

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-101

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022470

SUPPL #

HFD # 560

Trade Name Nexcede

Generic Name 12.5 mg ketoprofen

Applicant Name Novartis Consumer Health

Approval Date, If Known 11-25-09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-429 Orudis KT

NDA# 20-499 Actron

NDA# 18-754 Orudis

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Neel Patel
Title: Regulatory Project Manager
Date: 11-25-09

Name of Office/Division Director signing form: Andrea Leonard-Segal
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/

NEEL PATEL
11/25/2009

ANDREA LEONARD SEGAL
11/25/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-470 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Nexcede Established/Proper Name: 12.5 mg ketoprofen Dosage Form: oral soluble film		Applicant: Novartis Consumer Health Agent for Applicant (if applicable):
RPM: Neel Patel		Division: DNCE
NDA: NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)		505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #s) and drug name(s): Rx Orudis NDA 18-754 OTC Orudis KT NDA 20-429 Provide a brief explanation of how this product is different from the listed drug. New Dosage Form ☐ If no listed drug, check here and explain: Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review. ☒ No changes ☐ Updated Date of check: 11-24-09 If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug. <u>On the day of approval</u>, check the Orange Book again for any new patents or pediatric exclusivity.
❖ Actions		
• Proposed action • User Fee Goal Date is <u>11-26-09</u>		☒ AP ☐ TA ☐ CR
• Previous actions (<i>specify type and date for each action taken</i>)		☐ None

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ If accelerated approval, were promotional materials received? Note: For accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics²	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): ☐ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☒ Direct-to-OTC NDAs: Subpart H BLAs: Subpart E ☐ Accelerated approval (21 CFR 314.510) ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 314.520) ☐ Restricted distribution (21 CFR 601.42) Subpart I Subpart H ☐ Approval based on animal studies ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request Comments:	
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☐ Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) Approval on 11/25/09

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 12/4/09

❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	Approved labels submitted on October 29 and November 11, 2009
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>)	Non-acceptable letter on April 27, 2009 and Acceptable letter on September 3, 2009 Reviews dated April 24, May 13, and August 28, 2009
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☐ DMEDP ☐ DRISK ☐ DDMAC ☐ CSS ☒ Other reviews IDS: 8/27/09, 10/02/2009, 11/09/09, and 11/17/09
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM: 7/7/09, 11/24/09 CMC: 3/20/09 P/T: 4/14/09 Clinpharm: 3/25/09 Clinical: 3/20/09 Labeling: 3/13/09
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant in on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>7/8/09</u> If PeRC review not necessary, explain: _____ • Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	☐ Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 12/4/09

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	See outgoing Correspondence tab
❖ Internal memoranda, telecons, etc.	see memo to file tab
❖ Minutes of Meetings	
• Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)	X Not applicable
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☒ No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilot programs) (<i>indicates dates</i>)	PIND Meeting 2/6/07
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 11/24/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 11/6/09
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 12-14-09
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	11-6-09
• Clinical review(s) (<i>indicate date for each review</i>)	9/25/09, 11/24/09
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 13 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None PMHS Consult 5/12/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management	
• REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo (<i>indicate date</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☒ None

⁵ Filing reviews should be filed with the discipline reviews.
Version: 12/4/09

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	☐ None
Clinical Microbiology Review(s) (indicate date for each review)	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☐ None
Statistical Team Leader Review(s) (indicate date for each review)	☐ None
Statistical Review(s) (indicate date for each review)	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☒ None
Clinical Pharmacology review(s) (indicate date for each review)	☒ None 9/03/09, 9/30/09, 11/20/09
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☐ None 9/11/09, 9/30/09, and 11/19/09
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	☒ None
• Supervisory Review(s) (indicate date for each review)	☒ None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	☐ None 8/27/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	☒ None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	☒ None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	☐ None 9/15/09, 11/16/09, 8/31/09
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	CMC review- pg 102
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>)	Date completed: 11-13-09 ☒ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/

NEEL PATEL
12/14/2009



NDA 22-470

DISCIPLINE REVIEW LETTER

Novartis Consumer Health, Inc.
Attention: George Marchesini
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Marchesini:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexcede (12.5 mg ketoprofen) oral soluble film.

