

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-470

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 22-470
Priority or Standard S

Submit Date(s) 1/23/09
Received Date(s) 1/23/09
PDUFA Goal Date 11/26/09

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Review Completion Date 9/25/09

Established Name Ketoprofen
(Proposed) Trade Name Nexcede
Therapeutic Class Analgesic
Applicant Novartis Consumer Health, Inc.

Formulation(s) Oral Soluble Film
Dosing Regimen 12.5 mg every 4 to 6 hours;
Maximum daily dose is 75 mg
Indication(s) 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 relieves
fever
Intended Population(s) Patients age 16 and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The proposed new formulation for ketoprofen, oral soluble film 12.5 mg, is acceptable. The drug development program established bioequivalence between the film and the previously approved ketoprofen 12.5 mg tablet. The clinical trial also demonstrated the safe use of the film without water. The recommended regulatory action from a clinical perspective is approval pending satisfactory

- resolution of site inspection deficiencies
- submission of an acceptable pediatric plan
- negotiation of labeling

1.2 Risk Benefit Assessment

Oral ketoprofen 12.5 mg was approved for over-the-counter use in the United States in 1995 for the temporary relief of headache, backache, muscular aches, toothache, minor pain of arthritis, menstrual cramps, minor aches and pain associated with the common cold, and for the reduction of fever. Novartis Consumer Health (NCH) has developed a ketoprofen 12.5 mg oral soluble film product. In support of this application, NCH has demonstrated bioequivalence of the ketoprofen oral soluble film to Orudis KT (NDA 20-429) – OTC 12.5 mg oral ketoprofen. The pharmacokinetic bioequivalence approach is based on the rationale that once absorbed; ketoprofen delivered by the oral soluble film formulation is distributed, metabolized, and eliminated in the same manner as in the immediate release tablet formulation. No efficacy studies were performed to assess the ketoprofen oral soluble film. Successful demonstration of bioequivalence between the ketoprofen oral soluble film and the Orudis[®] KT tablet allows use of the same efficacy claims as the reference drug.

The sponsor completed two pharmacokinetic studies for this submission. In Protocol EDKT-PN-101 Part I, ninety healthy subjects participated in a randomized, open-label, crossover, single-center study under fasting conditions where one ketoprofen 12.5 mg oral soluble film or one Orudis[®] KT 12.5 mg tablet was administered with water in a crossover manner. As per the sponsor and confirmed after review by the clinical pharmacology team, C_{max} of one ketoprofen 12.5 mg oral soluble film was 103.6% (90% CI of 96.5 – 111.1%) compared to that of one Orudis[®] KT 12.5 mg IR tablet and AUC was 98.3% (90% CI of 93.2 – 103.7%), demonstrating bioequivalence. As part of the same study, the subjects were administered one ketoprofen 12.5 mg oral soluble film with and without water under fasting conditions in a crossover manner. As per the sponsor and confirmed by the clinical pharmacology review, C_{max} of one ketoprofen 12.5 mg oral soluble film administered without water was 92.4% (90% CI 86.1 – 99.1%) compared to that administered with water and AUC of 100.7% (90% CI 95.5 – 106.2%). These data support that administering ketoprofen 12.5 mg without water had no significant effect on the

bioavailability of ketoprofen. The results of Part I of this study were reanalyzed by the clinical pharmacology team with exclusion of the subjects of concern (as per the Division of Scientific Investigations report). Reanalysis of the data also showed bioequivalence between ketoprofen oral tablet and oral soluble film.

In Protocol EDKT-PN-101 Part II, forty two healthy subjects participated in a randomized, open-label, crossover, single-center study and were administered one and two ketoprofen 12.5 mg oral soluble film(s) under fasting conditions. The C_{max} of two ketoprofen 12.5 mg oral soluble films, after normalization to dose, was 91.6% (90% CI 83.1 – 100.9%) compared to that of one ketoprofen 12.5 mg oral soluble film and AUC of 97.3% (90% CI 92.1 – 102.8%), demonstrating dose proportional PK properties. This also served as the bridging study to demonstrate bioequivalence between the clinical service form (CSF) and the Final Market Image (FMI) of the ketoprofen 12.5 mg film.

In study EDKT-PN-102, the effect of food on the release and absorption of ketoprofen from the orally soluble film was studied in an open-label, randomized, single dose, two-period crossover study in healthy volunteers. Forty healthy subjects were administered two ketoprofen 12.5 mg oral soluble films under fasting or fed conditions. Under fed conditions, the C_{max} was 39.96% relative to that under fasting conditions, AUC_{0-t} was about 93%, and AUC_{0-inf} was 94.92%. These findings were similar to the Orudis[®] product information which reports that food intake decreases the rate of absorption of ketoprofen (C_{max} is reduced by approximately 50%) while the total bioavailability (AUC) remains unaffected.

General safety information was obtained during the PK studies through the collection of adverse events, physical examination, vital sign collection, pregnancy testing, and lab analysis of blood chemistry, hematology, and urinalysis. The sponsor is seeking to remove the instruction on approved labeling to take the product with water. To evaluate the safety of dosing without water, special focus was given to evaluation of the effects of the oral soluble film on the oral mucosa during the pharmacokinetic studies. This evaluation showed no significant difference in oral examinations performed on the subjects after dosing with ketoprofen oral soluble film whether administered with or without water.

The general safety information did not reveal any unexpected results. A total of 125 subjects received the clinical service form of ketoprofen 12.5 mg oral soluble film and 84 of these received two doses during the EDKT-PN-101 study. A total of 119 subjects received the final marketing image form of the ketoprofen in the EDKT-PN-101 study; 40 received one 12.5 mg film and 79 received two 12.5 mg films. A total of 88 subjects received 12.5 mg of Orudis KT (oral ketoprofen) in this study. An additional 40 subjects received two 25 mg doses of the final marketing image form of ketoprofen films during study EDKT-PN-102. There were no deaths and no serious adverse events reported in the pharmacokinetic studies.

The most frequent adverse event noted was headache. Overall, it was reported 12 times in 11 subjects. None of the headache cases were severe or serious. Other frequent adverse events were nausea, oral mucosa eruption, and vomiting; 2 subjects each. All were reported in Study EDKT-PN-101 Part I, which also included the largest number of subjects (90) and all were of mild

severity. Oral eruption was experienced by two subjects. One episode occurred following treatment with one ketoprofen oral soluble film without water and was suspected to be related to the drug. The second followed treatment with Orudis[®] KT tablet and was not believed to be related to study drug. Adverse events believed to be treatment related belonged to the gastrointestinal system (including epigastric pain, nausea, and vomiting) and hypersensitivity events (including rash and lip swelling - both in the same subject). Both gastrointestinal and hypersensitivity reactions are adverse events associated with the NSAID drug class and are expected for ketoprofen. The safety analysis showed the oral (b) (4) film to have a comparable safety profile to the approved oral ketoprofen tablet.

There were no meaningful changes in hematological parameters in the clinical pharmacology studies except for hemoglobin and hematocrit, which fell roughly about 1 g/dL and 3%, respectively at the end of the study compared to baseline. This was explained by the quantity of blood drawn from the subjects. There were no clinically meaningful trends in urinalysis in any of the studies. There were no clinically meaningful trends noted for abnormal chemistry tests in individual subjects except a change in CPK levels for three subjects in study EDKT-PN-101 Part II. This was carefully reviewed and felt unlikely to be related to the study drug. (See Section 7.4.2 for additional information.) No clinically relevant trends in vital sign assessments were noted in any of the studies.

In the pre-IND meeting, the sponsor agreed to provide a review of the published literature for photosensitivity potential of ketoprofen and other NSAIDs, especially those used OTC. Most of the photosensitizing reactions related to ketoprofen were associated with topical formulations. Reports of photoallergic reactions associated with oral ketoprofen are rare. A review of the available studies and case reports in the open literature as well as the search of the post-marketing databases indicate that photoallergy is unlikely to be a major safety issue with the ketoprofen 12.5 mg oral soluble film. The search of marketing databases revealed a total of 74 cases (12 from SRS and AERS and 62 from WHO Vigibase) of potential photosensitivity reactions possibly associated with the oral administration of ketoprofen. These reactions were classified as either photoallergic reactions, photosensitivity reactions or phototoxic reactions. Based on experimental studies, only dermal application appears to provide sufficiently high ketoprofen concentrations to induce or trigger photoallergy. A photosensitization response requires sufficiently high skin concentration of ketoprofen and sufficient UV irradiation for both induction and expression. There is no UV exposure in the mouth, and the skin concentrations after dosing with 12.5 mg oral soluble film are likely to be relatively low making photosensitization unlikely with this product.

Ketoprofen 12.5 mg orally-soluble film has not been approved for marketing in any country and no information on post-marketing experience for this formulation is available. In support of this application a review of the post-marketing experience for oral and topical ketoprofen was performed by the sponsor using the available post-marketing safety data from the Food and Drug Administration's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) databases, data from the World Health Organization's (WHO) International Drug Monitoring Program and data from the Drug Abuse Warning Network (DAWN).

The analysis of adverse events reported for ketoprofen to the FDA SRS and AERS databases was conducted from January, 1999 through 30 June 2008. There were a total of 3740 cases involving 9814 adverse event terms. Of the seven most commonly reported AE terms, Drug ineffective had the highest frequency, five of the seven terms were related to gastrointestinal disturbances, and the other term was renal failure acute. The analysis of information available from the FDA databases for ketoprofen reflected known pharmacologic properties of the drug and no unexpected adverse findings.

An analysis of the adverse events reported for ketoprofen in the WHO drug safety database from August, 1974 through 16 November 2008 revealed 6608 cases involving 10,873 MedDRA adverse event terms. Of these reports, 5707 cases involving 9014 terms were reported from outside the United States. A review of the data identified gastrointestinal disorders (ulcer and hemorrhage), allergic phenomena, and renal disorders (acute renal failure) as the adverse events of greatest frequency and clinical importance. These findings are consistent with known information regarding ketoprofen.

The data from the New DAWN database covered the period from January 2003 to 24 November 2008. There were 45,026 emergency department visits reported for the NSAIDs and ketoprofen accounted for 73. 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. Overall, the post-marketing information available for ketoprofen shows no evidence of unexpected adverse events.

Based on the previously established efficacy of oral ketoprofen, the documented bioequivalence of the oral soluble film to the oral product, and the documented safety profile, the risk-benefit assessment is favorable for this product.

1.3 Recommendations for Post-market Risk Management Activities

No special post-market risk management activities beyond routine pharmacovigilance are recommended.

1.4 Recommendations for Post-market Studies/Clinical Trials

Post-market clinical trials need to be completed as part of the Pediatric and Research Equity Act. These trials should include a pharmacokinetic evaluation for proper dosing in children and clinical trials which demonstrate efficacy for the pain indication for children ages 6 months to 15 years. The trials should be conducted using a pain model or models suitable for an over-the-counter population. In addition, a thorough safety trial should be conducted on a sizable population of children ages 6 months to 15 years that includes adequate representation of the age groups under “actual use” conditions.

2 Introduction and Regulatory Background

2.1 Product Information

Ketoprofen is a propionic acid derivative, non-steroidal anti-inflammatory drug (NSAID). This class of medications has analgesic, anti-inflammatory, and antipyretic properties. NSAIDs are commonly used for the management of mild to moderate pain, whether acute or chronic.

The over-the-counter (OTC) indications for ketoprofen include 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 OTC dosing regimen is 12.5 mg every 4 to 6 hours, with an initial dose of 12.5 mg or 25 mg. The maximum daily dose for OTC use is 75 mg per day. Maximum recommended duration of treatment is 3 days for fever and 10 days for pain. Ketoprofen is approved for patients age 16 and older.

Novartis Consumer Health (NCH) has developed a ketoprofen 12.5 mg oral soluble film product. The sponsor is seeking approval for OTC marketing of this product. In support of this 505(b)(2) NDA, NCH is referencing Orudis NDA 18-754 (prescription strength ketoprofen) and Orudis KT NDA 20-429 (12.5 mg OTC strength ketoprofen). The prescription strength product is referenced for preclinical and clinical safety; the OTC strength product for clinical safety and efficacy. There is no right of reference from the application holders.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many approved prescription and OTC products for relief of minor pain and temporary reduction of fever. The most commonly used products are aspirin and other salicylate products, acetaminophen, ibuprofen, and naproxen. All of these products have the indications that are proposed for ketoprofen. Ibuprofen and naproxen are nonsteroidal anti-inflammatory drugs with efficacy and safety profiles similar to ketoprofen.

2.3 Availability of Proposed Active Ingredient in the United States

Ketoprofen is a well-established non-steroidal anti-inflammatory drug (NSAID) belonging to the arylpropionic acid group. It is used as an anti-inflammatory, analgesic, and antipyretic agent. It was first synthesized in 1967 and was introduced into human medicine in France and Great Britain in 1973. NDA18-754 (Orudis®) was approved on January 9, 1986 for the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis. NDA 20-429 (Orudis® KT, ketoprofen, 12.5 mg) and NDA 20-499 (Actron®, ketoprofen, 12.5 mg) were approved for over-the-counter use on October 6, 1995.

Ketoprofen is currently available in immediate release and extended release oral formulations for prescription use in the United States. There are no currently marketed OTC forms. These

products were withdrawn from production but there is Federal Register determination that the products were not discontinued or withdrawn for safety or efficacy reasons.

2.4 Important Safety Issues with Consideration to Related Drugs

Nonsteroidal anti-inflammatory medications are commonly used in the United States. These are relatively safe medications but there are concerns in certain populations. The most common adverse reactions involve the upper gastrointestinal tract. These effects are usually mild; however, in 5-15% of patients the events are sufficient to require discontinuation of the drug. Risk of more severe gastrointestinal events such as ulceration or perforation increases with increased duration of therapy and higher doses.

Nonsteroidal anti-inflammatory medications are also associated with a relatively high incidence of renal adverse drug reactions. These agents may cause renal impairment, particularly when combined with other nephrotoxic agents such as diuretics or ACE inhibitors. There is an increased risk of congestive heart failure associated with the use of NSAIDs. Both the cardiac and renal risks are increased in older patients.

Photosensitivity is another concern with NSAIDs. This is more likely with the 2-arylpropionic acids but must be considered with any drugs in the non-steroidal class.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting was held with Novartis on February 6, 2007 to discuss the development plan for ketoprofen oral soluble film. The issues raised by FDA during the meeting have been addressed by the sponsor. These issues include:

1. Provide data regarding the exposure to sodium that could result from treatment with the (b) (4)
2. Submission of all of the stability data required to support the NDA,
3. Using the Orudis KT tablets within the expiry date,
4. Providing data regarding phototoxicity and photoallergenicity associated with ketoprofen,
5. Bioequivalence studies and multiple dose pharmacokinetic information that supports the proposed dosing regimen,
6. Using the to-be-marketed formulation in the bioequivalence study,
7. Assessment of food effect,
8. Assessment of local tolerance in the oral cavity (buccal mucosal irritation study),
9. Provide rationale to support safe dosing of the film without water,
10. Provide worldwide marketing and safety data for ketoprofen, and
11. Provide foreign labeling information (if available) with English translation.

The exposure to sodium is 1.894 mg for each oral (b) (4) film – well below the limit of 140 mg in 24 hours. The stability data required to support the NDA will be reviewed by the chemists. The phototoxicity and photoallergenicity data and the worldwide marketing and safety information are reviewed in the safety portion of this document. The other clinical information discussed in the pre-IND meeting is also reviewed in this document (pharmacokinetics, food

effect, local tolerance, and use of the film without water). All of the studies using the Orudis KT tablets as the reference product were completed prior to the product expiry date. A bioequivalence study was completed using the to-be-marketed formulation of the product.

2.6 Other Relevant Background Information

Ketoprofen oral soluble film has not been marketed outside of the United States. The English translations of the foreign marketing labels for oral ketoprofen were reviewed. The warnings on these labels are consistent with the proposed label included in this submission.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was complete and organized. Data was located easily within the electronic document. The clinical review team requested no additional information from the sponsor except a revised pediatric plan (see section 7.6.3 for details).

3.2 Compliance with Good Clinical Practices

The sponsor states that all new studies were conducted in full compliance with Good Clinical Practice and were closely monitored by Novartis personnel for compliance to the protocol and the procedures described in it.

An inspection was performed by Division of Scientific Investigations (DSI) to audit the clinical and analytical portions of the pivotal bioequivalence study (EDKT-PN-101).

Investigation of the clinical site revealed the following concerns:

- One subject was excluded for high blood pressure though the reading was within an accepted range for the protocol
- Re-collection of final visit hematology testing was done on 19 of 82 subjects due to a laboratory accident (IRB not notified)
- Two subjects had all or part of screening laboratory studies repeated (IRB not notified)

The DSI team believed these findings did not compromise subject safety or impact study integrity.

Investigation of the analytical site revealed the following concerns:

- In the bioequivalence study, the analysis of plasma from eight subjects did not meet quality control criteria
- The firm failed to conduct the Incurred Sample Reproducibility experiment for the bioequivalence study

- The firm failed to provide proper criteria of selection of initial integration parameters for the analytical runs during the study period. During the inspection, the staff of the firm was able to re-integrate the analytical runs with no discrepancies.

The DSI team believes the accuracy of the pharmacokinetic data from the eight subjects noted above cannot be assured. A re-analysis of the data from study EDKT-PN-101, excluding these subjects, will need to be completed to evaluate bioequivalence between the oral ketoprofen tablet and the ketoprofen oral film. The DSI team also states the firm should investigate and provide data to show that there is no issue with the Incurred Sample Reproducibility experiment for this study (EDKT-PN-101).

As a result of the inspection findings, the clinical pharmacology review team is re-analyzing the data from the bioequivalence study. The sponsor has been notified of the DSI findings and their response is pending.

3.3 Financial Disclosures

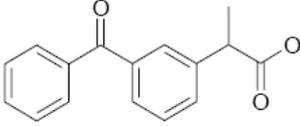
The sponsor submitted Form 3454 certifying that the investigator did not have any significant financial interests in these products, conducted studies, or the company conducting the studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The structure and properties of ketoprofen are shown in Table 1. The new formulation, a 12.5 mg oral soluble film, disintegrates in the mouth within approximately 10 to 15 seconds. The inactive ingredients included in the ketoprofen oral soluble film are sodium phosphate, dibasic, sodium hydroxide, FD&C blue No. 1 (in peppermint flavor film), FD&C Red No. 40, DM 2000 (in cinnamon flavor film), hypromellose, sucralose, acesulfame potassium, xylitol, maltodextrin, PEG 400 and peppermint flavor (b) (4) or cinnamon flavor (b) (4). Water (USP purified) and acetone (NF), present in the initial mix are evaporated off during the drying process. All excipients except the peppermint and cinnamon flavors are commonly used and recognized US pharmacopoeia/NF excipients. All main components in peppermint and cinnamon flavors have GRAS status. Additional details may be found in the chemistry review.

Table 1: Structure and Chemical Properties of Ketoprofen

| | |
|---------------------|---|
| Common name | Ketoprofen [INN, USAN, BAN, JAN] |
| Synonyms | 2-(3-benzoylphenyl)-propionic acid; CCRIS 4508; EINECS 244-759-8; m-benzoylhydratropic acid; Orudis; Oruvail; Profenid; RP 19583; RU 4733 |
| CAS No. | 22071-15-4 (also 154907-35-4, 172964-50-0 and 22161-86-0) |
| Systematic name | 3-benzoyl-alpha-methyl-benzeneacetic acid 2-(3-benzoylphenyl)-propionic acid |
| Molecular formula | C ₁₆ H ₁₄ O ₃ |
| Molecular weight | 254.3 |
| Chemical structure |  |
| Chemical properties | Melting point 94°C; vapor pressure 3.72E-07 mm Hg at 25°C; pKa 4.45; water solubility 51 mg/L at 22°C; log P (octanol-water) 3.12. |

(Source: NDA 22-470, Module 2.6.1, Table 1)

4.2 Clinical Microbiology

This does not apply.

4.3 Preclinical Pharmacology/Toxicology

The preclinical studies, in terms of pharmacodynamic and pharmacokinetic characterization in animals, and the toxicology studies conducted were submitted to NDA18-754 for Orudis[®] (prescription strength ketoprofen) which was approved in January, 1986. Orudis[®] KT (ketoprofen, 12.5 mg) tablet was approved as an OTC product by the FDA in October, 1995 (NDA 20-429). Reference is made to the Pharmacology and Toxicology review and approval of NDA 18-754 and NDA 20-429. The toxicology studies were conducted before the promulgation of GLP regulations and were therefore not conducted in accordance with GLP. Furthermore, the guidelines for toxicology study design in the 1970s did not correspond to current ICH guidelines. The nonclinical testing program did produce adequate acceptable data; specifically repeat dose toxicity in 3 species with treatment duration of one year, mutagenicity data, carcinogenicity assays into species, and reproduction studies covering all major phases (fertility, general reproductive performance and peri-postnatal toxicity in rats, embryo-fetal toxicity in rats and rabbits).

