the reviewers on this point and think that the OTC ketoprofen labeling allergy alert adequately covers this issue.

Postmarketing data for oral and topical ketoprofen:
The data sources for this review were the:

- FDA Spontaneous Reporting System (SRS) and the FDA Adverse Event Reporting System (AERS) from January 1999 through June 2008
- World Health Organization's (WHO) International Drug Monitoring Program from 1974 – 2008
- Drug Abuse Warning Network (DAWN) from 2003 – 2008

This new orally soluble film has not been approved for marketing anywhere in the world so there are no postmarketing data on this formulation. The review of the postmarketing data on ketoprofen did not identify any new safety signals for this active ingredient. The findings were consistent with what we already know about the pharmacological properties of this nonsteroidal anti-inflammatory drug. The data identified the typical NSAID associated gastrointestinal adverse events, allergic events, and acute renal failure as those of greatest frequency and clinical importance.

The DAWN data demonstrated that very few emergency department visits have been reported for ketoprofen (73) compared with other NSAIDs (44,953). No deaths were reported for ketoprofen and there were relatively fewer suicide attempts compared with other NSAIDs.

Safety Update:
The safety update did not provide new safety signals.

Pregnancy:
Because of the known effects of NSAIDS, which are prostaglandin-inhibiting drugs, on closure of the ductus arteriosus and the fact that this is a Category C drug, use during pregnancy, and especially late pregnancy, should be avoided.

Safety Data Summary:
No new safety signals were associated with ketoprofen in the safety review with the exception of the question of elevated CPKs in participants in the clinical pharmacology studies.

9. Advisory Committee Meeting
There was no Advisory Committee needed to discuss this efficacy supplement.

10. Pediatrics
This product is a new formulation and triggers the need for the applicant to address the Pediatric Research Equity Act (PREA) requirements. The applicant requested a waiver of pediatric studies.

The Pediatric and Maternal Health Staff provided a consult recommending that studies are needed in the pediatric population ages 6 months to < 17 years old for the pain reliever indication. The consult stated that the applicant will need to conduct pediatric PK and safety studies but that extrapolation of efficacy may be justifiable if the course of the disease/condition and the effects of the product are sufficiently similar between adults and the pediatric population. 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." However, imbedded in the consult the PMHS also states, "Given the presumed mechanism of action of NSAIDs and ibuprofen's proven efficacy for fever in children, the belief that ketoprofen likewise would reduce fever in children is reasonable."

FDA sent NCH a letter on June 11, 2009 denying their waiver request. In the letter the Agency advised NCH that they needed to submit a pediatric development plan and NCH responded one week later by submitting a plan based on a pharmacokinetic approach. They proposed an open-label PK study of a single dose of ketoprofen oral soluble film in sixteen healthy children and adolescents (6 months to < 16 years). They would assess safety from the PK study, post-marketing databases and also from data pooled from published manuscripts involving the pediatric population. NCH concluded that the available scientific evidence and clinical experience is sufficient to extrapolate efficacy from adult studies for fever and pain indications to children and provided data to support this position. They requested a waiver in infants < 6 months of age.

On July 8, 2009, the Pediatric Review Committee (PeRC) met to discuss the proposed waiver and pediatric plan. They stated that:

- Granting a waiver for infants < 6 months of age is reasonable because causes of pain for which OTC ketoprofen is indicated do not exist in children in this age range and ketoprofen does not represent a meaningful therapeutic benefit over existing therapies for infants in this range for treating fever.

- The proposed plan for children ages 6 months to >16 years old was inadequate. The PK study would be an appropriate initial trial, if conducted in symptomatic patients, but a more complete safety evaluation is needed on a sizable population with adequate representation of the age groups under actual use conditions.
- Extrapolation from adult studies is appropriate for demonstrating efficacy for the fever indication.
- For the pain indication, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) had not previously allowed extrapolation of efficacy from adults to children for pain treatment and NCH would need to conduct adequate and well-controlled superiority trials demonstrating efficacy in children ages 6 months to 15 years. The trials should be conducted using a pain model suitable for an OTC population. However, the PeRC noted that if adequate data on efficacy were available in children, it might be unethical to do another study. However, the sponsor did not provide adequate data.