We have reviewed your response to our audit of the analytical portion for the bioequivalence study EDKT-PN-101, and we have identified the following unresolved deficiency:

The incurred sample reproducibility (ISR) experiment was not conducted.

You will need to conduct an ISR assessment to confirm the reproducibility of the LC/MS/MS method. We suggest an ISR assessment of 5-10% of the subject samples based on study size. The samples used should be within the long term frozen storage stability period established during method validation.

We are providing this comment to you before we complete our review of the entire application to give you notice of an issue that we have identified. In addition, we may identify other information that must be provided before we can approve this application. You should respond to this issue no later than October 31, 2009. Depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Neel Patel, Regulatory Project Manager, at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22470

ORIG-1

NOVARTIS
CONSUMER
HEALTH INC

KETOPROFEN ORAL-ORAL
(b) (4)

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

/s/

ANDREA LEONARD SEGAL
10/07/2009

Patel, Neel (CDER)

Subject: FW: NDA 22-470 Ketoprofen Labeling Comments**"Patel, Neel (CDER)" <Neeli.Patel@fda.hhs.gov>**To george.marchesini@novartis.com

cc

10/05/2009 02:13 PM

Subject NDA 22-470 Ketoprofen Labeling Comments

Hi George,

We request that you make the following revisions to the labeling for all SKUs:

1. Provide all SKUs. The labeling submitted on September 24, 2009, did not include the pouch label for the cinnamon-flavored product.
2. Remove the statement (b) (4) and the statement (b) (4) for all labels. The submitted labeling may lead to potential consumer confusion and is promotional in nature. You would have to demonstrate what this statement means to consumers and how it impacts the self-selection process for it to be allowed in labeling.
3. Increase the font size of the statement "See new warnings information" on the principal display panels (PDPs) of all carton labels. The font size must be the larger of the size of the title "Drug Facts" or one quarter the size of the most prominent printed matter on the principal display panel (PDP) (21 CFR 201.322(b);74 FR 19385 at 19409).
4. Ensure that the inactive ingredient "dibasic sodium phosphate" is in alphabetical order under the heading ***Inactive ingredients*** as required in 21 CFR 201.66(c)(8).

Please call me if you have any questions.

Neel

Neel Patel, PharmD.
Regulatory Project Manager
Division of Nonprescription Evaluation
Office of Nonprescription Products
Tel: 301-796-0970

11/9/2009

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/

NEEL PATEL
11/09/2009



NDA 22-470

INFORMATION REQUEST

Novartis Consumer Health, Inc.
Attention: George Marchesini
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Kenny:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexcede (12.5 mg ketoprofen) oral soluble film.

We also refer to your June 19, 2009 submission, containing your proposed pediatric drug development plan.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You will need to provide efficacy data for children less than 16 years of age for the pain indication. The data provided in your submission are not sufficient for extrapolation of efficacy in children for the pain indication. You will need to conduct adequate and well-controlled superiority trials demonstrating efficacy for children ages 6 months to 15 years. These trials should be conducted using a pain model or models suitable for an over-the-counter population.
2. It is reasonable to conduct the pharmacokinetic trial prior to studying efficacy. However, the proposed single dose pharmacokinetic trial is inadequate. The PK trial should be done in children who may benefit from the drug rather than in otherwise healthy pediatric volunteers. Hence, we recommend conducting a single dose PK trial leading into a multiple dose PK trial that would evaluate the safety, tolerability and pharmacokinetics of an appropriate dose of ketoprofen in children. We recommend recruitment of children in the following age groups, which have been known for differences in developmental physiology as it relates to drug clearance:
 - 6 to < 12 months
 - 12 to < 24 months
 - 2 to < 6 years
 - 6 to < 16 years

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

3. Your proposed safety plan is inadequate. Monitoring these subjects for safety will not provide sufficient data. You should conduct a safety trial on a sizable population of children ages 6 months to 15 years of age. This trial should include adequate representation of the age groups and should be conducted in a symptomatic population under “actual use” conditions.