In support of this application, a new toxicology study on the local tolerability of the finished product in hamsters has been conducted in compliance with GLP. One ketoprofen film cut to size of 5 mm was applied to the cheek pouch of each hamster. This was repeated six times a day for 14 days. No water was administered during the treatment periods. The study indicated no macroscopic or histological signs of irritation in the buccal mucosa or esophagus.

When ketoprofen is applied topically in animals, it is a photoallergen. The induction dose was 10 mg/cm² followed by irradiation with 10 J/cm². This is unlikely to be a major safety issue with the

ketoprofen 12.5 mg oral soluble film. Photoallergy requires a sufficiently high skin concentration and sufficient UV irradiation for both induction and expression. Based on the pharmacovigilance data, only dermal application appears to provide sufficiently high ketoprofen concentrations to induce or trigger photoallergy. There is no UV exposure in the mouth, and the skin concentrations after dosing with 12.5 mg oral soluble film are likely to be relatively low.

Further details regarding preclinical data can be found in the Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ketoprofen inhibits prostaglandin synthesis and has antibradykinin activity. It has minimal effects on the cardiovascular system, the respiratory system, the autonomic nervous system, and the central nervous system. Ketoprofen has anti-inflammatory potency comparable to ibuprofen. Ketoprofen is a photoallergen following topical administration. This is unlikely to be an issue with oral administration and is discussed further as part of the safety review (Section 7.7).

4.4.2 Pharmacodynamics

There were no additional pharmacodynamic studies submitted to this NDA. The primary nonclinical pharmacodynamic studies for ketoprofen were reviewed in NDA 18-754, approved on January 6, 1986. A summary of these studies is shown in Table 2.

Table 2: Primary Pharmacodynamics of Ketoprofen: Summary of Animal Studies

| Test | Species | Route | Results |
|---|------------|--------|--|
| <u>Anti-inflammatory activity</u> | | | |
| Carrageenan-induced edema | Rat | oral | ED50 = 9 mg/kg |
| Carrageenan-induced abscess | Rat | oral | ED50 = 1.4 mg/kg |
| | | sc | ED50 = 0.5 mg/kg |
| | | dermal | ED50 = 1 mg/kg |
| | | rectal | ED50 = 5 mg/kg |
| UV-induced erythema | Guinea pig | oral | ED50 = 7.5 mg/kg |
| Experimental arthritis | Pigeon | sc | 2 and 5 mg/kg prolonged time to one-foot position after intra-articular talc injection |
| <u>Analgesic activity</u> | | | |
| Phenylbenzoquinone ip writhing test | Mouse | oral | ED50 = 2.3 mg/kg |
| Paw pressure test | Rat | oral | ED50 = 2.4 mg/kg |
| <u>Antipyretic activity</u> | | | |
| Subcutaneous yeast-induced hyperthermia | Rat | oral | ED50 = 0.5 mg/kg |
| Intravenous antigonococcal vaccine induced hyperthermia | Rabbit | sc | ED50 < 1 mg/kg |

ED50: Dosage which gives predicted pharmacological effect on 50% of treated animals
 (Source: NDA 22-470, Module 2.6.2, Table 2.6.2.1)

4.4.3 Pharmacokinetics

The pharmacokinetics of ketoprofen are reviewed in the clinical pharmacology review of NDA 18-754. The systemic availability of ketoprofen, when oral formulation is compared with IV administration, is approximately 90% in humans. Once absorbed, ketoprofen is > 99% bound to plasma proteins, mainly to albumin. Ketoprofen is extensively metabolized in the liver to the unstable acyl-glucuronide conjugates by hepatic microsomal enzymes with up to 80% of the administered dose recovered in the form of the acyl-glucuronide conjugate. The unstable acyl-glucuronide conjugates are excreted from the body in the urine. Other metabolic pathways such as hydroxylation have also been reported. There are no known active metabolites of ketoprofen. Ketoprofen has been shown not to induce drug-metabolizing enzymes. The elimination half-life of ketoprofen has been reported at approximately 2 hours following its administration in healthy young volunteers while in the elderly, glucuronide conjugation and renal excretion are delayed resulting in the increase in elimination half-life to 3-5 hours.¹

The tables and conclusions that appear in this section come from the sponsor's submission. Following the site inspection by FDA's Division of Scientific Investigations (section 3.2 of this review), the clinical pharmacology re-analyzed the sponsor's data, removing the data of eight subjects as recommended by DSI. The reanalysis did not change the bioequivalence conclusions. For the FDA analysis and pharmacokinetic parameters, see the clinical pharmacology review.

¹ Orudis Package Insert

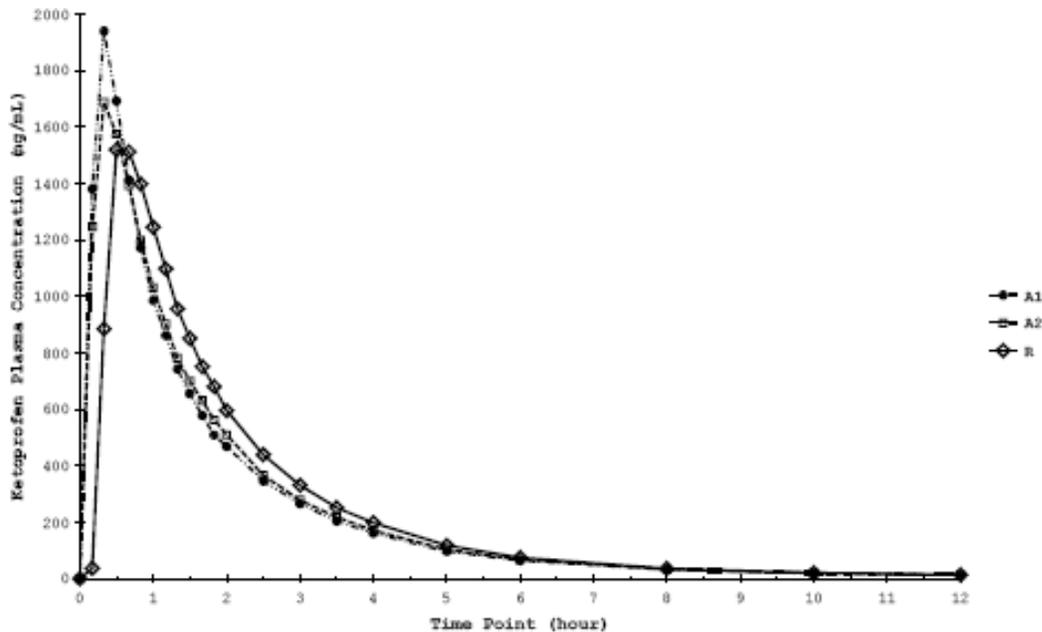
According to the sponsor, the clinical development program for ketoprofen film included demonstration of bioequivalence between ketoprofen 12.5 mg orally soluble film and the reference drug, Orudis[®] KT 12.5 mg tablet. The sponsor performed two pharmacokinetic studies (one protocol was in two parts). The first study, Protocol EDKT-PN-101 Part I, demonstrated bioequivalence between a single dose of Orudis KT 12.5 mg tablet and one ketoprofen 12.5 mg oral soluble film administered with and without water. The study also demonstrated administering the film with or without water had no significant effect on the pharmacokinetics of the drug. Table 3 and Figure 1 show the results of EDKT-PN-101, Part I. The results of the studies are reviewed in more detail in Section 5.3.

Table 3: Summary of Ketoprofen PK Analysis, Study EDKT-PN-101 Part I

| Parameter (Units)/ Statistic | A1 Ketoprofen 12.5 mg film with 150 mL water N=82 | A2 Ketoprofen 12.5 mg film without water N=82 | R Orudis KT 12.5 mg tablet with 150 mL water N=82 | p-value |
|--|---|---|---|---------|
| C_{max} (ng/mL) | | | | |
| Arithmetic mean (SD) | 2019.2 (487.91) | 1878.6 (540.16) | 1969.6 (591.49) | |
| Geometric mean | 1940.1 | 1793.0 | 1873.4 | |
| Test/Reference Ratio (%) (Reference=R) | 103.56 | 95.71 | — | 0.1798 |
| 90% Confidence Interval (Reference=R) | (96.53 – 111.10) | (89.22 – 102.67) | — | |
| 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) | | | | |
| Arithmetic mean (SD) | 2979.3 (646.62) | 3005.4 (673.89) | 3035.1 (696.44) | |
| 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) | | | | |
| Arithmetic mean (SD) | 3031.6 (663.75) | 3058.6 (689.24) | 3088.8 (712.67) | |
| 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 |

(Source: NDA 22-470, Module 5.3.1.2.3, Tables 11-3 and 11-4)

**Figure 1: Mean Plasma Ketoprofen Concentration versus Time (linear scale)
PK Analysis Population, Study EDKT-PN-101 Part I**



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.

(Source NDA 22-470, Module 5.3.1.2.3, Figure 11-1)

The second part of the PK study, Protocol EDKT-PN-101 Part II, demonstrated dose proportionality in pharmacokinetic properties between one and two ketoprofen 12.5 mg oral soluble film. In addition this study served as a bridging study to demonstrate bioequivalence between the clinical service form (CSF) and the final market image (FMI) of the ketoprofen 12.5 mg film. Tables 4, 5 and 6 and Figure 2 show the results of the EDKT-PN-101 Part II.

Table 4: Summary Statistic of PK Parameters, Study EDKT-PN-101 Part II

| Parameter (Units)/ Statistic | Treatment Group | | |
|--------------------------------------|---|---|---|
| | One Ketoprofen 12.5 mg Film FMI (N=39) | Two Ketoprofen 12.5 mg Film FMI (N=38) | One Ketoprofen 12.5 mg Film CSF (N=39) |
| C_{max} (ng/mL) | | | |
| Arithmetic mean (SD) | 1995.4 (434.96) | 1880.4 (527.49) | 1922.1 (502.49) |
| Geometric mean | 1948.7 | 1792.0 | 1856.2 |
| CV (%) | 21.80 | 28.05 | 26.14 |
| Median | 1991.7 | 1897.8 | 1937.2 |
| AUC_{0-t} (ng*h/mL) | | | |
| Arithmetic mean (SD) | 2954.1 (533.06) | 2928.5 (603.84) | 2891.8 (492.90) |
| Geometric mean | 2907.7 | 2855.0 | 2851.6 |
| CV (%) | 18.04 | 20.62 | 17.04 |
| Median | 2854.1 | 2874.2 | 2838.4 |
| AUC_{0-inf} (ng*h/mL) | | | |
| Arithmetic mean (SD) | 3027.9 (539.39) | 2983.1 (623.83) | 2942.9 (518.87) |
| Geometric mean | 2981.4 | 2905.9 | 2899.1 |
| CV (%) | 17.81 | 20.91 | 17.63 |
| Median | 2920.2 | 2919.7 | 2878.8 |

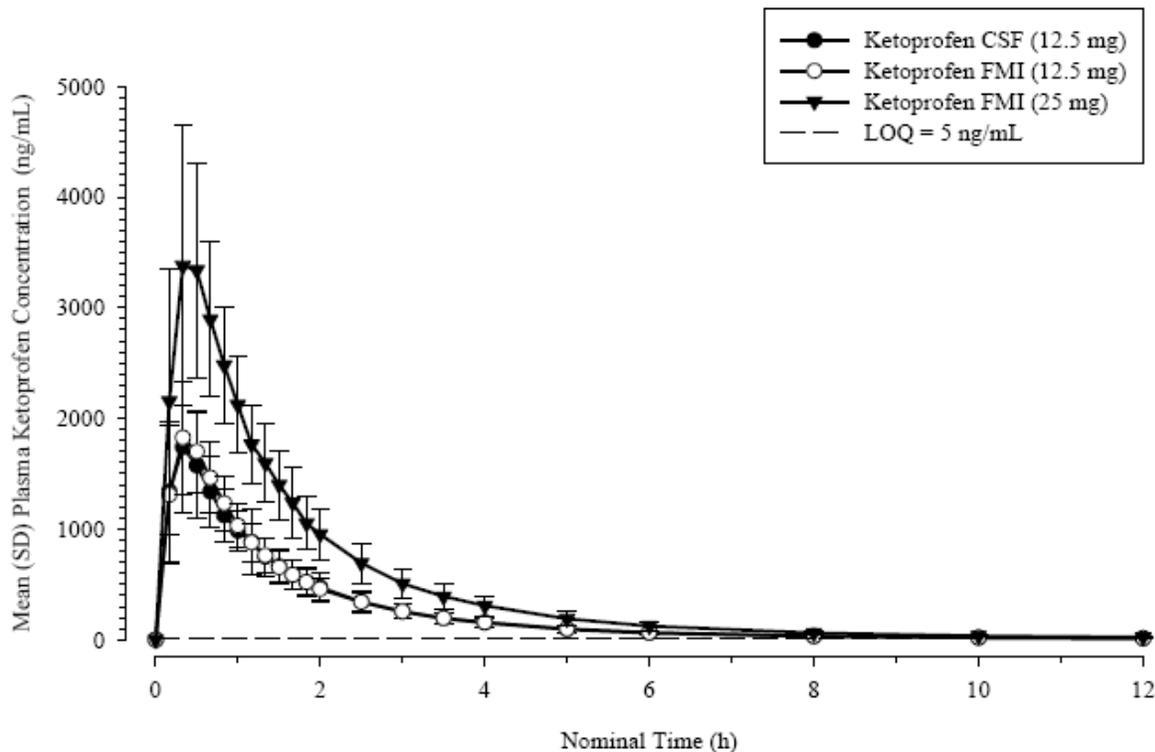
CV= Coefficient of Variation; CSF=Clinical Service Form; FMI=Final Marketed Image
(Source: NDA 22-470, Module 5.3.1.2.3, Table 11-3)

Table 5: Summary of Ketoprofen Bioequivalence Analysis, Study EDKT-PN-101, Part II

| Parameter/Statistic | Ketoprofen 12.5 mg Orally-soluble film FMI | Ketoprofen 12.5 mg Orally-soluble film CSF |
|---|--|--|
| C_{max} (ng/mL) | | |
| Geometric Mean | 1949.6 | 1858.0 |
| Test/Reference Ratio (%) (Reference=B3) | 104.93 | -- |
| 90% Confidence Interval (Reference=B3) | (97.79, 112.58) | -- |
| AUC_{0-t} (ng*h/mL) | | |
| Geometric Mean | 2903.1 | 2848.2 |
| Test/Reference Ratio (%) (Reference=B3) | 101.93 | -- |
| 90% Confidence Interval (Reference=B3) | (99.41, 104.50) | -- |
| AUC_{0-inf} (ng*h/mL) | | |
| Geometric Mean | 2948.6 | 2891.5 |
| Test/Reference Ratio (%) (Reference=B3) | 101.98 | -- |
| 90% Confidence Interval (Reference=B3) | (99.39, 104.63) | -- |

CSF=Clinical Service Form; FMI=Final Marketed Image
(Source: NDA 22-470, Module 5.3.1.2.3, Table 11-4)

Figure 2: Mean Plasma Ketoprofen Concentration versus Time (linear scale)



CSF=Clinical Service Form; FMI=Final Marketed Image
 LOQ=Low Limit of Qualification
 (Source: NDA 22-470, Module 5.3.1.2.3, Figure 11-1)

Table 6: Summary of Ketoprofen Dose Proportionality, Study EDKT-PN-101, Part II

| Parameter/Statistic | One Ketoprofen 12.5 mg Orally-soluble film FMI | Two Ketoprofen 12.5 mg Orally-soluble film FMI [#] |
|---|--|---|
| C_{max} (ng/mL) | | |
| Geometric Mean | 1935.0 | 1771.9 |
| Test/Reference Ratio (%) (Reference=B1) | -- | 91.57 |
| 90% Confidence Interval (Reference=B1) | -- | (83.11, 100.89) |
| AUC_{0-t} (ng*h/mL) | | |
| Geometric Mean | 2913.9 | 2830.9 |
| Test/Reference Ratio (%) (Reference=B1) | -- | 97.15 |
| 90% Confidence Interval (Reference=B1) | -- | (92.02, 102.57) |
| AUC_{0-inf} (ng*h/mL) | | |
| Geometric Mean | 2967.7 | 2887.7 |
| Test/Reference Ratio (%) (Reference=B1) | -- | 97.30 |
| 90% Confidence Interval (Reference=B1) | -- | (92.11, 102.79) |

[#]=Values displayed are normalized by dose; CSF=Clinical Service Form; FMI=Final Marketed Image
 (Source: NDA 22-470, Module 5.3.1.2.3, Table 11-5)

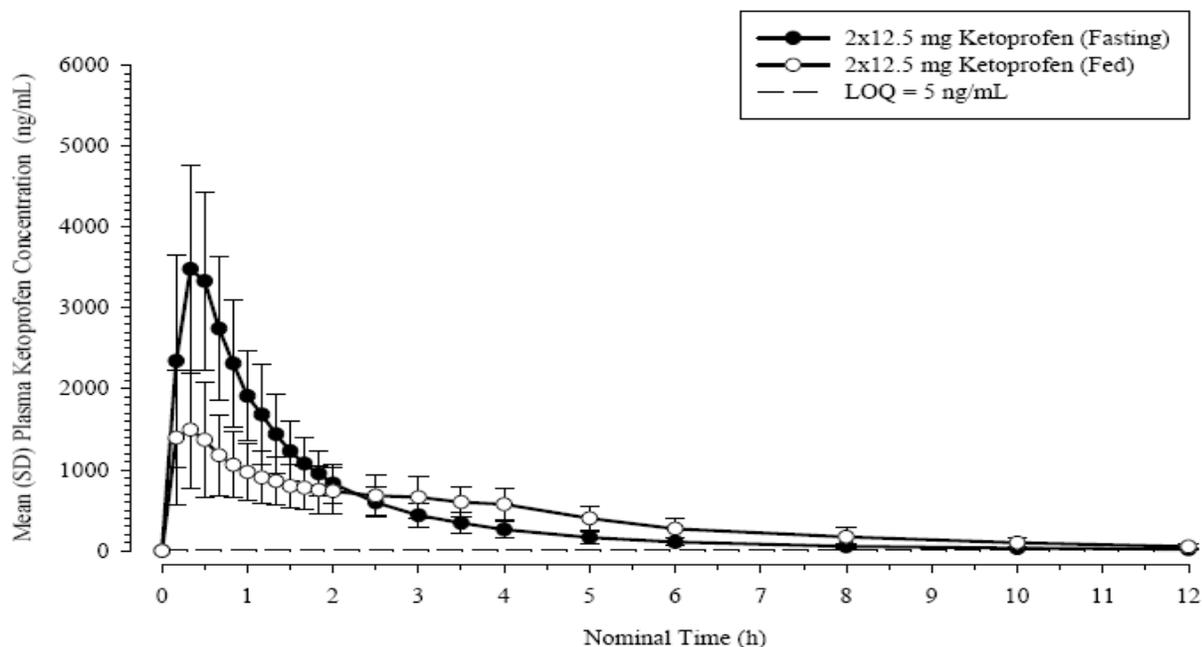
Protocol EDKT-PN-102 evaluated the bioavailability and bioequivalence of ketoprofen orally soluble film in fed and fasting conditions when compared to Orudis KT Tablets. This study showed that bioavailability of the ketoprofen film is affected by food with reduced C_{max}. For comparison, Orudis® product information reports that food intake decreases the rate of absorption of ketoprofen (C_{max} is reduced by approximately 50%) while the total bioavailability remains unaffected. When comparing this information to the PK data from the current study, it is evident that with concurrent food intake, AUC for ketoprofen is similar to that in the fasted state (90% CI of 85.22, 101.62) while C_{max} is reduced to ~40% with 90% CI of 34.7, 46.02. Table 7 and Figure 3 show the results of study EDKT-PN-102.

Table 7: Summary of Ketoprofen Pharmacokinetic Analysis, Study EDKT-PN-102

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

Fasting serves as reference treatment
(Source: NDA-22-470, Module 5.3.1.1.3, Table 11-4)

Figure 3: Mean Plasma Ketoprofen Concentration versus Time (linear scale)
Study EDKT-PN-102



LOQ=Low Limit of Qualification
(Source: NDA 22-470, Module 5.3.1.1.3, Figure 11-1)

Studies EDKT-PN-101, Parts I and II and EDKT-PN-102 will be discussed further in the efficacy portion of the review as these were the primary sources of clinical data. These studies will also be reviewed by the discipline-specific reviewers.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This new oral soluble film formulation has been developed by Novartis Consumer Health, Inc. for ketoprofen 12.5 mg and approval is pursued under 505(b)(2). Studies have been completed to demonstrate bioequivalence to an immediate release tablet of the same dosage strength (Orudis® KT). NCH is pursuing 'dosing without water' labeling after demonstrating that administering ketoprofen 12.5 mg oral soluble film with or without water does not change the pharmacokinetics of the drug.