The DNCE review team met with representatives from DAARP to discuss the available clinical efficacy data on treating pediatric pain with ketoprofen. DAARP did not think that those data were adequate to support a pain indication in children and explained their internal policy not to allow extrapolation from adults for the pain indication. DAARP has consistently requested clinical efficacy studies in children for pain endpoints. However, they commented that sponsors were having difficulty enrolling children in placebo controlled trials for the pain indication. Because of this, DAARP is holding a public workshop to discuss studies that should be required to study pain in children early in December, 2009. This workshop will occur after the PDUFA action date for this NDA.

On September 21, 2009, FDA sent a letter to the applicant addressing their pediatric plan. The letter stated that NCH would need to provide efficacy data from adequate and well-controlled superiority trials in children 6 months to 15 years of age for the pain indication and that the data they had provided to support extrapolation were inadequate. NCH would also need to provide pharmacokinetic data, but the study they proposed was inadequate. The PK study should be performed in children who could benefit from the drug, rather than healthy volunteers. A single dose PK study should be performed that leads into a multidose PK study that would evaluate the safety, tolerability and pharmacokinetics of an appropriate dose of ketoprofen in children. The letter advised the number of children per age group who should be enrolled. The letter also told NCH that they needed to conduct a safety trial in a sizable population of children ages 6 months to 15 years in a symptomatic population under actual use conditions.

On October 9, 2009, the applicant replied that they respectfully declined to perform the required pediatric clinical studies and that they feel that pain and fever mechanisms are generally the same in adults and children and that extrapolation is reasonable. They asked the agency to reconsider their pediatric plan.

(b) (4)

(b) (4)

Dr. Furlong, in her CDTL review, comments that she thinks that it would be acceptable for the applicant to extrapolate from adult efficacy to support the efficacy of ketoprofen to treat pain in children. I tend to agree with her since we have seen no evidence that the pathophysiology of pain in adults and children is different. Hopefully, the workshop in December that DAARP is sponsoring will clarify the best way to move forward. If extrapolation becomes a path that DAARP can accept, then we can inform the sponsor of that and modify the PREA post-marketing requirements accordingly.

Regarding the "fever reducer" indication, I also agree with Dr. Furlong that it makes sense, based upon pathophysiology, to extrapolate efficacy from adults to the pediatric population. I am not as certain as the PMHS that ketoprofen does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and that it is not likely to be used in a substantial number of pediatric patients. Ketoprofen could very well become a popular OTC alternative for treating pain and fever, especially in the oral soluble film formulation which should be easy to administer. As Dr. Furlong comments, labeling the product solely for pain in children could foster the less than ideal situation in which parents use this medication for pain in their children and a second NSAID labeled for fever simultaneously. However, I believe that regardless of whether it is appropriate to study and label the product for use in fever in some pediatric patients, it is appropriate to waive pediatric studies for fever below 6 months because it is unsafe to use an over-the-counter medication for fever in that population without consulting a physician.

11. Other Relevant Regulatory Issues
None.

12. Labeling
Trade Name:
The Division of Medication Error Prevention and Analysis reviewed the trade names proposed by the applicant. Ultimately, the division found that the trade name Nexcede is acceptable.

OTC Labeling:
There will be two flavors for the ketoprofen films, peppermint and cinnamon. This product should contain all of the OTC class NSAID labeling including the pregnancy and breastfeeding warnings.

Drs. Koenig and Holman reviewed the labeling and wrote four reviews detailing deficiencies. The Agency issued discipline review letters to the applicant and they responded acceptably. The reviewers recommended an approval action in their November 17, 2009 review of the labeling submission received November 11, 2009.