If you have any questions, call Neel Patel, Regulatory Project Manager, at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

Andrea Leonard-Segal, MD
Director
Division of Nonprescription Clinical
Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22470

GI-1

NOVARTIS
CONSUMER
HEALTH INC

KETOPROFEN ORAL-ORAL
(b) (4)

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

/s/

ANDREA LEONARD SEGAL
09/21/2009



NDA 22-470

DISCIPLINE REVIEW LETTER

Novartis Consumer Health, Inc.
Attention: George Marchesini
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Marchesini:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexcede (12.5 mg ketoprofen) oral soluble film.

Our review of the Labeling section of your submission is complete, and we have identified the following deficiencies:

1. Principal Display Panel (PDP)

- a. Remove the promotional statement (b) (4) This product does not contain any of the active ingredients found in the Excedrin products currently on the market. Therefore, comparing the product to (b) (4) may lead to consumer confusion.
- b. We have determined that the dosage form for your product is a “soluble film” as defined in the CDER Data Standards Manual (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm>) Therefore, revise the dosage form (b) (4) to read "Oral Soluble Films"
- c. Decrease the font size and revise the statement (b) (4) This product should not be identified as a (b) (4) because the dosage form is a “soluble film”. You must separate this statement from the proprietary name Nexcede. In accordance with 21 CFR 201.61(b), the statement of identity must be in direct conjunction with the most prominent display of the proprietary name.
- d. Remove or revise the promotional statement (b) (4) A claim that your product dissolves (b) (4) is ambiguous to the consumer because it does not specify a time of dissolution. However, you may include a specific time to complete dissolution but this must be determined by data that we have reviewed. As indicated above, (b) (4) is not the appropriate dosage form for this product.

- e. Add “See new warnings information” per 21 CFR 201.326(b) (74 FR 19385 at 19409).
- f. Designate a space for the expiration date in accordance with 21 CFR 201.17
- g. Designate a space for the lot/control number in accordance with (21 CFR 201.10(i)(iii)).

2. *Drug Facts Panel (Carton)*

- a. Revise the word (b)(4) wherever it appears on the Drug Facts label to read “film(s).”
- b. Under the heading “Directions,” make the following revisions:
 - 1. Use a table format as specified in 201.66(d)(9) or indent bullets under "adults and children 16 years and over" so that the directions for this age group are clearly distinct from the directions for children under 16 years of age.
 - 2. Revise the bulleted statement "children: do not give to children under age 16 unless directed by a doctor" to read "children under 16 years: ask a doctor."
- c. Under the heading “Inactive ingredients”, revise "sodium phosphate dibasic" to read "dibasic sodium phosphate" (USP name).

3. *Immediate Container Label (Pouch)*

Revise the label according to the comments provided for the carton labeling.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call me at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

Neel Patel, PharmD.
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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/

NEEL PATEL

09/04/2009

David, Jeannie C

From: David, Jeannie C
Sent: Wednesday, August 26, 2009 3:56 PM
To: Chang, Jane; Chen, Tien Mien
Cc: Dorantes, Angelica; Ding, Shulin; Rhee, Moo Jhong; Patel, Neel (CDER)
Subject: RE: NDA 22-470 - CMC teleconference with applicant

Attachments: NDA 22470-26AUG2009-Information Request.doc

Hi Jane and Albert,

Please review the following Information Request letter that will substitute for the telecon that was submitted today:

Cancelled 30 8/27/09



NDA
-26AUG2009-Inform

I spoke with the NDA applicant, and they agree to submit their responses to the NDA by Sept. 2.