The studies completed and submitted with this NDA are presented in Table 8. The goals of these studies were to demonstrate bioequivalence with the approved ketoprofen tablets and to show administration of the oral film with or without water had no effect on the pharmacokinetics.

Table 8: Pharmacokinetic Studies for Ketoprofen Orally soluble Film

| Study No. | Study objectives, population | No. of subjects | Aim(s) and evaluations |
|---------------------------|--|-----------------|--|
| Healthy volunteers | | | |
| EDKT-PN-101 Part I | A randomized, open-label, crossover, single-center study in healthy volunteers under fasting conditions. | 90 | <ul style="list-style-type: none"> Demonstrate BE between one ketoprofen 12.5 mg orally- (b) (4) and one ketoprofen 12.5 mg immediate release tablet (Orudis® KT) following single oral dose administration in fasting conditions. Demonstrate BE of one ketoprofen 12.5 mg orally- (b) (4) administered with and without water following single oral dose administration in fasting conditions. |
| EDKT-PN-101 Part II | A randomized, open-label, crossover, single-center study in healthy volunteers under fasting conditions. | 42 | <ul style="list-style-type: none"> Investigate dose proportionality of ketoprofen orally- (b) (4) (one and two (b) (4)). Demonstrate BE between the CSF and FMI formulations following single oral dose administration. |
| EDKT-PN-102 | A randomized, open-label, crossover, single-center study in healthy volunteers. | 40 | <ul style="list-style-type: none"> Evaluate the effect of food on the BA of two ketoprofen 12.5 mg orally- (b) (4) |

(Source: NDA 22-470, Module 2.5, Table 3-1)

5.2 Review Strategy

The sponsor performed two pharmacokinetic studies (one protocol was in two parts). There were no additional efficacy studies as approval is sought through the 505(b)(2) pathway. In support of this, NCH is referencing Orudis NDA 18-754 (prescription strength ketoprofen) and Orudis KT NDA 20-429 (12.5 mg OTC strength ketoprofen). The prescription strength product is referenced for preclinical and clinical safety; the OTC strength product for clinical safety and efficacy.

The pharmacokinetic studies are being reviewed in the efficacy and safety sections of the NDA review (in addition to the pharmacokinetic section) in order to present the clinical and safety data.

5.3 Discussion of Individual Studies/Clinical Trials

The clinical development program included the demonstration of bioequivalence between ketoprofen 12.5 mg oral soluble film and the reference drug, Orudis® KT 12.5 mg IR tablet. A summary of the pharmacokinetic study results as presented by the sponsor will be presented here with a detailed review of the clinical data in the efficacy and safety sections.

In Protocol EDKT-PN-101 Part I, ninety healthy subjects participated in a randomized, open-label, crossover, single-center study under fasting conditions where one ketoprofen 12.5 mg oral soluble film or one Orudis® KT 12.5 mg tablet was administered with water in a crossover manner. Cmax of one ketoprofen 12.5 mg oral soluble film was 103.6% (90% CI of 96.5 –

111.1%) compared to that of one Orudis® KT 12.5 mg IR tablet and AUC was 98.3% (90% CI of 93.2 – 103.7%), demonstrating bioequivalence.

Also in Protocol EDKT-PN-101 Part I, 90 healthy subjects were administered one ketoprofen 12.5 mg oral soluble film with and without water under fasting conditions in a crossover manner. The C_{max} of one ketoprofen 12.5 mg oral soluble film administered without water was 92.4% (90% CI 86.1 – 99.1%) compared to that administered with water and AUC of 100.7% (90% CI 95.5 – 106.2%). These data support that administering ketoprofen 12.5 mg without water had no significant effect on the bioavailability of ketoprofen.

Dose proportionality of ketoprofen oral soluble film was assessed in Protocol EDKT-PN-101 Part II. Forty two healthy subjects participated in a randomized, open-label, crossover, single-center study and were administered one and two ketoprofen 12.5 mg oral soluble film(s) under fasting conditions. The C_{max} of two ketoprofen 12.5 mg oral soluble films, after normalization to dose, was 91.6% (90% CI 83.1 – 100.9%) compared to that of one ketoprofen 12.5 mg oral soluble film and AUC of 97.3% (90% CI 92.1 – 102.8%), demonstrating dose proportional pharmacokinetic properties. This also served as the bridging study to demonstrate bioequivalence between the clinical service form (CSF) and the Final Market Image (FMI) of the ketoprofen 12.5 mg film.

In study EDKT-PN-102, the effect of food on the release and absorption of ketoprofen from the orally soluble film was studied in an open-label, randomized, single dose, two-period crossover study in healthy volunteers. Forty healthy subjects were administered two ketoprofen 12.5 mg oral soluble films under fasting or fed conditions. Under fed conditions, the C_{max} was 39.96% relative to that under fasting conditions, AUC_{0-t} was about 93%, and AUC_{0-inf} was 94.92%. Similarly, Orudis® product information (Orudis® Package Insert) reports that food intake decreases the rate of absorption of ketoprofen (C_{max} is reduced by approximately 50%) while the total bioavailability (AUC) remains unaffected.

6 Review of Efficacy

Efficacy Summary

No efficacy studies were performed to assess the ketoprofen oral soluble film. The sponsor believes demonstration of bioequivalence between the ketoprofen oral soluble film and the Orudis® KT tablet allows use of the same efficacy claims as the reference drug.

6.1 Indication

Ketoprofen 12.5 mg was approved for OTC use in the United States in 1995 (Actron® and Orudis®) for the temporary relief of headache, backache, muscular aches, toothache, minor pain of arthritis, menstrual cramps, minor aches and pain associated with the common cold, sore throat, and reduction of fever (NDA 20-499 and NDA 20-429).

6.1.1 Methods

NCH established efficacy for the proposed formulation by showing bioequivalence to an approved formulation. NCH believes that bioequivalence has been established between the study drug, ketoprofen 12.5 mg oral soluble film and the reference drug, Orudis KT 12.5 mg tablets and concludes that ketoprofen 12.5 mg oral soluble film has similar therapeutic properties as the reference drug. The pharmacokinetic bioequivalence approach is based on the rationale that once absorbed, ketoprofen delivered by the oral soluble film formulation is expected to be distributed, metabolized, and eliminated in the same manner as in the immediate release tablet formulation. Successful demonstration of bioequivalence between the ketoprofen 12.5 mg oral soluble film and the Orudis[®] KT 12.5 mg tablet allows use of the same efficacy claims as the reference drug.

Efficacy data submitted for the NDA approval of Actron[®] (NDA 20-499) and Orudis[®] KT (NDA 20-429) are summarized in Table 9.

Table 9: Efficacy Studies for Ketoprofen

| Medication | Indication | Total Patients | Patients Receiving Ketoprofen | Patients Receiving Ketoprofen 12.5 mg | Summary of Results for 12.5 mg Ketoprofen |
|------------------------------------|-----------------------------|----------------|-------------------------------|---------------------------------------|---|
| Actron (4 studies) | Dental Pain | 694 | 392 | 252 | Improved PR, PID, PRID c/w placebo in all studies |
| Orudis (6 studies) | Dental Pain | 647 | 379 | 64 (this dose only used in 3 studies) | Effective c/w placebo in 2 of the 3 studies where it was used |
| Actron (3 studies) | Dysmenorrhea | 1020 | 510 | 254 | Effective PR, PID, PRID |
| Orudis | Headache Muscle contraction | 252 | 202 | 101 | Improved over placebo for peak and total relief but not with periodic evaluation of PR, PID, PRID, analgesia onset & duration |
| Orudis | Headache Actual Use | 931 | 90% took ketoprofen | NA | Improved over placebo at 2 hours post-dosing |
| Orudis (3 studies, 2 disqualified) | Sore Throat | 246 | 122 | 60 | No difference c/w placebo |
| Actron (2 studies) | Fever-induced & natural | 232 | 117 | 59 | Improved c/w placebo for average and maximum temperature reduction |
| Orudis | Fever-induced | 107 | 54 | 28 | Improved c/w placebo |
| Orudis | Fever-natural | 44 | 21 | 21 | No difference c/w Ibuprofen 200 mg |
| Actron | Actual Use | 6205 | NA | NA | Compared ketoprofen 12.5 – 25 mg with Ibuprofen 200 – 400 mg; No difference in pain relief |
| Orudis | Actual Use | 931 | NA | NA | Compared ketoprofen 12.5 – 25 mg with Acetaminophen 500 – 1000 mg; No difference in pain relief |

PR=Pain Relief; PI=Pain Intensity; PID=Pain Intensity Difference; PRID=Combination of PR and PID
c/w=Compared with; NA=Not available

6.1.2 Demographics

The demographic characteristics of the populations included in the pharmacokinetic testing for this NDA are presented in Table 10.

Table 10: Subject Demographics of Pharmacokinetic Test Populations

| Parameter | Protocol EDKT-PN-102 N=40 | Protocol EDKT-PN-101 Part I N=90 | Protocol EDKT-PN-101 Part II | | |
|----------------------|------------------------------|-------------------------------------|------------------------------|------------------------|------------------------------|
| | | | Safety N=42 | Bioequivalence N=39 | Dose Proportionality N=38 |
| Age (years) n | 40 | 90 | 42 | 39 | 38 |
| Mean | 38.1 | 36.8 | 34.1 | 33.9 | 34.1 |
| Min, Max | 18, 64 | 18, 65 | 20, 57 | 20, 57 | 20, 57 |
| Sex n (%) | | | | | |
| Male | 23 (57.5) | 46 (51.1) | 17 (40.5) | 15 (38.5) | 14 (36.8) |
| Female | 17 (42.5) | 44 (48.9) | 25 (59.5) | 24 (61.5) | 24 (63.2) |
| Race n (%) | | | | | |
| Caucasian | 8 (20) | 18 (20) | 6 (14.3) | 6 (15.4) | 6 (15.8) |
| Black | 12 (30) | 26 (28.9) | 9 (21.4) | 8 (20.5) | 8 (21.1) |
| Asian | 1 (2.5) | 3 (3.3) | 2 (4.8) | 2 (5.1) | 1 (2.6) |
| Hispanic | 19 (47.5) | 43 (47.8) | 25 (59.5) | 23 (59) | 23 (60.5) |
| Weight (kg) | | | | | |
| Mean | 73.3 | 72.5 | 69.4 | 69.3 | 68.7 |
| Min, Max | 60.1, 91.6 | 50.1, 98.6 | 54.1, 93.2 | 54.1, 93.2 | 54.1, 91.4 |
| Height (cm) | | | | | |
| Mean | 169.3 | 168.6 | 166.1 | 165.9 | 165.3 |
| Min, Max | 150, 188 | 147, 192 | 148.5, 189 | 148.5, 189 | 148.5, 185 |
| BMI | | | | | |
| Mean | 25.5 | 25.4 | 25.1 | 25.1 | 25.1 |
| Min, Max | 21, 29.3 | 20.4, 30.3 | 19.3, 29.7 | 19.3, 29.7 | 19.3, 29.7 |

(Source: Study Data Tables, NDA 22-470)

6.1.3 Subject Disposition

The disposition of subjects involved in the pharmacokinetic studies is presented in Table 11.

Table 11: Disposition of Subjects in Pharmacokinetic Trials

| | EDKT-PN-102 | EDKT-PN-101 | EDKT-PN-101 |
|---|--------------------|--------------------|--------------------|
| | n | Part I n | Part II n |
| Subjects Screened | 98 | 208 | 130 |
| Subjects Failed Inclusion/Exclusion Criteria | 58 | 118 | 88 |
| Subjects Enrolled and Randomized | 40 | 90 | 42 |
| Subjects Completed Study n (%) | 40 (100) | 82 (91.1) | 38 (90.5) |
| Subjects Discontinued Study n (%) | 0 | 8 (8.9) | 4 (9.5) |
| Discontinued due to Adverse Event | | 2 (2.2) | |
| Subject Withdrew Consent | | 6 (6.7) | 3 (7.1) |
| Subject Lost to Follow-Up | | 0 | 1 (2.4) |

(Source: Study Synopsis Data Reports, NDA 22-470) n=number of subjects

6.1.4 Analysis of Primary Endpoint(s)

There were two pharmacokinetic studies submitted (one study had two parts). The results of these studies are reviewed in Section 4.4.3. Further analysis of the endpoints is in the Clinical Pharmacology Review.

7 Review of Safety

Safety Summary

General safety information was obtained during the pharmacokinetic studies. In addition, the sponsor provided post-marketing data for oral ketoprofen using the FDA AERS and SRS databases, the WHO database, and the DAWN database. The sponsor also included literature information regarding photosensitivity and photoallergenicity with ketoprofen. Results of all of these are included below. After review, it was found that there were no unexpected findings related to ketoprofen. The safety profile of the oral (b) (4) film is comparable to that of the approved oral tablet. The risk-benefit assessment is favorable for this product.

7.1 Methods

Once ketoprofen is absorbed from the oral soluble film formulation, its distribution, metabolism, and excretion is similar to the reference drug, Orudis[®] KT tablet. The establishment of bioequivalence supports the concept that the safety profile of the film is similar to the approved oral product. Since NCH is pursuing a ‘dosing without water’ claim, the new oral (b) (4) formulation brings the non-diluted active drug in direct contact with the oral mucosa. During the pharmacokinetic studies, special focus was given to local safety with respect to the effect on the oral mucosa in order to address this concern. The studies were designed to collect local safety information through the examination of the oral cavity before, immediately after, and at 2-hour intervals up to 12 hours post-dosing.

General safety information was obtained during the PK studies through the collection of adverse events, physical examination, vital sign collection, pregnancy testing, and lab analysis of blood chemistry, hematology, and urinalysis. Adverse events were coded using the Medical Dictionary for Regulatory Affairs (MedDRA version 9.1) terminology.

In the pre-IND meeting, NCH agreed to provide a review of the published literature for photosensitivity potential of ketoprofen and other NSAIDs, especially those used OTC. Cross reactivity between ketoprofen and other NSAIDs, delayed photosensitivity, and the extent of the dermatological reactions following oral versus topical ketoprofen use are evaluated. Most of the photosensitizing reactions were associated with topical ketoprofen formulations. Reports of photoallergic reactions associated with oral ketoprofen are rare. This is reviewed in detail in Section 7.7.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor conducted two pharmacokinetic studies and submitted the results for safety analysis. In addition, extensive review of the post-marketing surveillance data was performed and these results are reviewed in Section 8.

7.1.2 Categorization of Adverse Events

The most frequently observed adverse events in the clinical trials were gastrointestinal (GI) and neurological disorders. Of the GI adverse events, the common occurrences were nausea, oral mucosa eruption, and vomiting, 2 subjects each. Further discussion of the oral mucosa findings is found in section 7.4.5. Most of the GI adverse events were reported in Study EDKT-PN-101 Part I, which also included the largest number of subjects (90).

The most frequent neurological adverse event was headache. Overall, in the clinical pharmacology trials, 12 cases of headache were reported in 11 subjects. The headache events were not severe or serious. The frequencies of the above adverse events did not vary significantly in frequency between study and reference drug. Overall, major organ toxicity was not seen.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

There was no pooling of studies for safety evaluation of the ketoprofen oral soluble film, since the clinical pharmacology studies supporting this application involved administration of different formulations (CSF/FMI), different administration modes (with/without water) and different doses (one and two oral soluble film) were used in the studies. The safety population in each study consisted of all randomized subjects who participated in at least one study period and received at least one dose of study drug. Table 12 shows the adverse events reported by system organ class or syndrome for the safety population in the pharmacokinetic studies.

Table 12: Adverse Events by Frequent System Organ Class

Regardless of Relationship to Treatment: All Clinical Pharmacology Studies – Safety Population

| Primary System Organ Class | Orudis 12.5 mg N=88 | Ketoprofen 12.5 mg film CSF w/ water N=84 | Ketoprofen 12.5 mg film CSF w/o water N=84 | One Ketoprofen 12.5 mg film FMI N=40 | Two Ketoprofen 12.5 mg film FMI N=39 | Ketoprofen 12.5 mg film CSF N=41 | Fasted# N=40 | Fed# N=40 |
|--|---------------------|---|--|--------------------------------------|--------------------------------------|----------------------------------|--------------|-----------|
| Nervous System disorders – n (%) | 2 (2.3) | 6 (7.1) | 1 (1.2) | 2 (5.0) | 1 (2.6) | 1 (2.4) | 1 (2.5) | 2 (5.0) |
| Gastrointestinal disorders – n (%) | 4 (4.5) | 3 (3.6) | 2 (2.4) | 0 | 0 | 0 | 0 | 1 (2.5) |
| Hypersensitivity reactions – n (%) | 1 (1.1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Administrative site conditions – n (%) | 1 (1.1) | 1 (1.2)* | 1 (1.1) | 0 | 0 | 0 | 0 | 0 |

*=Sore throat; CSF=Clinical Service Form; FMI=Final Marketed Image

#Fasted and Fed: Dose was two ketoprofen 12.5 mg film FMI

(Source: NDA 22-470, Module 2.7.4, Table 2-8)

Bioequivalence has been established between the study drug, ketoprofen 12.5 mg oral soluble film and the reference drug, Orudis[®] KT 12.5 mg tablets. As ketoprofen has been available in the United States for prescription use since 1986 and for OTC use since 1995, abundant safety information is currently available for this drug. A summary of the clinical safety information provided by the sponsor for immediate release tablet formulation of OTC ketoprofen 12.5 mg, marketed under the trade names of Actron[®] and Orudis[®] KT, is provided below.

The pooled safety data for Actron[®] (NDA 20-499) consists of adverse reactions reported from 22 clinical trials, 16 of which were single-dose studies. In the remaining 6 multiple-dose studies, the maximum daily dose of ketoprofen was 150 mg for 7 days and the longest duration was 10 days at 75 mg per day. A total of 5,278 patients received ketoprofen. Over 10% of the patients on ketoprofen reported to have one or more adverse events (AEs) but most of the AEs occurred in <1% of the ketoprofen study population. Fever, chills, headache, dyspepsia, nausea, dizziness, and somnolence were reported in 1 to 2% of the subjects who received ketoprofen. Most of the adverse events reported were mild to moderate in severity and non-serious in nature. There was one report of death in a patient 3 days after receiving a single dose of ketoprofen 25 mg. The patient was known to have brain metastasis from melanoma. One report of esophagitis and one report of melena, both considered by the investigator to be related to ketoprofen, were recorded. There were no reports of peptic ulcer disease, GI perforation, renal insufficiency, or anaphylactic reactions. No specific treatment-gender interactions or treatment-age interactions could be concluded based on the data. A total of 25 cases of premature withdrawals due to adverse reactions occurred in the ketoprofen group; of which 50% were due to GI symptoms (dyspepsia, nausea, diarrhea, abdominal pain, etc.) while 20% were attributed CNS symptoms (dizziness, somnolence, etc.). Except the fatal case described above, none had serious outcomes and most events resolved spontaneously.

The pooled safety data for Orudis[®] KT (NDA 20-429) consists of adverse reactions reported

from 20 clinical trials, 17 of which were single-dose studies. In the remaining 3 multiple-dose studies, the maximum daily dose of ketoprofen was 300 mg for 3 days and the longest duration was 10 days at 75 mg per day. A total of 1,812 patients received ketoprofen. About 20% of the patients on ketoprofen reported to have one or more AEs with similar reporting rates among the different treatment groups. Most AEs reported were mild to moderate in severity and non-serious in nature. There were no reports of death, GI bleeding or perforation, peptic ulcer disease, renal insufficiency, or anaphylactic reactions. No specific treatment-gender interactions or treatment-age interactions could be concluded based on the data. A total of seven cases of premature withdrawals due to adverse reactions occurred in the ketoprofen group with most considered by the investigators to be not directly related to ketoprofen.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The population in each of the pharmacokinetic studies consisted of healthy male and female subjects, 18 to 65 years of age. The safety population in each study consisted of all randomized subjects who participated in at least one study period and received at least one dose of study medication. A total of 172 healthy subjects participated in the three studies. The demographic characteristics of the safety populations are shown in Table 13. Table 14 summarizes the overall exposure to ketoprofen oral soluble film by study periods.

A total of 125 subjects received the CSF form of ketoprofen 12.5 mg oral soluble film and 84 of these received two doses during the EDKT-PN-101 study. A total of 119 subjects received the FMI form of the ketoprofen in the EDKT-PN-101 study; 40 received one 12.5 mg film and 79 received two 12.5 mg films. An additional 40 subjects received two 25 mg doses of the FMI form of ketoprofen films during study EDKT-PN-102.