13. Decision/Action/Risk Benefit Assessment

Discussion:

The sponsor has demonstrated that the new oral soluble film formulation of ketoprofen 12.5 mg is bioequivalent to the already approved OTC ketoprofen 12.5 mg tablets, thus establishing that this new formulation should be safe and effective for the sought indications. This new formulation can benefit the OTC consumer by offering another NSAID OTC, since this active ingredient is currently not available OTC. Consumers, who do not usually benefit from ibuprofen or naproxen, may find that they derive benefit from this drug. Additionally, the new formulation may be very helpful to consumers who have difficulty swallowing pills or who find themselves in situations where they do not have ready access to water to take medicine.

There are no new signals in the safety database or literature to suggest new safety concerns for the marketing of ketoprofen 12.5 mg OTC. The new formulation does not appear to present local safety concerns for the buccal mucosa. Phototoxicity is very rare with oral formulations of ketoprofen and likely to be even more so with the low dose oral formulations. The allergy warning on the label should be sufficient to address this.

I doubt that CPK is truly a safety issue for this product. The laboratory elevations seen were most likely related to physical activity. They were not associated with abnormal symptoms and signs at the last study visit. Additionally, the study subjects who experienced these elevations did not report adverse events associated with them. That CPK elevations are related to drug use is a very remote possibility, so unlikely that I think the drug can be approved. As Dr. Callahan-Lyon points out in the addendum to her review, the isolated measurement of CPK levels, without consideration of context, is not useful. However, it is fair to say that the sponsor was sloppy with regard to follow-up of the few patients who had these elevations after treatment with study drug.

I agree with Dr. Callahan-Lyon that a postmarketing commitment is in order to provide closure to any lingering doubts created by the absence of follow-up data in these few study patients. The postmarketing commitment should be to conduct a randomized, placebo-controlled study to assess the CPK in users of the ketoprofen films. The study should enroll healthy subjects people should be excluded if they are at risk for CPK elevations of other causes. CPKs should be assessed at baseline and at the end of the study. Participants should take the study medication for ten days, the duration of use allowed on the product label. Normal physical activity should be allowed but exercise should be restricted. All subjects should be queried as to exercise and other exposures that could raise CPK during the course of the study. All CPK elevations should be followed to resolution and adverse events should be recorded. It appears, based upon the data from the PK studies that 200 people in the ketoprofen arm and 200 in the placebo arm should be an adequate enrollment.

On Tuesday, November 24, 2009, in a teleconference with the FDA, NCH agreed to the postmarketing commitment. They requested to enroll 200 people into the ketoprofen arm but only 100 into the placebo arm. FDA told the sponsor that this would be acceptable, but that enrolling fewer subjects into the placebo arm could potentially work to their disadvantage. NCH acknowledged that they understood this risk.

The applicant will need to comply with the PREA postmarketing requirement of which they were informed in the letter sent to them on September 21, 2009. In terms of the fever claim, it

is my view that the PK study required under PREA (see below) should provide adequate information to extrapolate dosing from adults to children at least 6 months of age. Because of potential seriousness of febrile illnesses in young infants and the wisdom of having any young infant with fever evaluated by a physician, fever should not be an OTC indication for babies less than 6 months of age.

Conclusion:
The data suggest that this new ketoprofen oral soluble film product will be safe and effective for OTC use.

Recommendations:
The NDA should be approved.

The sponsor needs to be reminded of the PREA pediatric studies requirement:

- You must to conduct a PK trial in children who may benefit from the drug rather than in otherwise healthy pediatric volunteers. You should conduct 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 top < 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. 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.

  Final Study Report Submission: November, 2010

- You must provide efficacy data for children less than 16 years of age for the pain indication. You must 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.

  Final Study Report Submission: October, 2012

- You must conduct a safety trial on a sizable population of children ages 6 months to 15 years of age. This trial must include adequate representation of the age groups and should be conducted in a symptomatic population under ‘actual use” conditions.

Final Study Report Submission:	June, 2014

The sponsor agreed to a Postmarketing Commitment to conduct a study to assess the CPK in users of the ketoprofen films.