Thanks,

Jeannie

From: David, Jeannie C
Sent: Wednesday, August 26, 2009 1:04 PM
To: Ding, Shulin; Chang, Jane; Chen, Tien Mien; Furlong, Lesley-Anne; Patel, Neel (CDER)
Cc: Dorantes, Angelica; Rhee, Moo Jhong
Subject: RE: NDA 22-470 - CMC teleconference with applicant
Importance: High

Dear all,

The telecon scheduled for today at 3:30 pm for NDA 22-470 is cancelled. The applicant has agreed to the 3 proposed discussion points.

Instead, I will be issuing a formal letter with the 3 discussion points, 1 additional point from Biopharm, and a request to formally submit their responses to the NDA by 9/2/09.

Thank you for your rapid feedback,

Jeannie

Jeannie David, M.S.
Regulatory Project Manager
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Phone: (301) 796-4247

From: Chang, Jane
Sent: Wednesday, August 26, 2009 12:55 PM
To: David, Jeannie C; Ding, Shulin
Cc: Rhee, Moo Jhong
Subject: RE: NDA 22-470 - CMC teleconference with applicant

No, there is no need for the t-con. However, I would like them to submit the revisions per the agreement by 9/2/09.

From: Ding, Shulin
Sent: Wednesday, August 26, 2009 12:53 PM
To: David, Jeannie C
Cc: Chang, Jane
Subject: RE: NDA 22-470 - CMC teleconference with applicant

Then I don't think that I need to be in the t-con if we still have it. If Jane chooses not to have the t-con, please send the IR letter and ask the firm to officially respond to the letter and amend the NDA accordingly.

By the way, we still have Albert's comment to be made known to the firm. What is your suggestion?

Shulin

From: David, Jeannie C
Sent: Wednesday, August 26, 2009 12:42 PM
To: Ding, Shulin; Chang, Jane
Cc: Rhee, Moo Jhong
Subject: RE: NDA 22-470 - CMC teleconference with applicant
Importance: High

Hi Jane and Shulin,

The applicant has read our 3 points and agrees to make all of the requested changes.

Would you like to still have the telecon scheduled for today at 3:30 pm?

Thank you,

Jeannie

From: David, Jeannie C
Sent: Tuesday, August 25, 2009 1:25 PM
To: David, Jeannie C; Ding, Shulin; Chang, Jane
Cc: Rhee, Moo Jhong; Furlong, Lesley-Anne; Patel, Neel (CDER)
Subject: NDA 22-470 - CMC teleconference with applicant
When: Wednesday, August 26, 2009 3:30 PM-4:00 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WO 1421 conf rm Bldg22 - AR

CMC Teleconference for NDA 22-470 (Novartis; ketoprofen oral (b) (4) 12.5 mg).

Points for discussion:

1. Revise your drug product specification to test for degradants at release for every batch. The proposed skip-lot testing for degradants at release after the first 15 batches is not acceptable. The level of degradants is a critical product quality attribute. It should always be monitored.
2. Perform microbiological testing on the first fifteen commercial batches from each identified converting/packaging site. If the requirements are met, testing frequency can be reduced to one batch in every three for that site.
3. Include microbiological testing for the 12-month time point for Batch 1 presented in your Table 2-1 of Section 3.2.P.8.2.

Toll Free: 1-866-866-5110

Passcode: *5037190*

David, Jeannie C

From: george.marchesini@novartis.com
Sent: Wednesday, August 26, 2009 1:25 PM
To: David, Jeannie C
Cc: Patel, Neel (CDER)
Subject: RE: NDA 22-470 Ketoprofen - Teleconference Inf.
Attachments: emfalert.txt

Hi Jeannie,

The proposals outlined below by the FDA Review Team are acceptable to Novartis Consumer Health, Inc.. NCH will perform degradation testing on every lot outlined in #1; NCH will perform microbiological testing on the first fifteen commercial lots from each converting/packaging site, then if requirements are met, testing can be reduced to one batch in every three for that site as in #2 and lastly, microbiological testing will be performed on Batch 1 in 3.2.P.8.2 table 2-1.