Table 13: Demographic Characteristics of Safety Populations in PK Studies

| Parameter | Protocol EDKT-PN-101 Part I N=90 | Protocol EDKT-PN-101 Part II N=42 | Protocol EDKT-PN-102 N=40 |
|----------------------|---|--|---------------------------------|
| Age (years) n | 90 | 42 | 40 |
| Mean | 36.8 | 34.1 | 38.1 |
| Min, Max | 18, 65 | 20, 57 | 18, 64 |
| Sex n (%) | | | |
| Male | 46 (51.1) | 17 (40.5) | 23 (57.5) |
| Female | 44 (48.9) | 25 (59.5) | 17 (42.5) |
| Race n (%) | | | |
| Caucasian | 18 (20) | 6 (14.3) | 8 (20) |
| Black | 26 (28.9) | 9 (21.4) | 12 (30) |
| Asian | 3 (3.3) | 2 (4.8) | 1 (2.5) |
| Hispanic | 43 (47.8) | 25 (59.5) | 19 (47.5) |

(Source NDA 22-470, Module 2.7.4, Table 1-3)

Table 14: Summary of Overall Exposure to Ketoprofen by Study Periods

| | EDKT-PN-101 (Part I) | | | EDKT-PN-101 (Part II) | | | EDKT-PN-102 | |
|--|----------------------|-----------------------------------|-----------------------------------|-----------------------------------|-------------------------------------|-----------------------------------|--------------------|-----------------|
| | Orudis 12.5 mg | Ketoprofen 12.5 mg film CSF | Ketoprofen 12.5 mg film CSF | Ketoprofen 12.5 mg film FMI | 2 Ketoprofen 12.5 mg film FMI | Ketoprofen 12.5 mg film CSF | Fasted# 2 films | Fed# 2 films |
| N^A (%) | 88 (97.8) | 84 (93.3) | 84 (93.3) | 40 (95.2) | 39 (92.9) | 41 (97.6) | 40 (100) | 40 (100) |
| Dose (mg ketoprofen) | 12.5 | 12.5 | 12.5 | 12.5 | 25 | 12.5 | 25 | 25 |
| Total dose per subject (mg ketoprofen) | 37.5 | | | 50 | | | 50 | |
| Formulation | Tablet | CSF | CSF | FMI | FMI | CSF | FMI | FMI |
| Water | With | With | W/O | W/O | W/O | W/O | W/O | W/O |

A=Number of subjects in the safety population in each study group

CSF=Clinical service formulation; FMI=Final marketing image

With=administered with water, 150 mL; W/O=administered without water

Fasted and Fed=each subject given two ketoprofen 12.5 mg oral soluble film (FMI)

(Source: NDA 22-460, Module 2.7.4, Table 1-2)

7.2.4 Routine Clinical Testing

The monitoring methods used during the pharmacokinetic studies were adequate for assessing the safety information needed to assess ketoprofen oral soluble film. In addition to physical examination, the investigators performed mouth examinations on the subjects to ensure a lack of oral mucosal irritation following use of the film. Subjects also had clinical laboratory testing before and after medication administration as well as vital signs and ECGs. The monitoring for adverse events was appropriate. The areas of concern for adverse events were monitored specifically.

7.2.5 Metabolic, Clearance, and Interaction Workup

Ketoprofen is a NSAID and the metabolism, clearance, and interactions have been well studied and described. Safety monitoring during the pharmacokinetic studies included evaluations for the specific areas of concern associated with this class of drugs.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Gastrointestinal adverse events are among the most common side effects related to NSAID use. GI-related AEs in the clinical pharmacology trials of ketoprofen were all mild to moderate and included upper abdominal pain, gastritis, nausea, and vomiting. In the first study (EDKT-PN-101 Part I), GI effects were reported by seven subjects; three were administered ketoprofen oral soluble film with water and two subjects each were administered ketoprofen oral soluble film without water or the Orudis® KT tablet comparator. No GI disorders were reported in the second study. In the third study, EDKT-PN-102, there was one report of mild diarrhea associated with two ketoprofen 12.5 mg oral soluble films taken after a meal.

The most frequent neurologic symptoms related to NSAID use are dizziness and headache. In the clinical pharmacology studies performed for this submission, headache, mild and moderate in severity, was noted in all treatment groups. Dizziness and paresthesias were also reported. These are known AEs for the NSAID class.

Hypersensitivity and allergic reactions to NSAIDs can manifest in a variety of clinical presentations. While anaphylactic and anaphylactoid reactions to NSAIDs are relatively rare, the clinical picture varies from vasomotor rhinitis, urticaria, and angioedema. Lip swelling and rash, observed in one subject during the clinical pharmacology trials following treatment with a dose of Orudis® KT tablet, and may represent an allergic immunological hypersensitivity reaction. Individuals who demonstrate hypersensitivity/allergic reactions should refrain from using ketoprofen in the future and should be aware that they may be cross-hypersensitive to other NSAIDs as well. (The involved subject was given this information.)

NSAIDs can also cause renal impairment. This is more common with prolonged use or higher doses. It is also more common in elderly patients or those with underlying cardiac or renal disease. There were no clinically significant ECG or clinical laboratory changes related to renal function during the pharmacologic studies.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in any of the studies.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events experienced in any of the studies.

7.3.3 Dropouts and/or Discontinuations

Two subjects withdrew from study participation due to adverse events in study EDKT-PN-101 Part I. The first experienced a mild oral rash upon admission to Period II, following treatment with Orudis[®] KT 12.5 mg tablets. The oral eruption was asymptomatic and not suspected to be related to study drug, but the subject was not dosed per protocol eligibility criteria. Since the rash was persistent on admission to Period III, the subject was not eligible for participation in the study. The second subject was removed from the study due to moderate lip swelling and mild rash, suspected to be related to the reference drug (Orudis[®] KT 12.5 mg tablets).

In study EDKT-PN-101 Part II, four subjects discontinued the study prematurely. Three (7.1%) subjects withdrew consent and 1 (2.4%) subject was lost to follow-up.

All randomized subjects completed study EDKT-PN-102.

7.3.4 Significant Adverse Events

There were no other significant adverse events in the studies.

7.3.5 Submission Specific Primary Safety Concerns

NCH is pursuing ‘dosing without water’ labeling for ketoprofen 12.5 mg oral (b) (4) film. In order to ensure that the new formulation taken without water is safe to the oral mucosa, oral cavity examinations were performed every 2 hours during the 12 hours following study medication administration. The results of these evaluations are reviewed in Section 7.4.5.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Due to the small sample size in each trial (<100 subjects), adverse events observed in at least 2 subjects are described as common. Common adverse events by Preferred Term are shown in Table 15.

Table 15: Common Adverse Events by Preferred Term

| System Organ Class | Orudis 12.5 mg N=88 | Ketoprofen 12.5 mg film CSF w/ water N=84 | Ketoprofen 12.5 mg film CSF w/o water N=84 | 1 Ketoprofen 12.5 mg film FMI N=40 | 2 Ketoprofen 12.5 mg film FMI N=39 | Ketoprofen 12.5 mg film CSF N=41 | Fasted N=40 | Fed N=40 |
|--|---------------------------|---|--|--|--|---|----------------|----------------|
| Any system organ class, total – n (%) | 6 (6.8) | 7 (8.3) | 4 (4.8) | 4 (10.0) | 4 (10.3) | 2 (4.9) | 1 (2.5) | 3 (7.5) |
| Gastrointestinal disorders – total | 4 (4.5) | 3 (3.6) | 2 (2.4) | 0 | 0 | 0 | 0 | 1 (2.5) |
| Nausea | 0 | 2 (2.4) | 0 | 0 | 0 | 0 | 0 | 0 |
| Oral mucosa eruption | 1 (1.1) | 0 | 1 (1.2) | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 0 | 2 (2.4) | 1 (1.2) | 0 | 0 | 0 | 0 | 0 |
| Nervous system disorders – total | 2 (2.3) | 6 (7.1) | 1 (1.2) | 2 (5.0) | 1 (2.6) | 1 (2.4) | 1 (2.5) | 2 (5.0) |
| Headache | 2 (2.3) | 5 (6.0) | 1 (1.2) | 0 | 0 | 1 (2.4) | 1 (2.5) | 2 (5.0) |
| Investigations | 0 | 0 | 0 | 2 (5.0) | 1 (2.6) | 0 | 0 | 0 |
| Blood CPK increased | 0 | 0 | 0 | 2 (5.0) | 1 (2.6) | 0 | 0 | 0 |

CSF=Clinical service formulation; FMI=Final marketing image

Fasted and Fed=each subject given two ketoprofen 12.5 mg oral soluble film (FMI)

(Source: NDA 22-470, Module 2.7.4, Table 2-3)

The most frequent adverse event noted in the pharmacokinetic studies was headache. Overall, it was reported 12 times in 11 subjects. None of the headache cases were severe or serious.

Other frequent adverse events were nausea, oral mucosa eruption, and vomiting; 2 subjects each. All were reported in Study EDKT-PN-101 Part I, which also included the largest number of subjects (90). All of these were of mild severity. The adverse events believed related to study treatment are shown in Table 16. Adverse events believed to be treatment related belonged to the gastrointestinal system (including epigastric pain, nausea, and vomiting) and hypersensitivity events (including rash and lip swelling - both in the same subject). Both gastrointestinal and hypersensitivity reactions are adverse events associated with the NSAID drug class and are expected for ketoprofen.

Oral eruption was experienced by two subjects. One episode occurred following treatment with one ketoprofen oral soluble film without water and was suspected to be related to the drug. The second followed treatment with Orudis[®] KT tablet and was not believed to be related to study drug but necessitated subject withdrawal from the study. Both subjects were asymptomatic, and the eruption was mild and resolved with no sequelae. No specific treatment was needed. Possible causes for these eruptions include allergic reaction, local effect of the oral soluble film on the oral mucosa, or idiopathic. Another subject experienced sore throat, following treatment with one ketoprofen 12.5 mg oral soluble film administered with water. This reaction could be a result of local effect of the drug, or GI in origin, as the subject experienced concomitant vomiting and epigastric pain. Taken together, there is no significant difference in the incidence of local oral reactions in association with oral soluble film, whether administered with or without water.

Table 16: Adverse Events Suspected Related to Study Drug by Preferred Term

| | Orudis 12.5 mg N=88 | Ketoprofen 12.5 mg film CSF w/ water N=84 | Ketoprofen 12.5 mg film CSF w/o water N=84 | 1 Ketoprofen 12.5 mg film FMI N=40 | 2 Ketoprofen 12.5 mg film FMI N=39 | Ketoprofen 12.5 mg film CSF N=41 | Fasted N=40 | Fed N=40 |
|---|------------------------------------|--|---|---|---|---|------------------------|---------------------|
| Subjects with > 1 AE | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| AE Preferred Term (Severity/ action taken) | | | | | | | | |
| Upper Abdominal Pain | | Mild No action ^A | | | | | | |
| Vomiting | | Mild No action ^A | | | | | | |
| Nausea | | Mild No action | | | | | | |
| Gastritis | Mod Con med | | | | | | | |
| Diarrhea | | | | | | | | Mild No action |
| Pharyngolaryngeal pain | | Mild No action ^A | | | | | | |
| Headache | | | | | | Mild No action | | Mild No action |
| Dizziness | | | | | Mild No action ^A | | | |
| Oral mucosal eruption | | | Mild No action | | | | | |
| Rash | Mild No action ^B | | | | | | | |
| Lip swelling | Mod Discontinued ^B | | | | | | | |
| Elevated CPK | | | | Mod No action | | | | |

A,B – Occurred in the same subject; Mod=Moderate; Con med=Concomitant medication
CSF=Clinical Service Form; FMI=Final Marketed Image
Fasted and Fed=each subject given two ketoprofen 12.5 mg oral soluble film (FMI)
(Source NDA 22-470, Module 2.7.4, Table 2-5)

7.4.2 Laboratory Findings

The clinical pharmacology trials had a crossover design, so each subject was assigned to receive all treatments in a given study. Blood hematology was analyzed during screening and on study completion meaning that end of study blood hematology reflected the net effect of all study periods. There were no meaningful changes in hematological parameters in the clinical pharmacology studies except for hemoglobin and hematocrit, which fell roughly about 1 g/dL and 3% respectively, at the end of the study compared to baseline. As the total amount of blood drawn from each subject was approximately 270-400 mL, depending on the study period, a decrease of 1g/L of hemoglobin was within the expected range.

Urinalysis was performed upon screening and on study completion. There were no clinically meaningful trends in urinalysis in any of the studies.

Blood chemistry was analyzed during subject screening and on study completion. There were no clinically meaningful trends noted for abnormal chemistry tests in individual subjects except a change in CPK levels for three subjects in study EDKT-PN-101 Part II. On screening, asymptomatic increased CPK levels was a common finding and was attributed to physical exercise. The Investigator set upon a cut-off of two-times the upper limit of normal (2X ULN) for asymptomatic abnormal CPK. If CPK levels exceeded 2X ULN the test was repeated. If the abnormality (> 2X ULN) persisted during screening; the subject was excluded from study participation. If observed during end of the study tests, it was noted as an adverse event.

Three subjects were noted with high CPK levels upon study completion of EDKT-PN-101 Part II.

- Subject 1004, a 21 year old Hispanic male, had a screening CPK of ^{(b) (4)}, the retest level was ^{(b) (4)} and the final CPK was ^{(b) (4)}. He reported no adverse events during the study. His other laboratory tests, including amylase and lipase levels, were normal. He received one CSF film in period 1, one FMI film I period 2, and two FMI films in period 3. The elevated CPK was felt by the sponsor to be unrelated to the study medication.
- Subject 1021, a 23 year old black male, had a screening CPK of ^{(b) (4)} and a final CPK of ^{(b) (4)}. He reported no adverse events during the study. His other laboratory tests, including amylase and lipase levels, were normal with the exception of an elevated non-fasting glucose level ^{(b) (4)} at the final visit. He received two FMI films in period 1, one CSF film in period 2, and one FMI film in period 3. The CPK elevation was considered by the sponsor to be mild in intensity, ongoing on final visit, not related to study drug, and no action was taken.
- Subject 1034, a 22 year old Hispanic female, had a CPK level of ^{(b) (4)} U/L upon study completion after a screening CPK of ^{(b) (4)}. All other laboratory values for this subject were carefully examined and no other significant abnormalities were noted. No other adverse events were recorded. She received one CSF film in period 1, two FMI films in period 2, and one FMI film in period 3. A repeat CPK was requested by the investigator but not performed as the subject was lost to follow-up. This was considered a moderate AE, ongoing at final visit, and suspected to be related to study drug.

No action was taken in any of these cases. In all cases, the investigator requested repeat CPK levels, but none were obtained as all subjects were lost to follow-up.

A careful review of the other two studies was performed focusing on the CPK results. Four subjects in EDKT-PN-101 Part I were noted to have elevated final CPK results. Two of these subjects also had elevated CPK at screening, but one of the subjects with elevated screening CPK had a significant rise in the final CPK.

- Subject 1027, a 37 year old Hispanic female, had a normal screening CPK of ^{(b) (4)} and a slightly elevated final CPK of ^{(b) (4)}. She reported no adverse events. Her laboratory testing showed no other significant abnormalities except a decreased hemoglobin/hematocrit in the final test. These findings were felt to be of no significance by the investigator.

- Subject 1049, a 43 year old black male, had a normal screening CPK of (b) (4) with an elevated final CPK of (b) (4). He reported no adverse events. There were no other significant laboratory findings. Again a repeat CPK was requested by the investigator but was not obtained.
- Subject 1082, a 31 year old black male, had an elevated screening CPK of (b) (4), a repeat CPK of (b) (4) and the final CPK was (b) (4). He reported no adverse events. He had no other significant laboratory abnormalities. The investigator did not regard this as an adverse event.

In study EDKT-PN-102, the only subjects that had an elevated CPK at the final visit also had an elevated screening CPK.

Table 17 shows the mean, median, and changes from screening to final for CPK in all three studies. Overall, the CPK values decreased after medication administration except in EDKT-PN-101 Part II and subject 1034's very high final CPK affects the mean in this small study. Elevated CPK can occur in normal situations without provocation. This may be due to genetic tendency, after strenuous activity, minor trauma, or a prolonged muscle cramp. There have been isolated case reports of NSAID-induced rhabdomyolysis, but these are very rare, associated with markedly elevated CPK levels, and are accompanied by clinical manifestations, especially muscle weakness and pain. Lower levels of elevated CPK, lack of accompanying symptoms and no additional lab abnormalities make this diagnosis unlikely. It is also unlikely that the elevated CPK levels were attributed to cardiac etiology, as these subjects are young and healthy with no significant past medical history and were asymptomatic with normal examinations, vital signs and no other lab abnormalities. Taken together, along with the fact that extensive knowledge is available on NSAID safety profile, it is likely that the elevated CPK levels were associated with physical activity. After careful analysis, this reviewer believes that the elevated CPK value for subject 1034 is likely an anomaly – either laboratory error or related to an undiagnosed condition.

Table 17: Screening and Final CPK results by Study

| | EDKT-PN-101 Part I | EDKT-PN-101 Part II | EDKT-PN-102 |
|----------------------------|-------------------------------|--------------------------------|--------------------|
| Screening CPK value | n=90 | n=42 | n=39 |
| Mean (SD) | 131 (66.87) | 117.1 (68.26) | 115.9 (55.38) |
| Median | 114.5 | 105.0 | 104.0 |
| Min, Max | (b) (4) | | |
| Final CPK value | n=90 | n=41 | n=40 |
| Mean (SD) | 128.4 (114.5) | 166.3 (211.26) | 110.6 (80.11) |
| Median | 99.0 | 92.0 | 88.0 |
| Min, Max | (b) (4) | | |
| Change during Study | n=90 | n=41 | n=39 |
| Mean | - 2.6 | 48.7 | - 4.28 |
| Median | - 12.0 | - 2.0 | - 12.0 |

(Source: NDA 22-470, Module 5.3.1)

7.4.3 Vital Signs

Healthy subjects ages 18 to 65 were included in the clinical pharmacology trials. The vital signs were defined within the inclusion criteria as follows: body weight \geq 50 kg (110 lb) and within \pm 20% of ideal weight based on height and body frame; oral body temperature between 35.0 and 37.5 °C; supine systolic blood pressure between 90 and 140 mmHg; supine diastolic blood pressure between 50 and 90 mmHg and pulse rate between 40 and 90 beats per minute. Vital signs were assessed upon screening, check-in to each study period and the end of the study.

There were scattered individual changes in vital sign assessments (primarily small changes in blood pressure) noted in a minority of subjects, none of which were considered clinically significant or were accompanied by symptoms. No clinically relevant trends in vital sign assessments were noted in any of the studies.

7.4.4 Electrocardiograms (ECGs)

ECG evaluation was only performed upon screening in all three clinical pharmacology trials in order to ensure the inclusion of healthy subjects. ECGs were not performed at the end of the study.

7.4.5 Special Safety Studies/Clinical Trials

NCH is pursuing ‘dosing without water’ labeling for ketoprofen 12.5 mg oral (b) (4) film. In order to ensure that the new formulation taken without water is safe to the oral mucosa, oral cavity examinations were performed every 2 hours during the 12 hours following study medication administration. Physical examination, including oral cavity examination, was performed in all three clinical pharmacology trials at screening and at the end of the study, as well as during check-in to each study period.

Oral findings were reported for two subjects, both in study EDKT-PN-101 Part I. One subject was withdrawn from the study due to oral rash. The first subject experienced a mild oral rash upon admission to Period II. The treatment prior was Orudis® KT 12.5 mg tablets (the reference treatment). The oral eruption was asymptomatic, not suspected to be related to study drug and the subject was not dosed, as per protocol eligibility criteria. Since the rash was persistent on admission to Period III, the subject was not eligible for participation in the study.

The second subject had a 2 mm papule noted on the right cheek during the oral cavity examination conducted 4 hours following administration of one ketoprofen 12.5 mg oral soluble film without water during Period I of study EDKT-PN-101 Part I. This finding was evident during each oral cavity examination until 12 hours post-dose. It was described as asymptomatic, considered drug related and not clinically significant by the investigator. The oral finding was documented as a mild AE of oral mucosal eruption. Upon admission during Period II the oral cavity examination findings were normal and the subject completed the study.

The possible causes for these findings could be allergic, local effect of the oral soluble film on the oral mucosa, or idiopathic. Taken together, there was no significant difference in the findings in the mouth associated with ketoprofen oral soluble film whether administered with or without

water. The findings reported were mild, resolved spontaneously and did not necessitate any specific treatment.