- The post marketing commitment is to conduct a randomized, placebo-controlled study to assess the CPK in users of the ketoprofen film. The study will enroll healthy subjects. People will be excluded if they are at risk for CPK elevations for reasons other than the study drug. CPKs will be assessed at baseline and at the end of the study. Participants will take the study medication for ten days, the duration of use allowed on the product label. Normal physical activity will be allowed but physical exercise will be restricted. All subjects will be queried as to exercise and other exposures that could raise CPK during the course of the study. All CPK elevations will be followed to resolution and adverse events will be recorded. The study will enroll 200 subjects in the ketoprofen arm and 100 in the placebo arm.

- The timelines for the submission of the proposed PMC are as follows:

Final Study Protocol Submitted:	June, 2010
Study Completion	March, 2011
Final Study Report Submission:	December, 2011

Appendix 1

This is an e-mail exchange between Dr. Cindy Li and myself to clarify some points about the pharmacology/toxicology data on this formulation that are important in furthering the understanding of the elevated CPKs seen in subjects in the Clinical Pharmacology Studies.

From: Li, Cindy (Xinguang)
Sent: Tuesday, November 17, 2009 11:57 AM
To: Leonard Segal, Andrea
Cc: Brown, Paul C; Harrouk, Wafa; Callahan-Lyon, Priscilla; Chang, Jane
Subject: FW: Ketoprofen oral soluble film NDA 22-470

Hi, Andrea,
Please see below response to your questions:

Because the application for NDA22-470 is a 505b2, the sponsor only conducted a bridging local toxicity study which did not include the standard toxicology assessment. Here are some specific comments:

- In the buccal mucosal tolerability study, muscle were not examined. The study evaluated local reactions at the treatment site and histopathologic changes in cheek pouch and esophagus: there were no test article-related changes;
- CPKs were not drawn in the buccal study;
- The excipients do not pose any safety concerns from the nonclinical's perspective because there were no novel components included as inactive ingredients in the product. Excipients were either categorized as GRASE, or are below the levels allowed in the approved products in FDA's inactive ingredient guide, or are present in trace negligible amounts.

In addition, with the great help of Pricilla and Jane, we figured out the following for the differences of the CSF and FMI:

	CSF (1588-01)	FMI (1588-02)
Total Film weight	60mg	70mg
Hypromellose	(b) (4)	(b) (4)
Hypromellose	(b) (4)	(b) (4)
Maltodetrin	(b) (4)	(b) (4)
Sodium phosphate dibasic	(b) (4)	(b) (4)

Neither of the two forms poses any safety concerns from nonclinical perspective, because all the excipients above were listed in FDA's inactive ingredient guide for oral approved products and fell below the levels listed there.

Please feel free to let us know if you have any questions,

Cindy

From: Leonard Segal, Andrea
Sent: Monday, November 16, 2009 10:45 AM
To: Li, Cindy (Xinguang)
Cc: Harrouk, Wafa
Subject: Ketoprofen oral soluble film NDA 22-470

Hi Cindy,

There are some strange CPK values in the study participants for the Clin Pharm studies that I am trying to make sense out of. I'm going back to the Pharm/Tox to look for some answers.

Based upon the data you reviewed for the NDA can you please tell me the following:

- The review is silent on the excipients with regard to stating that they were of quantity in the formulation that is considered to be safe based upon what we know of each of them. I'm assuming that they are, but can you please confirm this for me.

- In the hamster buccal study, was there any evidence of muscle damage? The necropsy inventory chart in the review doesn't state that they looked at muscles. Please confirm one way or the other.

- Were CPKs drawn in the hamster study?

I'm going to archive the e-mail exchange that we have on this topic so you don't need to write an addendum to your review.
Thanks,
Andrea

Andrea Leonard-Segal, M.D.

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One more question. Do you have the excipients that were in the clinical service form of the drug that was used as a comparator for the to-be-marketed formulation in clinical pharmacology EDKT-PN-101? Were they okay?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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/

ANDREA LEONARD SEGAL
11/24/2009