Based on our telephone discussion this afternoon, we will update the appropriate modules and submit as a minor amendment to the FDA's request by September 2.

Regards,
George

George Marchesini
Associate Director, Global Regulatory Affairs

Novartis Consumer Health, Inc.
200 Kimball Drive
Parsippany, NJ 07054-0622
USA
Phone: +1 973 503 7190
Fax: +1 973 503 8405
Email : george.marchesini@novartis.com



"David, Jeannie C" <Jeannie.David@fda.hhs.gov>

08/26/2009 11:31 AM

To george.marchesini@novartis.com

CC "Patel, Neel (CDER)" <Neel.Patel@fda.hhs.gov>

Subject RE: NDA 22-470 Ketoprofen - Teleconference Inf.

Hi George,

Below are the CMC comments for today's discussion on NDA 22-470:

1. Revise your drug product specification to test for degradants at release for every batch. The proposed skip-lot testing for degradants at release after the first 15 batches is not acceptable. The level of degradants is a critical product quality attribute. It should always be monitored.
2. Perform microbiological testing on the first fifteen commercial batches from each identified converting/packaging site. If the requirements are met, testing frequency can be reduced to one batch in every three for that site.

8/27/2009

3. Include microbiological testing for the 12-month time point for Batch 1 presented in your Table 2-1 of Section 3.2.P.8.2.

The tentative list of FDA participants is:

Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA)

Jane Chang, Ph.D., Chemistry reviewer, ONDQA

Leslie Furlong, M.D., Clinical Division Team Lead, Division of Nonprescription Clinical Evaluation (DNCE)

Neel Patel, Regulatory Project Manager, DNCE

Jeannie David, Regulatory Project Manager, ONDQA

I would appreciate if you can sent me a list of participants from you end. Please let me know if you will need further information prior to our call.

Regards,

Jeannie

Jeannie David, M.S.

Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

Office of New Drug Quality Assessment

10903 New Hampshire Avenue

Building 22, Mail Room 1491

Silver Spring, MD 20993

Phone: (301) 796-4247

Fax: (301) 796-9877

jeannie.david@fda.hhs.gov

From: george.marchesini@novartis.com [mailto:george.marchesini@novartis.com]

Sent: Tuesday, August 25, 2009 11:55 AM

To: David, Jeannie C

Cc: Patel, Neel (CDER)

Subject: NDA 22-470 Ketoprofen - Teleconference Inf.

Dear Jeannie:

I am confirming our teleconference for 3:30 PM on Wednesday, August 26, 2009 for ketoprofen (b) (4) 12.5 mg CMC questions. Below is the teleconference information.

Toll Free: 1-866-866-5110

Passcode: *5037190*

If you have any issues with the call in number, please contact my administrative assistant, MaryEllen Weikel at 973-503-7479.

As we discussed earlier today, any further information you may be able to provide on the microbiology question would be helpful.

Regards,

George

George Marchesini

Associate Director, Global Regulatory Affairs

Novartis Consumer Health, Inc.

200 Kimball Drive

Parsippany, NJ 07054-0622

8/27/2009

USA

Phone: +1 973 503 7190

Fax: +1 973 503 8405

Email : george.marchesini@novartis.com



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- 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/

JEANNIE C DAVID
08/27/2009

David, Jeannie C

From: Chen, Tien Mien
Sent: Wednesday, August 26, 2009 11:49 AM
To: David, Jeannie C
Cc: Dorantes, Angelica
Subject: RE: NDA 22-470 Ketoprofen (b)(4)- Information Request

Jeannie: Hi,

I looked at the response and I think it is adequate for me to complete my review. But I'd like the sponsor to do me a favor to plot the new "mean" dissolution data points (n=12 strips/batch) of two formulations together in a graph for pHs 5.8 and 7.2, similar to previous Figure 2-3 (P. 17/26) . Thanks!!