7.5 Other Safety Explorations

The pharmacokinetic studies performed for this NDA did not evaluate adverse events with regards to dose dependency, time dependency, demographics, or diseases. The subjects were healthy and received single doses of the study medications, so this information is not available from these studies. NSAIDs are known to have increased risk of gastrointestinal events when used for longer duration or in higher doses. NSAIDs may also cause renal impairment and are associated with an increased risk of congestive heart failure. Both the cardiac and renal risks are increased in older patients.

7.5.5 Drug-Drug Interactions

There has been no drug interaction studies performed for ketoprofen oral soluble film. Results from drug interaction studies with ketoprofen doses of 200 mg/day, as outlined in the Orudis package insert, are listed below:

- ACE inhibitors: NSAIDs may diminish the antihypertensive effect of these drugs. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.
- Antacids: Concomitant administration of magnesium hydroxide and aluminum hydroxide does not interfere with the rate or absorption of ketoprofen administered as Orudis tablets.
- Aspirin: Ketoprofen does not alter aspirin absorption; however, in a study of 12 normal subjects, concurrent administration of aspirin decreased ketoprofen protein binding and increased ketoprofen plasma clearance from 0.07 L/kg/h without aspirin to 0.22 L/kg/h with aspirin. The clinical significance of this is not known. As with other NSAIDs, concomitant administration of ketoprofen and aspirin is not generally recommended because of the potential of increased adverse effects.
- Diuretics: NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. Hydrochlorothiazide, given concomitantly with ketoprofen, produces a reduction in urinary potassium and chloride excretion compared to hydrochlorothiazide alone. Patients taking diuretics are at a greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.
- Digoxin: In a study of 12 patients with congestive heart failure where ketoprofen and digoxin were concomitantly administered, ketoprofen did not alter the serum levels of digoxin.
- Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. When NSAIDs and lithium are administered concurrently, patients should be observed carefully for signs of lithium toxicity.

- **Methotrexate:** Ketoprofen, like other NSAIDs, may cause changes in the elimination of methotrexate leading to elevated serum levels of the drug and increased toxicity. NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.
- **Probenecid:** Probenecid increases both free and bound ketoprofen by reducing the plasma clearance of ketoprofen to about one-third, as well as decreasing its protein binding. Therefore, the combination of ketoprofen and probenecid is not recommended.
- **Warfarin:** The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. In a short-term controlled study in 14 normal volunteers, ketoprofen did not significantly interfere with the effect of warfarin on prothrombin time. Bleeding from a number of sites may be a complication of warfarin treatment and GI bleeding a complication of ketoprofen treatment. Because prostaglandins play an important role in hemostasis and ketoprofen has an effect on platelet function as well, concurrent therapy with ketoprofen and warfarin requires close monitoring of patients on both drugs.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were no carcinogenicity studies performed as part of this NDA application. Previously conducted preclinical studies (for prescription strength ketoprofen) have not indicated a carcinogenic potential for ketoprofen.

7.6.2 Human Reproduction and Pregnancy Data

No assessment of use in pregnancy and lactation was performed as part of this NDA application. Preclinical teratology studies showed embryo toxicity in rabbits but not teratogenicity. There have been no adequate and well controlled studies in pregnant women. The current label for ketoprofen states “Ketoprofen should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.” Also, because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided.

7.6.3 Pediatrics and Assessment of Effects on Growth

Novartis Consumer Health initially requested a full waiver from the requirements for data on the safety and efficacy of the drug product in the pediatric subpopulations for the ketoprofen oral soluble film, 12.5mg. The reasons given for requesting a waiver were:

1. the drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and

2. the drug product is not likely to be used in a substantial number of pediatric patients. After discussion within the Division of Nonprescription Clinical Evaluation and consultation from the Pediatric and Maternal Health team, the request for a waiver was denied and NCH was advised that a Pediatric Plan would be required.

Novartis Consumer Health submitted a plan based on a pharmacokinetic approach. They propose an open-label PK study of a single dose of ketoprofen oral soluble film in healthy children and adolescents. The primary objective would be to determine the basic PK profile of ketoprofen oral soluble film in the following populations: children ages 6 months to 12 years and adolescents ages 12 to <16 years. The age groups would be dosed in a sequential fashion proceeding from the older to the younger groups (group D to group A) to confirm the hypothesis of dose-linearity. This approach will provide additional protection from over-dosing the children at the lowest age ranges.

- group A: 6 mo. to <2 years,
- group B: 2 to <6 years,
- group C: 6 to <12 years and
- group D: adolescents ages 12 to <16 years

The secondary objectives would be to assess overall safety and tolerability, as well as the acceptability of ketoprofen oral soluble film in children. The sponsor plans to evaluate safety from data pooled from published manuscripts involving pediatric population and by collecting safety information during the proposed PK study (AEs, laboratory evaluation, ECG, oral mucosa repeated examinations and tolerability questionnaires). NCH is requesting a waiver from the requirement to study children less than 6 months old.

The proposed single dose of ketoprofen is based on an age-weight dosing scheme (shown in Table 18). The rationale for dose selection assumes that the pharmacokinetics of ketoprofen are not age dependent.

Table 18: Proposed Age-Weight Dosing Regimen for Pediatric PK Study

| Age in Years | Weight Range | | Ketoprofen dose extrapolated from 12.5 mg adult dose film based on child's weight | Ketoprofen dose calculated from 0.5 mg/kg pediatric dose per literature | Ketoprofen dose proposed as a fraction of the 12.5 mg film size |
|----------------|--------------|----------|---|---|---|
| | Lb | Kg | | | |
| 6 mo to < 2 yr | 14 - 24 | 6.4 - 11 | 1.83 – 3.16 mg | 3.2 mg | 3.1 mg (1/4 film) |
| 2 to 6 | 24 - 27 | 11 – 21 | 3.16 – 4.61 mg | 5.5 – 8 mg | 4.6 mg (1/3 film) |
| 6 to < 12 | 48 – 95 | 21 – 43 | 6.06 – 9.3 mg | 10.5 – 16.0 mg | 12.5 mg (1 film) |
| 12 to < 16 | > 95 | > 43 | 12.5 mg | 21.5 mg | 12.5 mg (1 film) |
| ≥ 16 | NA | NA | 12.5 mg | 21.5 mg | 12.5 mg (1 film) |

(Source NDA 22-470, Module 1.9.4, Table 2-1)

NCH plans to recruit a sufficient number of children for each age group that the standard errors of clearance and of volume of distribution will be no more than 20% of the mean. To determine the appropriate sample size, two articles were identified in the literature, which provided PK results for N=13 and N=18 children, respectively, dosed with an IV ketoprofen formulation.^{1,2}

From these results, it was projected that three children per age group were likely to provide standard errors for clearance and volume of distribution that were no more than 20% of the mean. To account for subject drop-out, NCH plans at least four children per age group for a total of 16 children.

The primary endpoint will be the plasma concentration profile of total ketoprofen (*R*- and *S*-enantiomers) over 12 hours following study medication administration. PK parameters will be calculated based on the measured total ketoprofen concentration over time. If possible, PK parameters will be compared to NCH adult PK data for ketoprofen 12.5mg oral soluble film. The subjects' blood will be drawn at 13 time-points and analyzed for total ketoprofen levels (*R* and *S* enantiomers). The time points planned are: Pre-dose, 10, 20, 30 and 45 minutes and 1, 2, 3, 4, 6, 8, 10 and 12 h post-dose.

Safety monitoring is planned as follows:

- Oral cavity examination will be performed on enrollment, within an hour before dosing, immediately after dosing and thereafter at 2 hour intervals up to 12 hours following dosing, for signs and symptoms of irritation, ulceration/erosion, or bleeding of the mucosal membranes;
- Adverse reactions information will be collected. Hematology, blood chemistry, ECG, and vital signs will be monitored. A physical examination will be performed.

NCH also plans to obtain safety information from post-marketing databases, published literature and through the proposed clinical program.

NCH has 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 has provided medical literature they believe supports that conclusion.

The Pediatric Review Committee (PeRC) met July 8, 2009 to discuss the proposed Pediatric Research and Equity Act Waiver (PREA) and the study proposal submitted by Novartis Consumer Health. The waiver for studying children less than 6 months of age was granted. It was agreed that the causes of pain for which ketoprofen is indicated do not exist in children in this age range and that ketoprofen does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age range for the treatment of fever.

The plan for evaluation of children ages 6 months to < 16 years was felt to be inadequate. The PK study is an appropriate initial trial but a more complete safety evaluation is needed. The pharmacokinetic study will need to be conducted in symptomatic patients. In addition to the planned PK study, a safety trial on a sizable population with adequate representation of the age groups is needed. This trial needs to be conducted in a symptomatic population under "actual use" conditions.

The Pediatric Review Committee agreed that extrapolation from adult studies was appropriate for efficacy data for the fever indication but not for the pain indication. The sponsor will need to conduct adequate and well-controlled superiority trials demonstrating efficacy in children ages 6 months to 15 years for the pain indication. The trial will need to be conducted using a pain model suitable for an over-the-counter population.

The sponsor has been informed of these decisions and a revised pediatric plan will be reviewed upon receipt.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No withdrawal or rebound assessment was performed. There were no studies performed on drug abuse. No overdose assessment was performed.

7.7 Additional Submissions

The NSAIDs of the arylpropionic acid group have been reported to exhibit photosensitizing properties. As part of this NDA submission, NCH performed a review of available studies and case reports in the open literature on the photosensitization properties of ketoprofen. NCH also completed a search of the post-marketing databases (AERS and WHO Vigibase) for potential photosensitivity reactions associated with ketoprofen.

Drug-induced photosensitivity may be expressed as phototoxicity and/or photoallergy. Phototoxic reactions do not require prior sensitization and mimic exaggerated sunburn, whereas photoallergic reactions are immunologically mediated, require prior sensitization and clinically resemble allergic contact dermatitis. Drug induced phototoxic reactions are more common than drug-induced photoallergic reactions. They are postulated to arise from cellular toxicity, are not immunologically mediated, and generally do not exhibit cross-reactivity to other drugs.

In humans, ketoprofen is reported to be both phototoxic and photoallergenic. Prolonged photosensitivity from one up to 14 years after discontinuing ketoprofen application has been reported in some patients. In some cases this is due to unintended re-exposure to ketoprofen (contaminated clothing or physical contact with others using topical ketoprofen), but a significant factor may be cross-reactivity to related chemical excipients and agents such as benzophenone-3, a UV filter widely incorporated in commonly used skin cosmetics (skin moisturizers, aftershaves, shower and bath gels, etc).^{3,4,5,6}

Based on experimental studies, only dermal application appears to provide sufficiently high ketoprofen concentrations to induce or trigger photoallergy. A search of Medline from 1966 to the present, performed by the sponsor, using the terms “ketoprofen and photosensitization” identified 81 publications. About 1/3 of them are experimental studies on ketoprofen to determine its photosensitizing potential and the mechanism of action. Among those of relevance to photosensitization potential of ketoprofen in humans, only one was related to oral dosing. All other case reports were of patients exposed to topical ketoprofen.

A case was reported⁷ of photoallergic reaction after oral dosing with dexketoprofen, the S(+)-enantiomer of ketoprofen. Oral treatment for three days produced pruritic papulovesicular dermatitis in the body and arms; the patient did not recall sun exposure. Within 2 weeks of the rash resolving, the patient took one dose of oral dexketoprofen with moderate sun exposure on the beach, and similar symptoms appeared. The authors describe this as the first report of

photoallergy to oral ketoprofen, but since the patient had a history of acute dermatitis after applying topical ketoprofen to the back during a previous summer, it appears as if induction of the ketoprofen photoallergy actually occurred after topical administration; only the expression of the allergy was provoked by oral dosing.

The sponsor performed a search of the FDA Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) databases from 1969 through 30 June 2008 and identified 17 cases which reported photosensitivity reaction or photosensitivity allergic reaction with 63 associated AE terms. Of the 17 cases, examination of the individual case data indicated that 2 of the reports were probably duplicates. A total of 12 of the case reports were associated with oral administration of ketoprofen; six were from prescription doses, two were from OTC doses and in four cases the dose was not specified. Three of the case reports were associated with topical administration and no route of administration information was available for 2 cases. Seven cases with hospitalization as an outcome were categorized as serious, 7 were not serious, and 3 had no outcome data. Of the serious cases, 2 were associated with oral exposure to the drug (one was with prescription dose and dose for the second was not specified), 3 were associated with topical exposure, and 2 had no route of administration data. No clustering by gender, age, or concomitant medication was apparent in the data for the cases of photosensitivity. There were no deaths reported for the cases.

A search of the WHO Vigibase System (over 30 years through 16 November 2008) was performed by NCH on information involving oral ketoprofen. A total of 62 cases of patients with photosensitivity reactions were identified with 82 associated AE terms. Of these, 58 reports with 70 associated AE terms originated outside of the United States (exUS). There were four cases from the United States with 12 AE terms. Only 1 of the cases was categorized as serious (Caused/Prolonged hospitalization) and the most frequently reported outcome was 'recovered' (27 instances). The serious case was from outside the United States and details of the case are unknown. Five reports had 'not recovered' as an outcome and 26 reports had either 'unknown outcome' or 'no data.' There were no pediatric reports. No clustering by gender was apparent from the data.

In summary, NCH believes the review of the available studies and case reports in the open literature as well as the search of the post-marketing databases indicate that photoallergy is unlikely to be a major safety issue with the ketoprofen 12.5 mg oral soluble film. Based on experimental studies, only dermal application appears to provide sufficiently high ketoprofen concentrations to induce or trigger photoallergy. Case reports available in the open literature indicates that photosensitization reactions from ketoprofen are mainly associated with topical administrations. The search of marketing databases revealed a total of 74 cases (12 from SRS and AERS and 62 from WHO Vigibase) of potential photosensitivity reactions possibly associated with the oral administration of ketoprofen (doses, brands and indications varied). These reactions were classified as either photoallergic reactions, photosensitivity reactions or phototoxic reactions. A photosensitization response requires sufficiently high skin concentration of ketoprofen and sufficient UV irradiation for both induction and expression. There is no UV exposure in the mouth, and the skin concentrations after dosing with 12.5 mg oral soluble film are likely to be relatively low making photosensitization unlikely with this product.

8 Post Market Experience

Ketoprofen 12.5 mg orally-soluble film has not been approved for marketing in any country. Therefore, no information on post-marketing experience for this formulation is available.

In support of the application for approval of ketoprofen 12.5 mg orally-soluble film for over-the-counter (OTC) use, a review of the post-marketing experience for oral and topical ketoprofen was performed by the sponsor using the available post-marketing safety data from the Food and Drug Administration's Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) databases, data from the World Health Organization's (WHO) International Drug Monitoring Program and data from the Drug Abuse Warning Network (DAWN). The findings are summarized below.

FDA SRS and AERS Databases

The analysis of adverse events reported for ketoprofen to the FDA SRS and AERS databases was conducted from January, 1999 through 30 June 2008. To enable the databases to be merged, the COSTART AE terms in the SRS database were mapped to MedDRA terminology using the appropriate field in the dictionary file of the preferred term (PT) or lower level MedDRA term (Version 11) files. There were a total of 3740 cases involving 9814 adverse event (AE) terms. Of these reports, 36.0% (1345/3740) were not serious; 30.2% (1130/3740) were serious; 28.8% (1077/3740) had no outcome information; and 5.0% (188/3740) involved reports of a death. Reports classified as serious do not include the reports of death.

Overall, five SOCs accounted for 60.6% (5943/9814) of all the reported terms. These were: Gastrointestinal disorders (21.8%, 2143/9814), General disorders and administration site conditions (14.0%, 1372/9814), Skin and subcutaneous tissue disorders (10.1%, 988/9814), Investigations (7.8%, 762/9814) and Nervous system disorders (6.9%, 678/9814). Table 19 presents the adverse event reports by SOC and by seriousness. Among the deaths, five SOCs had notably higher than overall relative reporting rates. These were: Blood and lymphatic system disorders (8.0%, 92/1153 versus 4.2%, 408/9814), Cardiac disorders (7.4%, 85/1153 versus 2.5%, 242/9814), Hepatobiliary disorders (4.7%, 54/1153 versus 2.7%, 263/9814), Infections and infestations (7.5%, 86/1153 versus 2.8%, 273/9814) and Respiratory, thoracic and mediastinal disorders (7.2%, 83/1153 versus 4.1%, 402/9814).

Table 19: SRS and AERS Adverse Event Reports for Ketoprofen by SOC and Seriousness

| SOC | Not serious | Serious | Death | No outcome data | Overall total |
|-----------------------|-------------------|-------------------|-------------------|-------------------|---------------|
| Blood & Lymphatic | 30 (1.2) | 279 (6.0) | 92 (8.0) | 7 (0.5) | 408 (4.2) |
| Cardiac disorders | 36 (1.5) | 105 (2.3) | 85 (7.4) | 16 (1.0) | 242 (2.5) |
| Congenital/Genetic | 9 (0.4) | 39 (0.8) | 9 (0.8) | 1 (0.1) | 58 (0.6) |
| Ear | 28 (1.1) | 19 (0.4) | | 13 (0.8) | 60 (0.6) |
| Endocrine disorders | | 5 (0.1) | | | 5 (0.1) |
| Eye disorders | 73 (2.9) | 62 (1.3) | 8 (0.7) | 17 (1.1) | 160 (1.6) |
| Gastrointestinal | 720 (29.1) | 835 (18.0) | 125 (10.8) | 463 (29.8) | 2143 (21.8) |
| General & Admin Site | 356 (14.4) | 467 (10.1) | 84 (7.3) | 465 (29.9) | 1372 (14.0) |
| Hepatobiliary | 20 (0.8) | 188 (4.1) | 54 (4.7) | 1 (0.1) | 263 (2.7) |
| Immune system | 59 (2.4) | 58 (1.3) | 8 (0.7) | 14 (0.9) | 139 (1.4) |
| Infection/infestation | 30 (1.2) | 147 (3.2) | 86 (7.5) | 10 (0.6) | 273 (2.8) |
| Injury/Poisoning | 98 (4.0) | 124 (2.7) | 45 (3.9) | 38 (2.4) | 305 (3.1) |
| Investigations | 104 (4.2) | 494 (10.7) | 148 (12.8) | 16 (1.0) | 762 (7.8) |
| Metabolism | 21 (0.8) | 125 (2.7) | 31 (2.7) | 7 (0.5) | 184 (1.9) |
| Musculoskeletal | 35 (1.4) | 118 (2.5) | 22 (1.9) | 20 (1.3) | 195 (2.0) |
| Neoplasms | 4 (0.2) | 21 (0.5) | 10 (0.9) | | 35 (0.4) |
| Nervous system | 209 (8.4) | 268 (5.8) | 58 (5.0) | 143 (9.2) | 678 (6.9) |
| Pregnancy | 7 (0.3) | 14 (0.3) | 2 (0.2) | | 23 (0.2) |
| Psychiatric | 85 (3.4) | 117 (2.5) | 21 (1.8) | 65 (4.2) | 288 (2.9) |
| Renal | 59 (2.4) | 267 (5.8) | 76 (6.6) | 33 (2.1) | 435 (4.4) |
| Reproductive | 28 (1.1) | 17 (0.4) | 2 (0.2) | 6 (0.4) | 53 (0.5) |
| Respiratory | 82 (3.3) | 199 (4.3) | 83 (7.2) | 38 (2.4) | 402 (4.1) |
| Skin | 321 (13.0) | 466 (10.1) | 35 (3.0) | 166 (10.7) | 988 (10.1) |
| Social Circumstances | 3 (0.1) | 8 (0.2) | | 1 (0.1) | 12 (0.1) |
| Surgery | 6 (0.2) | 29 (0.6) | 5 (0.4) | | 40 (0.4) |
| Vascular disorders | 54 (2.2) | 159 (3.4) | 64 (5.6) | 14 (0.9) | 291 (3.0) |
| Total terms (%) | 2477 (100) | 4630 (100) | 1153 (100) | 1554 (100) | 9814 (100) |
| Total terms (row %) | 2477 (25.2) | 4630 (47.2) | 1153 (11.7) | 1554 (15.8) | 9814 (100) |
| Total cases (row %) | 1345 (36.0) | 1130 (30.2) | 188 (5.0) | 1077 (28.8) | 3740 (100) |

The percent basis is the total number of preferred terms in each seriousness category. Terms with >10 events and a relative reporting rate $\geq 20\%$ higher than the corresponding overall rate are highlighted in bold.
(Source: NDA 22-470, Module 5.3.6.1, Table 4-2, SRS/AERS Adverse Event reporting)

For serious reports, there were 1130 cases with 4630 associated AE terms and four SOCs accounted for 48.9% (2262/4630) of the reported terms. These were: Gastrointestinal disorders (18.0%, 835/4630), Investigations (10.7%, 494/4630), General disorders and administration site conditions (10.1%, 467/4630) and Skin and subcutaneous tissue disorders (10.1%, 466/4630). The individual adverse event terms for the serious reports were distributed across a wide range of events and the absolute reporting rates were, in general, low. The two most frequently reported terms were: Renal failure acute (2.1%, 98/4630) and Gastrointestinal haemorrhage (1.9%, 87/4630).