Albert

From: David, Jeannie C
Sent: Tuesday, August 25, 2009 4:16 PM
To: Chen, Tien Mien
Cc: Dorantes, Angelica; Chang, Jane; Ding, Shulin
Subject: FW: NDA 22-470 Ketoprofen (b)(4) - Information Request

Hi Albert,

Attached is the response to your information request to NDA 22-470 (Novartis; Ketoprofen Oral (b)(4)) for your review. Also, attached is our most recent email discussion on this for your information.

Please let me know if the applicant's response is adequate. FYI, I have set up a CMC teleconference with the applicant for tomorrow (Aug 26) at 3:30pm. If after review of the information, you would like me to notify the applicant that you would like to add a point(s) for discussion, please let me know ASAP, so that the applicant can invite the appropriate personnel to interact with you.

Thank you,

Jeannie

From: george.marchesini@novartis.com [mailto:george.marchesini@novartis.com]
Sent: Tuesday, August 25, 2009 4:07 PM
To: David, Jeannie C
Cc: Patel, Neel (CDER)
Subject: NDA 22-470 Ketoprofen oral (b)(4) - Information Request

Dear Jeannie:

Reference is made to the CMC/Biopharm Information Request sent to Mr. Michael Kenny, Novartis Consumer Health, Inc. from Moo-Jhong Rhee, Ph.D., Office of New Drug Quality Assessment, FDA, dated August 11, 2009. Reference is also made to our telephone conversation on August 17 and on August 19, 2009 regarding the timing for providing the response to the Information Request. As discussed, we are providing these responses today, August 25, 2009. These

8/27/2009

responses will also be submitted to the NDA.

Please let me know if you have any further questions.

Regards,
George

George Marchesini
Associate Director, Global Regulatory Affairs

Novartis Consumer Health, Inc.

200 Kimball Drive

Parsippany, NJ 07054-0622

USA

Phone: +1 973 503 7190

Fax: +1 973 503 8405

Email : george.marchesini@novartis.com



David, Jeannie C

From: David, Jeannie C
Sent: Wednesday, August 19, 2009 2:59 PM
To: Chen, Tien Mien
Cc: Dorantes, Angelica; Chang, Jane; Ding, Shulin
Subject: RE: Message from 9735037190 Regarding IR Letter for NDA 22-470 (Keptoprofen Oral (b) (4))

Hi Albert,

I communicated your feedback to the NDA applicant, and they will provide the newly generated 12-point comparative dissolution profiles, along with the other points requested in Q#2 on Tuesday, Aug 25, 2009.

Thank you for getting back to me right away to address the applicant's questions,

Jeannie

From: Chen, Tien Mien
Sent: Wednesday, August 19, 2009 10:34 AM
To: David, Jeannie C
Cc: Dorantes, Angelica; Ding, Shulin; Chang, Jane
Subject: RE: Message from 9735037190 Regarding IR Letter for NDA 22-470 (Keptoprofen Oral (b) (4))

Jeannie: Hi,

I listened George's voice message. It is clear to me now for the batches used. His suggestion is fine with me,

1.) To generate new comparative dissolution profiles (similar to Figure 2-3, Section 32P2, p. 17/26) using the biobatch No. Z214871A (with peppermint flavor) vs. stability batch No. Z214923A (with cinnamon flavor) and using n=12/batch instead of n=6/batch (used previously to generate Figure 2-3) and

2.) To submit the data next Tuesday (08/25/09) for review.

However, the sponsor needs to provide detailed information as stated in the IR letter Q#2.

PS. Shuling just called me and I'll let you know hopefully by 08/31/09 if the new data looks OK or not once I reviewed it. Thanks!!

Albert

From: David, Jeannie C
Sent: Wednesday, August 19, 2009 9:12 AM
To: Chen, Tien Mien
Subject: FW: Message from 9735037190

Hi Albert,

I just left you a voicemail. The voicemail below relates to your IR letter sent for NDA 22-470 (ketoprofen oral (b) (4)). Please listen, and let me know your thoughts, so that I can communicate them back to the applicant.