There were 188 reported deaths with 1153 associated AE terms. The AE terms were distributed across a broad range of SOCs. Overall, no single SOC accounted for more than 12.8% of all terms. The two SOCs with the highest reporting rates were: Injury, poisoning and procedural complications 12.8%, 148/1153) and Gastrointestinal disorders (10.8%, 125/1153). With respect

to individual AE terms among the reports of death, the most frequently reported term was renal failure acute which accounted for 2.0% (23/1153) of all terms.

Among serious reports and deaths, the majority of reports were in the 18-65 and > 65 age ranges both in absolute and relative terms. There were relatively few reports in the age groups \leq 11 years (1.6%, 60/3740) and 12-17 years (1.9%, 70/3740) and a substantial fraction of the cases had no age data (16.4%, 613/3740). Across the age groups, there were numerous variations in reporting rates without any consistent pattern. In the > 65 year age group, Blood and lymphatic system disorders had a notably higher than overall reporting rate (6.2%, 171/2740 versus 4.2%, 408/9814) as did Renal and urinary disorders (6.0%, 164/2740 versus 4.4%, 435/9814). With respect to the gender differences in the overall distribution of AEs, no apparent clustering by SOC or AE term was observed in the data.

There were 17 reports of patients with Photosensitivity reaction or Photosensitivity allergic reaction. These reports involved a total of 63 AE terms. Two of the cases were most likely duplicated, but since duplication could not be confirmed, for the purposes of this presentation they were retained in the dataset. There were no deaths reported for the cases. The gender distribution and mean age of cases was similar to the overall population with ketoprofen reports. No cases were reported in the pediatric age ranges. A total of 70.6% (12/17) of the cases were related to an oral exposure to ketoprofen and 17.6% (3/17) were related to a topical exposure.

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' had the highest frequency, five of the seven terms were related to gastrointestinal disturbances, and the other term was 'renal failure acute.'

World Health Organization Database

An analysis of the adverse events reported for ketoprofen in the WHO drug safety database from August, 1974 through 16 November 2008 revealed 6608 cases involving 10873 MedDRA AE terms. Of these reports, 5707 cases involving 9014 terms were reported from outside the United States. The 901 US cases with 1859 associated AE terms reported by the FDA to the WHO were also tabulated for completeness; however, cases of US origin are more completely presented in the review of the FDA's SRS and AERS databases.

Although the WHO Monitoring Centre has 77 participating countries, only a small number provide the vast majority of cases which is a significant limitation for this database. In addition, the database does not allow for the identification of primary or secondary AE terms for a given case. As a result, it is not possible to sort the listing of AE terms according to their relative importance.

For cases outside of the United States (exUS), 5 countries accounted for 72.6% (4141/5707) of the reports. These were: France 25.2% (1437/5707), the United Kingdom 23.3% (1329/5707), Australia 14.5% (829/5707), Italy 5.0% (285/5707), and the Netherlands 4.6% (261/5707). Among the exUS reports, 60.4% (3449/5707) were for females, 37.3% (2126/5707) were

for males, and 2.3% (132/5707) had no reported gender. For the cases of exUS origin, the mean age was 56.4 years (range: <0.1 to 98 years) and 91.1% (5200/5707) had a reported age. In this group, 57.1% (3261/5707) of the cases were in the 18-65 age ranges.

There were a total of 549 serious reports from outside of the United States with 1024 associated adverse event terms. Of the 549 reports 86.3% (474/549) were in the adult age ranges. Four System Organ Classes (SOC) accounted for 65.9% (675/1024) of the terms. They were: Gastrointestinal Disorders (33.5%, 343/1024), Skin and Subcutaneous Tissue Disorders (17.1%, 175/1024), Blood and Lymphatic System Disorders (8.0%, 82/1024) and Renal and Urinary Disorders (7.3%, 75/1024). The frequency of reports by SOC for US and exUS cases is presented in Table 20.

Table 20: WHO Adverse Event Term Frequencies for all US and exUS reports by SOC

| MedDRA SOC | ExUS n (%) | US n (%) | Overall Total n (%) |
|-------------------------------------|--------------------|-------------------|----------------------------|
| Blood & Lymphatic | 366 (4.1) | 78 (4.2) | 444 (4.1) |
| Cardiac | 88 (1.0) | 36 (1.9) | 124 (1.1) |
| Congenital, Familial, Genetic | 6 (0.1) | 2 (0.1) | 8 (0.1) |
| Ear & Labyrinth | 104 (1.2) | 26 (1.4) | 130 (1.2) |
| Gastrointestinal | 4012 (44.5) | 611 (32.9) | 4623 (42.5) |
| General Disorders | 569 (6.3) | 195 (10.5) | 764 (7.0) |
| Hepatobiliary disorders | 158 (1.8) | 52 (2.8) | 210 (1.9) |
| Infection & Infestations | 65 (0.7) | 25 (1.3) | 90 (0.8) |
| Injury, Poisoning and Procedures | 17 (0.2) | 5 (0.3) | 22 (0.2) |
| Investigation | 211 (2.3) | 78 (4.2) | 289 (2.7) |
| Metabolism & Nutrition | 67 (0.7) | 21 (1.1) | 87 (0.8) |
| Musculoskeletal & Tissue | 81 (0.9) | 20 (1.1) | 101 (0.9) |
| Neoplasms, benign malignant | 6 (0.1) | 5 (0.3) | 11 (0.1) |
| Pregnancy | 10 (0.1) | 0 | 10 (0.1) |
| Psychiatric | 181 (2.0) | 55 (3.0) | 236 (2.2) |
| Renal & Urinary | 287 (3.2) | 70 (3.8) | 357 (3.3) |
| Reproductive System & Breast | 27 (0.3) | 15 (0.8) | 42 (0.4) |
| Respiratory, Thoracic & Mediastinal | 248 (2.8) | 70 (3.8) | 318 (2.9) |
| Skin & Subcutaneous | 1687 (18.7) | 190 (10.2) | 1877 (17.3) |
| Social Circumstances | 1 (0.0) | 3 (0.2) | 4 (0.0) |
| Surgical and Medical Procedures | 0 | 3 (0.2) | 3 (0.0) |
| Vascular | 117 (1.3) | 60 (3.2) | 177 (1.6) |
| Total Terms n | 9014 | 1859 | 10873 |
| Total Cases n (%) | 5707 (86.4) | 901 (13.6) | 6608 (100) |

n = number

(Source: NDA 22-470, Module 5.3.6.3.2, Table 3-3, WHO Database Report)

For serious reports from outside the United States, 11 adverse event terms had reporting rates $\geq 2\%$. They were: Renal Failure, acute (5.6%, 57/1024), Melaena (4.3%, 44/1024), Angioedema (3.2%, 33/1024), Anaemia (3.0%, 31/1024), Urticaria (2.8%, 29/1024), Gastric Ulcer (2.7%, 28/1024), Haematemesis (2.5%, 26/1024), Gastrointestinal Haemorrhage (2.3%, 24/1024), Pruritus (2.3%, 24/1024), Rectal Haemorrhage (2.2%, 23/1024) and Gastric Ulcer Haemorrhage (2.1%, 21/1024). Together these 11 terms accounted for 33.2% (340/1024) of all reported terms. Of note in the geriatric age group (age > 65), five terms had notably higher than overall relative

reporting rates. They were: Renal Failure, acute (7.6%, 20/262 versus 5.6%, 57/1024), Anaemia (5.0%, 13/262 versus 3.0%, 31/1024), Gastrointestinal Haemorrhage (5.0%, 13/262 versus 2.3%, 24/1024), Rectal Haemorrhage (4.6%, 12/262 versus 2.2%, 23/1024) and Gastric Ulcer Haemorrhage (4.6%, 12/262 versus 2.1%, 21/1024).

Among exUS reports, there were 117 deaths with 210 associated adverse event terms. A majority (72.6%, 85/117) of the reports were in the geriatric age range (age > 65). There was one death in the pediatric age ranges. Two SOCs had relative reporting rates exceeding 25% of all reported terms for the cases of death. Together they accounted for 71.0% (149/210) of the total terms. They were: Gastrointestinal disorders (45.2%, 95/210) and General Disorders and Administration Site Conditions (25.7%, 54/210).

With regard to individual AE terms, among the deaths, Gastrointestinal Haemorrhage had 21 reports (10.0%, 21/210) and, of these, 19 reports were in the > 65 year age range. Similarly, Haematemesis had 14 reports overall (6.7%, 14/210) and 9 of these were in the > 65 year age range. The adverse event term frequencies for all exUS reports by SOC and seriousness are presented in Table 21.

There were too few reports of individual terms in the pediatric (≤ 17 years) to permit reliable inter-group comparisons. However, the most frequently reported term for the 11-17 age range was Renal Failure acute (38.9%, 7/18).

The patients with either Photosensitivity reaction or Photosensitivity allergic reaction reported as an AE term were broken out for a separate examination of the seriousness of their reactions, as well as their age and gender distribution. There were 58 exUS cases of photosensitivity with a total of 70 associated AE terms. Of the 70 terms, 60 were Photosensitivity reaction or Photosensitivity allergic reaction and of the remaining AE terms only dermatitis bullous (three instances) had more than one report. There was a single serious report with no additional AE terms. The majority (79.3%, 46/58) of the reports were in the 18-65 year age range. There were no pediatric reports. No clustering by gender was apparent from the data.

Table 21: WHO Adverse Event Term Frequencies for all exUS reports by SOC and Seriousness

| MedDRA SOC | Not Serious N (%) | Serious N (%) | Death N (%) | No Data N (%) | Overall Total N (%) |
|----------------------------------|----------------------|------------------|------------------|------------------|------------------------|
| Blood & Lymphatic | 271 (3.5) | 82 (8.0) | 13 (6.2) | | 366 (4.1) |
| Cardiac | 66 (0.9) | 15 (1.5) | 7 (3.3) | | 86 (1.0) |
| Congenital, Familial, Genetic | 2 (0.0) | 2 (0.2) | 2 (1.0) | | 6 (0.1) |
| Ear & Labyrinth | 95 (1.2) | 9 (0.9) | | | 104 (1.2) |
| Endocrine | 5 (0.1) | 1 (0.1) | | | 6 (0.1) |
| Eye | 111 (1.4) | 15 (1.5) | | | 126 (1.4) |
| Gastrointestinal | 3532 (45.8) | 343 (33.5) | 95 (45.2) | 42 (67.7) | 4012 (44.5) |
| General Disorders | 461 (6.0) | 53 (5.2) | 54 (25.7) | 1 (1.6) | 569 (6.3) |
| Hepatobiliary disorders | 132 (1.7) | 25 (2.4) | 1 (0.5) | | 158 (1.8) |
| Immune System | 67 (0.9) | 17 (1.7) | 2 (1.0) | 2 (3.2) | 88 (1.0) |
| Infection & Infestations | 45 (0.6) | 19 (1.9) | 1 (0.5) | | 65 (0.7) |
| Injury, Poisoning and Procedures | 9 (0.1) | 5 (0.5) | 1 (0.5) | 2 (3.2) | 17 (0.2) |
| Investigations | 168 (2.2) | 41 (4.0) | 2 (1.0) | | 211 (2.3) |
| Metabolism & Nutrition | 47 (0.6) | 18 (1.8) | 2 (1.0) | | 67 (0.7) |
| Musculoskeletal & Tissue | 66 (0.9) | 14 (1.4) | 1 (0.5) | | 81 (0.9) |
| Neoplasms, benign malignant | 2 (0.0) | 3 (0.3) | 1 (0.5) | | 6 (0.1) |
| Nervous System | 446 (5.8) | 35 (3.4) | 4 (1.9) | 1 (1.6) | 486 (5.4) |
| Pregnancy | 7 (0.1) | 2 (0.2) | 1 (0.5) | | 10 (0.1) |
| Psychiatric | 168 (2.2) | 12 (1.2) | 1 (0.5) | | 181 (2.0) |
| Renal & Urinary | 201 (2.6) | 75 (7.3) | 11 (5.2) | | 287 (3.2) |
| Repro | 27 (0.3) | | | | 27 (0.3) |
| Resp | 201 (2.6) | 42 (4.1) | 3 (1.4) | 2 (3.2) | 248 (2.8) |
| Skin & Subcutaneous | 1497 (19.4) | 175 (17.1) | 3 (1.4) | 12 (19.4) | 1687 (18.7) |
| Social Circumstances | | 1 (0.1) | | | 1 (0.0) |
| Vascular | 92 (1.2) | 20 (2.0) | 5 (2.4) | | 117 (1.3) |
| Total Terms | 7718 (100) | 1024 (100) | 210 (100) | 62 (100) | 9014 (100) |
| Total Cases | 5015 (87.9) | 549 (9.6) | 117 (2.1) | 26 (0.5) | 5705 (100) |

Percents are calculated based on the total number of terms for each seriousness group. Cells with more than 10 reports and relative reporting rates 20% or more higher than the corresponding overall relative reporting rates are highlighted in bold type. N=number
(Source: NDA 22-470, Module 5.3.6.2, Table 3-5, WHO Database Report)

No unexpected findings emerged from this analysis of the adverse event data for ketoprofen from the WHO drug safety database. A review of the data identified gastrointestinal disorders (ulcer and hemorrhage), allergic phenomena, and renal disorders (acute renal failure) as the adverse events of greatest frequency and clinical importance. This is consistent with the known information regarding ketoprofen.

DAWN

The data used for this report were made available through the online DAWN Live/ facility which accesses the New DAWN database. The data cover the period from January 2003 to 24 November 2008. New DAWN began in 2003 and collects information for all types of drug-related emergency department visits from a sample of the nation's emergency departments. The old DAWN collected information on visits to emergency departments related to drug abuse only.

The data available were confined to reports involving ketoprofen or other generically identified NSAIDs. The NSAIDs included in the search were ketoprofen, fenoprofen, flurbiprofen, ibuprofen, and naproxen. Ibuprofen and naproxen are widely available OTC NSAIDs in the United States, whereas, fenoprofen and flurbiprofen are available by prescription only. For purposes of this review, comparisons were made to ibuprofen and naproxen.

DAWN Live! uses a unique descriptive vocabulary for diagnoses. Diagnostic categories are Drug-related diagnoses, Diagnoses related to Body systems, Other conditions, and a Miscellaneous category. Diagnoses were coded only for the period from July 2003 through December 2004. No diagnostic information is available for the years 2005 through 2008.

Table 22 provides the case report data for adverse event reports associated with NSAIDs stratified by drug. Ketoprofen is only 0.16% of the total, making any comparisons with ibuprofen, naproxen, or the overall total reports problematic. There were 45,026 emergency department visits reported for the NSAIDs and ketoprofen accounted for 73 whereas ibuprofen accounted for 75.2% (33,882/45,026) of the reports and naproxen accounted for 24.5% (11,039/45,026) of the reports.

Where the numbers were large enough for reliable comparisons (ibuprofen and naproxen), the age distributions of the cases reported were generally similar between the drugs. The relative frequency of cases in age groups appeared to decline with increasing age. For the 12-17 year age range, the relative frequency of cases was approximately 3% (16.7%/6 years) of total cases per year of age, whereas in the 55-64 year age range the relative frequency declined to 0.5% (5.2%/10 years) of total cases per year of age. The only notable difference in distribution across the drugs was the relatively large percentage of reports in the five years and younger age range for ibuprofen (8.7%, 2934/33,882) compared to the other drugs. Naproxen had 1.6% (179/11,039) of reports in this age range. This is not unexpected as pediatric labeling is only found on ibuprofen.

With respect to the types and proportions of cases recorded for the drugs and overall, the proportions of case types were, in general, similar among the drugs. Naproxen did have a higher proportion of adverse reactions compared to ibuprofen (50.2%, 5539/11,039 versus 37.0%, 12,521/33,882). The three case types with the largest overall proportions of reports were: "Adverse reaction" (overall: 40.3%, 18,125/45,026 versus ketoprofen: 67.1%, 49/73), "Overmedication" (overall: 27.5%, 12,360/45,026 versus ketoprofen: 11.0%, 8/73) and "Suicide attempt" (overall: 21.2%, 9548/45,026 versus ketoprofen: 2.7%, 2/73).

From the available data, it appears that the demographic and case characteristics for ketoprofen do not differ importantly from those of the other NSAIDs taken as a group. For ketoprofen there were relatively fewer suicide attempts and relatively more reports of adverse reactions than observed in the overall population.

There were a total of 15 deaths reported; 13 for ibuprofen and two for naproxen. No deaths were reported for ketoprofen.

Table 22: DAWN Case Report Data for Adverse Events, Stratified by Drug

| Category | Ketoprofen | Ibuprofen | Naproxen | Overall Total |
|--------------------------------------|------------|--------------|--------------|---------------|
| Total case reports | 73 (0.16) | 33882 (75.2) | 11039 (24.5) | 45026 (100) |
| N (%) | | | | |
| Gender N (%) | | | | |
| Male | 23 (31.5) | 11573 (34.2) | 3541 (32.1) | 15147 (33.6) |
| Female | 50 (68.5) | 22286 (65.8) | 7494 (67.9) | 29852 (66.3) |
| Age Group N (%) | | | | |
| ≤5 years | 2 (2.7) | 2934 (8.7) | 179 (1.6) | 3116 (6.9) |
| 6 – 11 years | 0 | 812 (2.4) | 44 (0.4) | 856 (1.9) |
| 12 – 17 years | 3 (4.1) | 6109 (18.0) | 1405 (12.7) | 7518 (16.7) |
| 18 – 54 years | 52 (71.2) | 21516 (63.5) | 7442 (67.4) | 29035 (64.4) |
| 55 – 64 years | 5 (6.8) | 1327 (3.9) | 987 (8.9) | 2319 (5.2) |
| ≥65 years | 11 (15.1) | 1169 (3.5) | 975 (8.8) | 2160 (4.8) |
| Not documented | 0 | 15 (0.0) | 7 (0.1) | 22 (0.0) |
| Type of Case N (%) | | | | |
| Suicide attempt | 2 (2.7) | 7523 (22.2) | 2014 (18.2) | 9548 (21.2) |
| Seeking Detox | 2 (2.7) | 62 (0.2) | 17 (0.2) | 81 (0.2) |
| Adverse reaction | 49 (67.1) | 12521 (37.0) | 5539 (50.2) | 18125 (40.3) |
| Overmedication | 8 (11.0) | 9857 (29.1) | 2490 (22.6) | 12360 (27.5) |
| Malicious poisoning | 0 | 9 (0.0) | 2 (0.0) | 11 (0.0) |
| Accidental ingestion | 3 (4.1) | 1275 (3.8) | 209 (1.9) | 1488 (3.3) |
| Other | 9 (12.3) | 2635 (7.8) | 768 (7.0) | 3413 (7.6) |
| Route of Administration N (%) | | | | |
| Oral | 29 (39.7) | 16406 (48.4) | 5074 (46.0) | 21523 (47.8) |
| Other | 4 (5.5) | 86 (0.3) | 26 (0.2) | 116 (0.3) |
| Not documented | 40 (54.8) | 17390 (51.3) | 5939 (53.8) | 23387 (51.9) |

N=number; (Source: NDA 22-470, Module 5.3.6.3, Table 3-1, Dawn Live Report)

Body system-related diagnoses were reported in 16.4% (1725/10,527) of cases overall and by 38.1% (8/21) of the ketoprofen cases. The small number of reports for ketoprofen makes comparisons with ibuprofen and the overall total unreliable. For ketoprofen and overall, the body system with the highest reporting rate was gastrointestinal (14.3%, 3/21 versus 6.6%, 691/10,527, respectively). The four categories of high level terms with the highest overall frequencies of reporting were: Suicide (overall: 24.0%, 2527/10,527 versus ketoprofen: 4.8%, 1/21), Psychiatric conditions (overall: 23.7%, 2495/10,527 versus ketoprofen: 9.5%, 2/21), Allergies (overall: 10.5%, 1101/10,527 versus ketoprofen: 14.3%, 3/21) and Pain (overall: 7.2%, 759/10,527 versus ketoprofen: 14.3%, 3/21).

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.