Thanks

Jeannie

From: Unity Messaging System - FDAOIP14

Sent: Tuesday, August 18, 2009 2:01 PM
To: David, Jeannie C
Subject: Message from 9735037190

<< File: VoiceMessage >>

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- 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/

JEANNIE C DAVID
08/27/2009



NDA 22-470

INFORMATION REQUEST

Novartis Consumer Health, Inc.
Attention: George Marchesini
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Marchesini:

Please refer to your January 23, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ketoprofen oral (b) (4) 12.5 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Your response is requested no later than September 2, 2009:

1. Revise your drug product specification to test for degradants at release for every batch. The proposed skip-lot testing for degradants at release after the first 15 batches is not acceptable. The level of degradants is a critical product quality attribute. It should always be monitored.
2. Perform microbiological testing on the first fifteen commercial batches for each flavor of ketoprofen drug products from each identified converting/packaging site. If the requirements are met, testing frequency can be reduced to one batch in every three for each flavor of the drug products for that site.
3. Include microbiological testing for the 12-month time point for Batch 1 presented in your Table 2-1 of Section 3.2.P.8.2.
4. Generate new comparative dissolution profiles using mean data from n = 12 strips/batch, rather than the previous n = 6 strips/batch, to compare the two formulations, No. Z214871A with peppermint flavor vs. No. Z214923A with cinnamon flavor, in a single graph. Please provide one comparative profile graph for dissolution at pH 5.8, and another graph at pH 7.2, similar to Figure 2-3 in Section 3.2.P.2 (p. 17/26).

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (jeannie.david@fda.hhs.gov), and Neel Patel, Regulatory Project Manager in the Office of New Drugs (neel.patel@fda.hhs.gov).

If you have any questions, contact Jeannie David, Regulatory Project Manager, at phone number 301-796-4247 or email at jeannie.david@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE

08/27/2009

Chief, Branch III



NDA 22470

INFORMATION REQUEST

Novartis Consumer Health, Inc.
Attention: Michael Kenny
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Kenny:

Please refer to your new drug application (NDA) dated January 23, 2009, received January 26, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for 12.5 mg ketoprofen oral (b)(4).

We are reviewing the Biopharmaceutics and Chemistry, Manufacturing and Controls (CMC) sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Under Section 3.2.R.3, Comparative Dissolution Profiles, you provided comparative dissolution data for the to-be-marketed (TBM) formulations of oral strip formula # 1588-02 with peppermint flavor, and oral strip formula # 1589-01 with cinnamon flavor. The batch Z214875A that used formula # 1588-02 is a stability batch, not a biobatch (Table 2-1, p. 4/7).

Therefore, please provide the comparative dissolution data using the biobatch Z214871A (with peppermint flavor) vs. the stability batch Z214923A (with cinnamon flavor).

2. Under Section 3.2.P.2, Pharmaceutical Development, you provided Figure 2-3 (P. 17/26) for , which shows significant differences in the early time points of the dissolution profiles between formulas 1589-1 (yellow curve) and 1588-2 (pink curve). Please provide the information used to generate Figure 2-3, including:
 1. The lot number, date, and size of manufacture of the TBM formulations and indicate if they are biobatches or stability batches,
 2. the number of strips tested per each batch and their individual raw data sets (in tabular format),
 3. the results of f2 calculations between the two TBM formulations and
 4. the rationale for the differences observed in the comparative dissolution profiles recorded in Section 3.2.R.2 and Section 3.2.P.2.

If you have previously provided these data for review, please specify the module, section, volume and page numbers of the location of these data; if not, please submit this information to the administrative file electronically. Please include the individual raw data sets for analysis.

If you have any questions, call Jeannie David, MS, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE

08/11/2009

Chief, Branch III

From: Patel, Neel (CDER)
Sent: Tuesday, July 07, 2009 4:09 PM
To: 'george.marchesini@novartis.com'
Subject: NDA 22-470 Ketoprofen

Hi George,

Per our conversation, we are reviewing the labeling section of your submission and have the following preliminary comments on the DF label.