120 Day Safety Update

The sponsor provided a 120-day safety update to the post-marketing safety review. This included a review from literature published on ketoprofen from 11 November 2008 to 23 March 2009. The search performed by the sponsor produced seven clinical articles. The indications for ketoprofen use in the references included joint/musculoskeletal pain, soft tissue inflammation, acute dental pain, dysmenorrhea, and postoperative conditions such as head and neck tumor surgery, uvulopalatopharyngoplasty, and pelvic pain after uterine artery embolization. This literature review identified known and mostly mild expected adverse events associated with ketoprofen. There was no evidence of treatment related serious adverse events such as severe renal, gastrointestinal, or cardiovascular events. This review did not identify any evidence to suggest new risks to the safety profile of oral ketoprofen.

Other Information

As part of the review process, a search was done in the FDA AERS database for reports of elevated CPK associated with ketoprofen use. A total of 10 reports were identified and 9 of these were reviewed. None of the cases showed a clear cause and effect relationship for elevated CPK and Ketoprofen. In addition, a PubMed search was done for similar reports (ketoprofen and elevated CPK) and no reports were found. An additional search in the AERS database for all reports related to ketoprofen showed no unexpected findings.

9 Appendices

9.2 Labeling Recommendations

The initial trade name proposed by Novartis Consumer Health for ketoprofen oral soluble film was (b) (4). Consultation was obtained from Division of Medication Error Prevention and Analysis (DMEPA) and the name Excella was found to be unsatisfactory. The results of the Proprietary Name Risk Assessment found that the proposed name, (b) (4), is vulnerable to name confusion that could lead to medication errors with the name Ocella, Savella, and Excedrin. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC), and the Division of Nonprescription Clinical Evaluation (DNCE) feel that the name, (b) (4) is promotional in nature and overstates the efficacy of this product.

Novartis submitted *Nexcede* as the second proposed proprietary name. This proposed name was evaluated from a safety and promotional perspective by DMEPA based on the product characteristics provided by the Applicant. In addition, input was obtained from pertinent disciplines involved with the review of this application. The evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of the review. DMEPA found the proposed proprietary name, Nexcede, conditionally acceptable for this product and Division of Nonprescription Clinical Evaluation concurs.

The proposed Drug Facts label states the following:

Active Ingredient (in each strip): Ketoprofen 12.5 mg (NSAID)*

Purpose: Pain reliever/fever reducer

*nonsteroidal anti-inflammatory drug

Uses

- temporarily relieves minor aches and pains due to:
- headache
- the common cold
- toothache
- backache
- minor pain of arthritis
- muscular aches
- menstrual cramps
- temporarily reduces fever

Warnings

Allergy alert: Ketoprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away

Stomach bleeding warning: This product contains a nonsteroidal anti-inflammatory drug (NSAID) which may cause stomach bleeding. The chance is higher if you

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing a NSAID (aspirin, ibuprofen, naproxen, or others)
- have 3 or more alcoholic drinks every day while using this product
- take more of for a longer time than directed

Do not use

- If you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- heart or kidney disease
- bleeding problems
- taken a diuretic
- high blood pressure
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- long term continuous use may increase the risk of heart attack or stroke

Stop use and ask a doctor if

- you feel faint, vomit blood, or have bloody or black stools. These are sign of stomach bleeding
- pain gets worse or last for more than 10 days
- fever gets worse or lasts for more than 3 days
- stomach pain or upset gets worse or lasts
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ketoprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- **do not take more than directed**
- **the smallest effective dose should be used**
- do not take longer than 10 days, unless directed by a doctor (see Warnings)
- If taken with food, this product may take longer to work
- adults and children 16 years and over: allow 1 strip to dissolve on tongue every 4 to 6 hours while symptoms persist

- If pain or fever dose not get better in 1 hour, you may take 1 more strip. With some experience, some people may find they need 2 strips for the first dose.
- do not take more than:
 - 2 strips in any 4 to 6 hour period
 - 6 strips in any 24 hour period
- children: do not give to children under age 16 unless directed by a doctor

The proposed labeling has been reviewed by the Interdisciplinary Science (IDS) reviewer as well as by this reviewer. Please refer to the IDS review for additional information. The following items will need to be addressed regarding the proposed label:

- Use of the term (b) (4). This is not an approved term and the approved drug category is ‘oral soluble film.’ The sponsor will need to change the labeling accordingly.
- Patients are directed ‘when using this product’ to ‘take it with food or milk if stomach upset occurs’ and then the directions state ‘if taken with food, this product may take longer to work.’ The Orudis KT labeling (for the original OTC ketoprofen) did not include the statement about the drug possibly taking longer to work if taken with food. It is presumed the sponsor based this change on the longer Tmax for ketoprofen soluble film taken with food; however, the longer Tmax was also seen for Orudis KT. The efficacy of the product is not known to be changed by food and the delayed action is a possibility, not an absolute. The statement ‘take it with food or milk if stomach upset occurs’ is acceptable class labeling for an NSAID, and is supported by a tentative final monograph. This will be discussed among the members of the review team during labeling meetings.

9.3 Advisory Committee Meeting

This does not apply.

¹ Kokki H, Karvinen M, and Jekunen A. Pharmacokinetics of a 24-hur intravenous Ketoprofen Infusion in Children, *Acta Anaesthesiol Scand* 2002; 46: 194-198.

² Kokki H, Karvinen M, and Suhonen P. Pharmacokinetics of Intravenous and rectal Ketoprofen in Young Children, *Clin Pharmacokinet* 2003; 42(4): 373-379.

³ Pigatto P, Bigardi A, Legori A, Valsecchi R, and Picardo M. Cross-reactions in patch testing and photopatch testing with ketoprofen, thiaprophenic acid, and cinnamic aldehyde. *Am J Contact Dermat*. 1996; 7(4): 220 - 223.

⁴ Mozzanica N, Pigatto P. Contact and photocontact allergy to ketorpofen; Clinical and experimental study. *Contact Dermatitis*. 1990; 23(5): 336 – 340.

⁵ Matthieu L, Meuleman L, Van Hecke E, Blondeel A, Dezfoulian B, et. al. Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis*. 1990. 23(5):336 – 340.

⁶ Devleeschouwer V, Roelandts R, Garmyn M, and Goossens A. Allergic and photoallergic contact dermatitis from ketoprofen: results of (photo) patch testing and follow-up of 42 patients. *Contact Dermatitis*. 2008 Mar; 58(3): 159 – 166.

⁷ Asensio T, Sanchis ME, Sanchez P, Vega JM, Garcia JC. Photocontact dermatitis because of oral dexketoprofen. *Contact Dermatitis*. 2008 Jan;58(1): 59-60.

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/

PRISCILLA R CALLAHAN-LYON
09/25/2009

LESLEYANNE A FURLONG
09/25/2009

Addendum to Clinical Review

This is a review of the Novartis Consumer Health response to FDA's request for additional information regarding elevated creatine phosphokinase (CPK) levels in some of the subjects in study EDKT-PN-101. On November 13, 2009, a telephone request was made requesting an explanation for the increase in CPK noted for five subjects in EDKT-PN-101 Part I and II. FDA also requested an explanation for the elevation of baseline CPK levels noted in many subjects in this study. On November 16, 2009 FDA asked Novartis to provide the number of subjects, by study, who were "screen failures" due to elevation of the CPK.

Novartis responded to these questions on November 18, 2009.

Study EDKT-PN-101 Part I had eight subjects with elevated CPK levels who failed screening. Seven of these failed due to the CPK elevation; one had CPK elevation but failed for other reasons. These results are shown in Table 1. Since the laboratory reference range in Part I was 30 – 223 U/L, CPK levels among the screen failures were up to 4.5 times the reference range.

(b) (4)

Study EDKT-PN-101 Part II had one additional subject with elevated CPK that failed screening. This 19 year old female failed screening due to low hemoglobin (10.6) but had

an elevated CPK of (b) (4). This was less than twice upper limit of normal (b) (4) U/L for the laboratory used in Part II), and was not in the screen failure range.

There were five subjects in study EDKT-PN-101 in whom the CPK levels increased during the study. Novartis reports that all of these subjects were in good health at screening, demonstrated by laboratory assessment, physical examination, and ECG. None of these subjects had a medical history suggestive of myopathic or metabolic disorders which could explain the CPK increase. The study drug was administered in three oral doses, separated by a wash-out period. After drug administration, there was no evidence of changes in physical examination or laboratory testing that would indicate a pathological condition. In addition, there were no adverse reports suggestive of a change in condition. No additional information was provided about the individual subjects.

All of the subjects in study EDKT-PN-101 were relatively young (<50 years of age); the two subjects with elevated CPK in EDKT-PN-101 Part II were < 25 years of age. Three of these subjects had normal CPK values at screening and elevated values at the final visit. The other two subjects had elevated CPK at screening (but less than twice normal) and then the level increased at the final visit. As noted in Table 2, the number of subjects with baseline CPK elevation for Part I the study was significant (3.8%). This was less in Part II of the study (< 1%) but the two studies used different “normal range” criteria. In Part I, the normal range was (b) (4) U/L for all subjects – regardless of race, age, or gender. For Part II, the normal range for males was (b) (4) U/L, and for females, (b) (4) U/L. The narrower range for Part II of the study may account for the higher percentage of enrolled subjects with CPK elevation. The mean screening CPK was lower in Part II than Part I; it did increase due to subject 1034 whose CPK rose from (b) (4) to (b) (4). The final median CPK actually decreased in both Part I and Part II.

Table 2: Screening, Baseline, and Final CPK Levels for Study EDKT-PN-101

| | EDKT-PN-101 Part I | EDKT-PN-101 Part II |
|--|--------------------|---------------------|
| Number Subjects Screened | 208 | 130 |
| Number Subjects Failed Screen with Elevated CPK (%)# | 8 (3.8) | 1 (0.77) |
| Number Subjects Enrolled | 90 | 42 |
| Number Enrolled Subjects with elevated baseline CPK (%)* | 13 (14.4) | 9 (21.4) |
| Number Enrolled Subjects with elevated final CPK (%) | 8 (8.8) | 13 ((30.9) |
| Screening Mean CPK Value U/L | 131 | 117.1 |
| Screening Median CPK Value U/L | 114.5 | 105.0 |
| Final Mean CPK Value U/L | 128.4 | 166.3 |
| Final Median CPK Value U/L | 99.0 | 92.0 |

* CPK elevated above normal range but < 2X upper limit of normal

The normal range for CPK was different in the two parts of the study. For Part I the range for males and females was 30 – 223 U/L. In Part II, the range for males was 38 – 174 U/L, for females 26 – 140 U/L.

The sponsor has submitted three references regarding elevation of CPK. These were reviewed and add little additional information. CPK levels can fluctuate during the day, based on physical activity. Elevation of CPK is due to muscle damage and with strenuous activity; significant elevations can occur (as much as 40 to 80 times the normal levels). The activity level of the subjects was not restricted or recorded during the study. Since there were no other physical or laboratory test findings that suggested another etiology, Novartis Consumer Health concludes that the CPK elevation in these subjects was related to physical exertion.

Reviewer Comments:

A literature search was conducted and three references were located that provide additional insight into the routine measurement of CPK and the expected variations depending on patient population.

- 1. In a study conducted by Neal, et. al¹ the CPK levels of 11,346 patients were evaluated by age, gender, and race. Results are seen in Table 3. In addition, the study noted that 144 (1.3%) of the patients had CPK elevation >3X upper limit of normal at screening. In this study the upper limit of normal was > (b) (4). The authors concluded that creatine kinase levels vary significantly by racial/ethnic origin, gender, and age. An age-dependent decrease in CPK levels is seen in men but not in women. For African American patients the CPK levels are generally higher. The authors recommend multiple CPK measurements over time to establish a particular patient's true baseline CPK value.*

Table 3: Ethnic, Gender, and Age Variations on CPK Values

| Race | Number of Subjects N=11,346 | Median CPK level Men | Median CPK level Men < age 50 | Median CPK level Women |
|-------------------------|--|---------------------------------|---|-----------------------------------|
| African American | 2760 | 135 | 154 | 73 |
| White | 3301 | 64 | 80 | 42 |
| Hispanic | 2939 | 69 | 79 | 48 |
| South Asian | 3455 | 74 | 79 | 50 |

- 2. A study conducted by Brewster, et. al² evaluated 1411 individuals ages 34 to 60 years after three days of rest for baseline CPK levels. They found 36% of the subjects had baseline CPK levels above the upper limit of normal and for Black subjects 49% were above the normal limit. The results of shown in Table 4. These authors conclude that due to wide variation within the population, the current reference limits for CPK tests may not be appropriate.*

¹ Neal RC, Ferdinand KC, Ycas J, and Miller E. Relationship of Ethnic Origin, Gender, and Age to Blood Creatine Kinase Levels, *The American Journal of Medicine*, Jan 2009;122(1): 73-78.

² Brewster LM, Mairuhu G, Sturk A, and Montfrans GA. Distribution of creatine kinase in the general population: Implications for statin therapy. *American Heart Journal*. 2007;154:655-661.

Table 4: Distribution of CPK Levels by Race and Gender

| Sex and Ethnicity | Number | Median CPK (U/L) | Above ULN* (N %) |
|-----------------------------|--------|------------------|------------------|
| All Subjects | 1411 | 111 | 508 (36) |
| Women | 831 | 95 | 304 (37) |
| Men | 580 | 143 | 204 (35) |
| White Subjects | 503 | 88 | 64 (13) |
| Women | 252 | 72 | 21 (8) |
| Men | 251 | 110 | 43 (17) |
| South Asian Subjects | 270 | 104 | 62 (23) |
| Women | 147 | 87 | 23 (16) |
| Men | 123 | 143 | 39 (32) |
| Black Subjects | 570 | 149 | 278 (49) |
| Women | 387 | 124 | 164 (42) |
| Men | 183 | 213 | 114 (62) |

3. Clarkson et. al³. evaluated CPK levels in 203 volunteers who performed repetitive exercise. The study was conducted to evaluate the association of elevated CPK levels and renal function. The results are shown in Table 5. Four days after the exercise, 111 of the 203 participants had CPK levels >2000 U/L. In addition, there were no significant changes in the tests of renal function.

Table 5: Baseline and After-Exercise CPK levels and Renal Function Tests

| Mean Value | CPK (U/L) | Potassium (mmol/L) | BUN (mg/dL) | Creatinine (mg/dL) |
|---------------|-----------|--------------------|-------------|--------------------|
| Baseline | 118 | 4.4 | 14 | 0.9 |
| 4 days after | 7713 | 4.6 | 13 | 0.9 |
| 7 days after | 2603 | 4.6 | 13 | 0.9 |
| 10 days after | 486 | 4.6 | 13 | 0.9 |

After review of the data submitted by the sponsor and the reference articles and other published literature regarding CPK levels, I have the following conclusions:

- CPK levels are extremely variable and are influenced by age, gender, race, recent activity level, and medical conditions. The isolated measurement of CPK levels, without consideration of the situation, is not useful.
- There is not a clear explanation for the elevation in CPK levels that occurred in the subjects in study EDKT-PN-101. It is likely the elevations were related to any combination of the factors listed above. While the lack of reported adverse events for the subjects who had elevated CPK levels is reassuring, the sponsor did not collect adequate follow-up information on the subjects who had increasing CPK levels over the course of the study. We do not know if the elevated CPK levels resolved or if the subjects remained asymptomatic. While physical exertion seems the most likely cause

³ Clarkson PM, Kearns AK, Rouzier P, Rubin R, and Thompson PD. Serum Creatine Kinase Levels and Renal Function Measures in Exertional Muscle Damage. *Medicine and Science in Sports and Exercise*. 2006;38: 623-627.

of the increased CPK levels that were observed in the subjects of interest, the lack of history and follow-up has left the issue incompletely resolved.

- *There is no obvious association between ketoprofen oral film and CPK elevation, but our information is limited. In the 25 years that oral ketoprofen has been used (prescription and OTC), there has not been any association with CPK elevation.*
- *I believe it is unlikely that ketoprofen oral film is the etiology of the CPK elevations observed in study EDKT-PN-101.*

Due to the limited information available from the sponsor's data, I recommend the following:

- *The NDA for ketoprofen oral film should be approved because, overall, the data support that it is safe and effective. An association between increased CPK levels and the use of ketoprofen oral film is unlikely, and no adverse events were reported in association with the elevated CPK levels.*
- *To address the residual uncertainty produced by inadequate history and follow-up, the sponsor should conduct a randomized, placebo-controlled, post-marketing study to evaluate CPK levels in subjects using the ketoprofen oral film for several days. The study should include baseline and follow-up CPK levels and be conducted in a healthy population. The study should follow subjects who develop CPK elevations to resolution; adverse event data should be collected during the follow-up period. The subjects should be restricted from strenuous exercise.*

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/

PRISCILLA R CALLAHAN-LYON
11/24/2009

LESLEYANNE A FURLONG
11/24/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

Date: April 28, 2009

From: Felicia Collins, MD, MPH, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

Through: Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

To: Andrea Leonard-Segal, MD, Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products, Office of New Drugs

Re: Requested PREA waiver for ketoprofen

Background

Sponsor: Novartis Consumer Health, Inc.

Product: (b) (4) (ketoprofen)

Dosage form: (b) (4) (12.5 mg/strip)

Route of administration: Oral

Indications (proposed): (OTC) Pain reliever in adults and children \geq 16 years old
(OTC) Fever reducer in adults and children \geq 16 years old

Application: NDA 22-470 (IND 74,282)

Division's Consult Comments

The Sponsor has filed an NDA that proposes a new formulation for ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID) approved for over-the-counter (OTC) use as a pain reliever and fever reducer in 1995. The previously approved product is a tablet with labeling that states "do not give to children under age 16 unless directed by a doctor." However, the new formulation is a colored (blue or red), flavored (peppermint or cinnamon), (b) (4) that dissolves on the tongue. The Sponsor has requested a waiver of pediatric studies, but the Division of Nonprescription Clinical Evaluation (Division) questions the Sponsor's assertion that the new product is unlikely to be used in a substantial number of pediatric patients.

The PDUFA goal date is November 26, 2009. If a pediatric plan is necessary, the Division would like to communicate general guidelines to the Sponsor so that the Sponsor can submit a plan for FDA review and Pediatric Review Committee (PeRC) consideration on July 8, 2009.

Materials Reviewed/Consulted

- Sponsor's ketoprofen submissions (NDA 22-470): January 23, 2009 and January 26, 2009
- Division's Pre-IND Meeting minutes for ketoprofen, March 5, 2007
- PMHS consultation regarding waiving PREA studies for naproxen sodium 220 mg capsules (NDA 21-920), January 25, 2007
- Ketoprofen and naproxen drug labelings on Drugs@FDA and Daily Med websites
- Ketoprofen: Drug Information Provided by Lexi-Corp, www.merck.com/mmpe/print/lexicomp/ketoprofen.html
- Ibuprofen: Drug Information Provided by Lexi-Corp, www.merck.com/mmpe/print/lexicomp/ibuprofen.html
- Pub Med

Product Description

According to an industry website, ketoprofen is a NSAID that reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes to decrease formation of prostaglandin precursors. The website notes that ketoprofen has antipyretic, analgesic, and anti-inflammatory properties and is labeled for acute and long-term treatment of rheumatoid arthritis and osteoarthritis, primary dysmenorrhea, and mild-to-moderate pain. Dental uses include the management of pain and swelling (www.merck.com/mmpe/print/lexicomp/ketoprofen.html).

Clinical Comments

A. Regulatory History

Ketoprofen Products Marketed in the US and Internationally

The Drugs@FDA website lists four brand name ketoprofen products that have been approved under the NDA process in the US. Per the website, on January 9, 1986, Orudis (ketoprofen) oral capsules (NDA 18-754) obtained marketing approval. According to an August 5, 1997 letter on the website, Orudis and Oruvail (ketoprofen) extended release capsules' indications included osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea. On October 6, 1995, Actron (ketoprofen) 12.5 mg oral tablets (NDA 20-499) and Orudis KT (ketoprofen) 12.5 mg oral tablets (NDA 20-429) obtained OTC marketing approval. According to the approval letter posted on the website, Actron was approved for OTC pain reliever and fever reducer indications. Currently, all four brand name ketoprofen products are no longer marketed in the US. Drugs@FDA does note that Oruvail and Orudis KT were not discontinued or withdrawn for safety or efficacy reasons.

The Drugs@FDA website also lists ten generic ketoprofen products that have been approved under the ANDA process in the US. Currently marketed ketoprofen products include five generic immediate release capsules or tablets with 12.5 mg, 25 mg, or 75 mg strengths and three extended release capsules with 100 mg, 150 mg, and 200 mg strengths. According to the Daily Med website, ketoprofen capsules' [prescription] indications include the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis, the management of pain, and the treatment of primary dysmenorrhea in adults ≥ 18 years old. According to the Sponsor's NDA submission, the currently approved OTC ketoprofen indications include temporarily relieves minor aches and pains due to

headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and the minor pain of arthritis; and temporarily reduces fever.

Reviewer Comment: Per the Drugs@FDA website, PMHS notes there have been no US-approved ketoprofen products with formulations appropriate for children who are unable to swallow tablets or capsules (i.e., typically children < 6 years old).

According to an industry website, ketoprofen is marketed under fifty-seven different brand names in numerous countries internationally (www.merck.com/mmpe/print/lexicomp/ketoprofen.html). Of note, ketoprofen 1 mg/ml syrup from the French pharmaceutical company Rhône-Poulenc Rorer has been studied in European pediatric trials (Kokki and Liboux, *et al.*, 2000).

Reviewer Comment: PMHS is unclear whether ketoprofen 1 mg/kg syrup has been and/or is currently approved for marketing in Europe.

Sponsor's Ketoprofen Product

On February 6, 2007, the Division held a Pre-IND Meeting with the Sponsor to provide guidance on the development plan to support approval of OTC ketoprofen oral (b) (4) for adults and children ≥ 16 years old for pain reliever and fever reducer indications. There was no discussion of pediatric studies in the meeting minutes. See Section C below for the discussion of ketoprofen's association with photosensitivity reactions.

On January 23, 2009, the Sponsor submitted an original NDA for OTC marketing of ketoprofen 12.5 mg oral (b) (4) for pain reliever and fever reducer indications. The Sponsor's NDA included two pharmacokinetic studies (bioequivalence and bioavailability studies). The Sponsor's 505(b)(2) application referenced discontinued Orudis KT for efficacy and discontinued Orudis for preclinical and clinical safety, without a right of reference from the application holders.

In its NDA submission, the Sponsor requested a full waiver from conducting an assessment of the safety and efficacy of ketoprofen in the pediatric population according to the Pediatric Research Equity Act (PREA). The Sponsor asserted that the product 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.

Reviewer Comment: PMHS agrees with the Sponsor's request for a full waiver of pediatric studies required under PREA for the fever reducer indication but disagrees with the full waiver request for the pain reliever indication. See Section E below for the related discussion.

PREA Requirements for Naproxen Sodium

On June 13, 2006, the Sponsor for naproxen sodium 220 mg capsules (NDA 21-920), another NSAID product, asserted that the FDA should grant a partial waiver of pediatric studies required under PREA for the treatment of fever and the treatment of minor aches and pains in children < 12 years old because naproxen sodium does not offer a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used by a substantial number of pediatric patients. The Sponsor's related submission included four published PK studies of naproxen suspension and/or tablets in children 5 to 15 years old and twenty-two published studies evaluating the efficacy and/or

safety of naproxen suspension and tablets in children 5 months to 16 years old with fever, arthritis, rheumatoid fever, and various categories of pain.

Reviewer Comment: With regard to pediatric naproxen data, PMHS also references the drug labeling for Naprosyn[®] (naproxen suspension) which has a pediatric indication for juvenile arthritis and notes that related pediatric naproxen dosing is based on well-controlled studies in pediatric patients ≥ 2 years old.

In a January 25, 2007 memorandum to the Division, PMHS recommended waiving PREA studies for naproxen sodium 220 mg capsules' OTC pain reliever indication because naproxen sodium did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and was not likely to be used by a substantial number of pediatric patients. PMHS' memorandum included summaries of relevant pediatric naproxen PK, safety and efficacy studies from the literature which had been submitted by the Sponsor.

Reviewer Comment: PMHS acknowledges that our rationale for not recommending naproxen sodium pediatric studies was suboptimal. The more accurate rationale is that pediatric studies required under PREA for naproxen sodium's OTC pain reliever indication already had been completed, as adequate PK and safety data (and supportive efficacy data) were available via the pediatric literature and the Naprosyn[®] NDA and extrapolation of efficacy from adult trials to pediatric patients was scientifically justifiable.

In the same January 25, 2007 memorandum to the Division, PMHS also recommended waiving PREA studies for naproxen sodium 220 mg capsules' OTC fever reducer indication. In the memorandum, PMHS asserted that there is no scientific justification for fever reduction for the vast majority of children (see Section B below for this discussion). PMHS also noted the availability and consumer acceptance of other OTC fever reducer products with pediatric indications (i.e., acetaminophen and ibuprofen). Therefore, PMHS recommended waiving PREA studies for naproxen sodium's OTC fever reducer indication because PMHS believed that naproxen sodium did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and was not likely to be used by a substantial number of pediatric patients.

On May, 30, 2007, the Division released the naproxen sodium Sponsor from the PREA requirement to study the treatment of fever and the treatment of minor aches and pain due to the common cold, flu, sore throat, headaches, and toothaches in pediatric patients 6 months to 11 years old.

B. Sponsor's Product/Indication

Sponsor's Proposed Indication

The Sponsor has requested approval to market ketoprofen for the following indications in adults and children ≥ 16 years old.

- (1) temporarily relieves minor aches and pains due to the common cold, toothache, backache, menstrual cramps, headache, muscular aches and the minor pain of arthritis
- (2) temporarily reduces fever

Appropriateness of a Pediatric OTC Pain Reliever Indication for Ketoprofen

Multiple analgesic products have been studied in and/or approved for the pediatric population in the US and internationally. Acetaminophen and the NSAID ibuprofen are the primary medications used in the US for the treatment of minor aches and pains in children (Perrott *et al.*, 2004; Dlugosz *et al.*, 2006; Bilenko *et al.*, 2006). The mechanism for their analgesic (and antipyretic) effect probably involves the inhibition of prostaglandin synthesis (Dlugosz *et al.*, 2006). Per an industry website, ibuprofen is approved for OTC use in the US in children ≥ 6 months old with pain or fever (www.merck.com/mmpe/print/lexicomp/ibuprofen.html). The NSAID naproxen has a pediatric indication in the US for the relief of the signs and symptoms of juvenile arthritis in pediatric patients ≥ 2 years old. In addition, European authors have reported the use of multiple ketoprofen formulations (i.e., intravenous, rectal suppositories, and oral tablets and syrup) to treat post-operative pain in pediatric patients (Kokki and Nikanne *et al.*, 2000; Kokki and Liboux *et al.*, 2000; Kokki *et al.*, 2002; Kokki and Karvinen *et al.*, 2002; Salonen *et al.*, 2002; Kokki *et al.*, 2003; Kokki and Karvinen *et al.*, 2003; Messeri *et al.*, 2003).

Reviewer Comment: Given literature reports of ketoprofen's effectiveness for post-operative pain in pediatric patient and pediatric pain relief indications for other NSAIDs (i.e., ibuprofen and naproxen), the Sponsor's proposed OTC indication for minor aches and pains appears appropriate for pediatric patients as well.

Appropriateness of a Pediatric OTC Fever Reducer Indication for Ketoprofen

Acetaminophen and ibuprofen again are the primary medications used for the treatment of fever in children in the US (Perrott *et al.*, 2004; Goldman *et al.*, 2004; Taylor, 2006; Hay *et al.*, 2006; Bilenko *et al.*, 2006). However, although pediatric formulations and recommended dosing exist for these antipyretic drugs, whether and when fever should be treated is the subject of considerable debate. Parents' anxiety regarding a febrile child can be a strong driving force for reducing fever with an antipyretic (Robertson, 2002; Kayman, 2003; Goldman *et al.*, 2004; Pearce and Curtis, 2005; Dlugosz *et al.*, 2006; Walsh and Edwards, 2006; Hay *et al.*, 2006). However, multiple authors report that fever is not harmful unless a child has a chronic disease, such as asthma, sickle cell disease, or cystic fibrosis (Robertson, 2002; Kayman 2003; Dlugosz *et al.*, 2006; Bilenko *et al.*, 2006). In fact, experimental work suggests several possible benefits to a high temperature, including enhanced helper T cell proliferation and killing, enhanced interferon production and function, and enhanced death of some viruses (e.g., rhinovirus and polio virus) and bacteria (e.g., pneumococcus and gonococcus). A meta analysis of paracetamol [acetaminophen] in the prevention of febrile convulsions concluded that there is no evidence that antipyretics reduce the risk of subsequent febrile convulsions in at risk children (Pearce and Curtis, 2005). In addition, the American Academy of Pediatrics has made the following statement regarding the treatment of fevers.

Fevers under 101° F generally do not need to be treated Even higher temperatures are not themselves dangerous or significant unless your child has a history of convulsions or a chronic disease. It is more important to watch how your child is behaving. If he is eating and sleeping well and has periods of playfulness, he probably doesn't need any treatment (Shelov and Hannemann, 2002).

“So science probably comes down on the side of not treating fevers; we should not try to lower the fever just because it is there” (Pearce and Curtis, 2005).

Reviewer Comment: Given the presumed mechanism of action of NSAIDs and ibuprofen's proven efficacy for fever reduction in children, the belief that ketoprofen likewise would reduce fever in

children is reasonable. However, see Section E below for PMHS' rationale for not recommending pediatric ketoprofen studies for an OTC fever reducer indication under PREA.

C. Demonstration of Adequate Safety Information to Proceed with Pediatric Trials Safety Labeling for Ketoprofen Oral Capsules

Per the Daily Med website, ketoprofen capsules have significant safety labeling, much of which is class labeling for NSAIDs.

Boxed Warnings

- NSAIDs may cause increased risk of serious cardiovascular thrombotic events such as myocardial infarction and stroke.
- Ketoprofen immediate- and extended-release capsules are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft.
- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines.

Contraindications

- Ketoprofen immediate- and extended-release capsules should not be given to patients who have experienced asthma, urticaria, or allergic type reactions after taking aspirin or other NSAIDs.

Other Warnings

- NSAIDs, including ketoprofen immediate- and extended-release capsules, can lead to the onset of new hypertension or worsening of preexisting hypertension.
- Fluid retention has been observed in some patients taking NSAIDs. Peripheral edema has been observed in approximately 2% of patients taking ketoprofen.
- Long-term NSAID administration has resulted in renal papillary necrosis and other renal injury.
- As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to ketoprofen. Ketoprofen immediate- and extended-release capsules should not be given to patients with the aspirin triad.
- NSAIDs, including ketoprofen immediate- and extended-release capsules, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Photosensitivity Associated with Ketoprofen Use

During the February 6, 2007 Pre-IND Meeting with the Sponsor, the FDA noted that when compared to other NSAIDs, ketoprofen was more commonly associated with photosensitivity reactions.

Although these reactions usually are associated with topical ketoprofen, phototoxicity and photoallergenicity have been reported with oral ketoprofen. Thus, FDA stated that the Sponsor should provide any available information (i.e., literature, original NDA information, postmarketing safety, or existing animal studies) on photosensitivity associated with topical and oral ketoprofen and other NSAIDs, especially OTC analgesics (e.g., ibuprofen and naproxen).

The Sponsor's NDA submission includes a discussion of the photosensitization potential of ketoprofen and concludes that photosensitization from oral ketoprofen at therapeutic levels is unlikely following sun exposure at non- or minimal-erythemal doses. The Sponsor asserts that ketoprofen

phototoxicity has not been confirmed in standardized (guinea pig) studies, but ketoprofen is clearly photoallergenic and shows photocrossreactivities to a variety of related structures. In most studies, photosensitization was observed following topical administration of 10% ketoprofen. The Sponsor reports that the results from dermal administration indicate that levels of ketoprofen needed to induce photosensitization can be reached following oral administration only at doses that are accompanied by systemic toxicity. Furthermore, the Sponsor asserts that doses of ultraviolet irradiation used in animal studies would lead to significant dermal toxicity in humans.

Literature Reports of Adverse Events Associated with Ketoprofen Use in Pediatric Trials

Three articles in the literature report observed adverse events during European pediatric oral ketoprofen trials. For each study, the authors conclude that oral ketoprofen is a safe analgesic in the pediatric population.

- In a pharmacokinetic study of a single 0.5 mg/kg ketoprofen syrup dose prior to day surgery in twenty children, 6 months to 7 years old, five adverse events were observed in four children (1 single episode of bradycardia and hypotension during spinal anesthesia, 2 vomiting in the recovery room, and 1 scrotal hematoma). There were no serious adverse events leading to discontinuation of treatment (Kokki and Liboux, *et al.*, 2000).
- In a study of ketoprofen tablets, 5 mg/kg/day divided into two or three doses, for the treatment of post-adenoidectomy pain in 611 pediatric patients, 1 to 9 years old, 329 patients had one or more adverse events (190 somnolence, 105 fever, 46 each for nausea/vomiting and pain or redness at the infusion site, 43 vertigo, 39 headache, 34 epigastric or other gastric distress, 33 constipation, 29 excessive sweating, 25 diarrhea, 11 minor bleeding at the adenoid area, 5 epistaxis, 6 difficulty passing urine, 17 other (rash, visual disturbance, flatulence, neck pain, cough, loss of appetite, or anxiety). Twelve children needed intervention for the adverse event (6 more caring/consolation from their parents and 6 parents contacted the physician for further advice) (Kokki and Nikanne, *et al.*, 2000).
- In a safety and efficacy study of ketoprofen capsules, 3 to 5 mg/kg/day, for the treatment of post-tonsillectomy pain in 102 pediatric patients, 3 to 16 years old, forty-eight patients had one or more adverse events (33 minor bleeding, 8 significant bleeding in the tonsillar bed, 5 excessive sedation, 2 each for vertigo and gastric distress, and 1 each for vomiting, nausea, constipation, abdominal rumbling noises, dry mouth, and disturbed sleep) (Salonen, 2002).

Reviewer Comment: PMHS notes that much of the safety labeling for ketoprofen oral capsules is class labeling applicable to other NSAID products with pediatric indications (i.e., ibuprofen and naproxen). In addition, PMHS did not identify any safety issues from the European pediatric ketoprofen studies that should preclude additional pediatric trials. Thus, PMHS believes that pediatric ketoprofen studies could safely be conducted in the US, provided there are no safety issues identified in the NDA for adult marketing approval or in any future pediatric study protocol proposed by the Sponsor.

D. Pediatric Ketoprofen Dosing

Adult Ketoprofen Dosing

In its NDA submission, the Sponsor has noted that its proposed 12.5 mg oral (b) (4) is designed to be taken whole as there is no reproducible method to split or otherwise divide the dosage form to deliver a consistent reduced dose of ketoprofen. Thus, the Sponsor's recommended OTC ketoprofen dosing regimen for minor aches and pains or fever in adults and children ≥ 16 years old is 12.5 mg (1 strip) every 4 to 6 hours with an initial dose of 12.5 mg or 25 mg (2 strips) and a maximum

daily dose of 75 mg (6 strips). In comparison, according to the ketoprofen drug labeling on the Daily Med website, the usual recommended ketoprofen immediate-release oral capsule dose for adults with mild to moderate pain or dysmenorrhea is 25 mg to 50 mg every 6 to 8 hours.

Pediatric Ketoprofen Dosing

The Sponsor has not proposed a pediatric dosing regimen for its ketoprofen product. However, the literature includes reports of European pediatric ketoprofen studies utilizing the following formulations and doses in pre-operative or post-operative pediatric patients.

- 25 mg tablets with a dose of 5 mg/kg/day divided into two or three doses in 1 to 9 year olds
- 25 mg, 50 mg, or 100 mg tablets with a dose of 3 to 5 mg/kg/day in 3 to 16 year olds
- 1 mg/ml syrup with a dose of 0.5 mg/kg in 6 month to 7 year olds

Reviewer Comment: Comparing the ketoprofen strengths studied in pediatric patients in Europe to the Sponsor's formulation, the Sponsor's 12.5 mg strength appears most problematic for the youngest children (e.g., < 1 year old).

E. Pediatric Research Equity Act

PREA Requirements

PREA (21 USC 355c) requires sponsors to submit pediatric assessments when they submit an application or supplemental application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. Per 21 USC 355c(a)(2)(A),

The assessment shall contain data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate —

- i) to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations; and
- ii) to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective.

The CDER (and CBER) Pediatric Page, which is completed by the review divisions, outlines the various options a sponsor has for addressing PREA requirements for all or selected pediatric age groups at the time of original NDA or efficacy supplement submission.

- request a full waiver or partial waiver of pediatric studies
- request a deferral of pediatric studies (and submit a description of planned or ongoing pediatric studies)
- provide data establishing that adequate pediatric studies have been completed
- establish that the product already has appropriate pediatric labeling
- present a scientifically justifiable rationale for the extrapolation of efficacy to pediatric patients from adult data if the course of the disease/condition and the effects of the product are sufficiently similar between adults and the pediatric population

Under PREA of 2007, a full waiver of pediatric studies can be issued if the following criteria have been met.

- Necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed)
- There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group

- The drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group and is not likely to be used by a substantial number of pediatric patients in that age group or
- The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed

Of note, if a pediatric population is excluded from drug studies for lack of efficacy or safety reasons, this information must be included in the drug labeling.

Sponsor's Request for a Full Waiver of PREA Requirements

In its NDA submission, the Sponsor has requested a full waiver of pediatric studies for its ketoprofen product for the pain reliever and fever reducer indications in children < 16 years old. The Sponsor has asserted that its ketoprofen product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients (e.g., acetaminophen, ibuprofen, and naproxen sodium) and is not likely to be used in a substantial number of pediatric patients.

Reviewers Comment:

(b) (4) *PMHS disagrees with the Sponsor's request for a full waiver of pediatric studies required under PREA. Given ibuprofen's labeling for OTC pain relief in children ≥ 6 months old, PMHS believes that a partial waiver of pediatric ketoprofen studies in children < 6 months old would be reasonable. However, PMHS believes that the Sponsor should conduct a pediatric ketoprofen assessment for children ≥ 6 months old for the OTC pain reliever indication. Thus, at the time of NDA submission, the Sponsor should address the PREA requirement in pediatric patients 6 months to < 17 years old by requesting a deferral of pediatric studies (and submitting a description of planned or ongoing pediatric studies), providing data establishing that adequate pediatric studies have been completed, establishing that the product already has appropriate pediatric labeling, and/or presenting a scientifically justifiable rationale for the extrapolation of efficacy to pediatric patients from adult data if the course of the disease/condition and the effects of the product are sufficiently similar between adults and the pediatric population. PMHS anticipates that the Sponsor will need to conduct pediatric PK and safety studies, but extrapolation of efficacy to pediatric patients from adults may be reasonable.*

(b) (4) *PMHS agrees with the Sponsor's request for a full waiver of pediatric studies required under PREA. Since there is no scientific justification for fever reduction for the vast majority of children and pediatric appropriate antipyretics products are available in the US (e.g., acetaminophen and ibuprofen), PMHS believes that 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.*

Conclusions and Recommendations (in response to the Division's specific questions)

Division's Specific Questions: We seek your advice regarding whether pediatric studies should be waived for this NDA and if so, for which ages. If not, would single-dose PK studies suffice? If PK studies would not suffice, should the sponsor study both indications (pain reliever and fever reducer)? Which ages should be studied?

(b) (4), PMHS disagrees with the Sponsor's request for a full waiver of pediatric studies required under PREA. PMHS believes a partial waiver for children < 6 months old would be reasonable at the time of NDA approval, but the Sponsor should conduct a pediatric ketoprofen assessment for children 6 months to < 17 years old for the OTC pain reliever indication. PMHS anticipates that the Sponsor will need to conduct pediatric PK and safety studies. Extrapolation of efficacy to pediatric patients from adults may be scientifically justifiable if the course of the disease/condition and the effects of the product are sufficiently similar between adults and the pediatric population.

(b) (4), PMHS agrees with the Sponsor's request for a full waiver of pediatric studies required under PREA. Since there is no scientific justification for fever reduction for the vast majority of children and pediatric appropriate antipyretics products are available in the US (e.g., acetaminophen and ibuprofen), PMHS believes that 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.

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/s/

Felicia Collins
4/28/2009 11:51:21 AM
MEDICAL OFFICER

Lisa Mathis
5/12/2009 09:07:54 AM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|----------------------|---|-----|----|----|--|
| | Pivotal Study #2 | | | | |
| | Indication: | | | | |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | X | | | |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | X | | | |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | | X | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | X | | | |
| 19. | Has the applicant submitted adequate information to assess the arrhythmia potential of the product (<i>e.g.</i> , QT interval studies, if needed)? | | | X | |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | X | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | X | | | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | | | X | |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | X | | | |
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | X | | | |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | X | | | |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | X | | | Special studies requested for photosensitization |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|--|
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)? | | | X | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | X | | | Waiver requested for patients < age 16 |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | X | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | | X | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | X | | | |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | X | | | |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | | | X | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | X | | | |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | X | | | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | X | | | |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | | | X | |
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | X | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | X | | | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

/s/

Priscilla Callahan-Lyon
3/20/2009 02:46:29 PM
MEDICAL OFFICER

Lesley-Anne Furlong
3/20/2009 03:34:32 PM
MEDICAL OFFICER