1. Include the bulleted statement "asthma" under the "*Warnings*" subheadings "**Ask a doctor before use if you have**".
2. Revise the current bulleted statement "long term continuous use may increase the risk of heart attack or stroke" under the "When using this product" subheading on the Drug Facts label to read "the risk of heart attack or stroke may increase if you use more than directed or for longer than directed".
3. Review the Stomach bleeding warnings for NSAID-containing products - final rule (*Federal Register* vol. 74, pages 19385 - 19409, April 29, 2009) and make the appropriate revisions.

<http://www.regulations.gov/fdmspublic/component/main?main=DocumentDetail&o=090000648096ef53>

Please don't hesitate to contact me if you have any questions.

Neel

Neel Patel, PharmD.
Regulatory Project Manager
Division of Nonprescription Evaluation
Office of Nonprescription Products
Tel: 301-796-0970

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

/s/

Neel Patel
7/14/2009 05:32:49 PM
CSO



NDA 22-470

INFORMATION REQUEST LETTER

Novartis Consumer Health, Inc.
Attention: George Marchesini
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Marchesini:

Please refer to your January 23, 2009 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ketoprofen oral (b) (4) 12.5 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Your response is requested no later than August 20, 2009.

Drug Substance:

1. Provide a table for ketoprofen regulatory specification including testing for residual solvents, namely (b) (4). Provide the analytical procedure and method validation data if a non-compendial method is used. The residual (b) (4) are listed in the certificate of analysis provided by (b) (4)

Drug Product:

2. Regarding the manufacture of the drug product:
 - a. Add in-process testing, e.g. pH, solids content, and viscosity, for the liquid mix. Provide analytical procedure for the solids content test. Provide data to support homogeneity of the liquid mix or commit to address the homogeneity issue in your process validation runs.
 - b. Provide a justification for the proposed pH range (5 – 9) or (b) (4)
 - c. Provide numerical values of target and range of the dry coat weight for the in-process control.
 - d. Provide information for the cause of an out-of specification result for the in-process testing of Batch SZ234837, i.e. average coat weight of (b) (4), and the corrective actions taken.
 - e. Provide information on the critical equipment parameters (b) (4)
 - f. Identify the critical process parameters (b) (4)
 - g. Provide the step numbers in the master batch records for Batches ACZ234837 and ACZ234838, where the in-process samples (b) (4) were obtained for solids testing, viscosity, and pH.
 - h. Commit to submit a prior approval supplement for reworking operations. Also commit to submit a prior approval supplement for reprocessing operations if there is a significant potential to adversely affect the identity, strength, quality, or purity of the drug product.

3. Address the concern as to whether the ICH Class 1 or 2 solvents are present in the peppermint and cinnamon flavors. Either include a test for residual solvents in the specifications for the peppermint and cinnamon flavors or provide a statement to certify that no ICH Class 1 or 2 solvents are used in the manufacture of these flavoring agents. Alternatively, the testing can be performed on the finished product.
4. Revise the drug product specifications:
 - a. Include the HPLC test for degradation product in the drug product release specifications for both the peppermint and cinnamon flavor drug products.
 - b. Tighten dissolution test acceptance criterion to $Q = (b) (4)$ at 30 minutes.
 - c. Perform microbial limits test for every batch. The stability data of the drug products do not support the proposed skip-lot testing for microbial limits test of the drug products (see Item 6 below). The skip-lot testing may be justified when acceptable significant body of data for each flavor of the drug product manufactured from each site, including $(b) (4)$ are provided. The microbiological quality attributes of the drug product is site specific; therefore, they cannot be inferred from one site to another.

$(b) (4)$

5. Specify the solvents to be tested per USP <467> Residual Solvents for the bulk drug films.
6. Perform microbial limits test as soon as possible on the currently available stability samples of Formulation 1589-01, Lots Z214873A, Z214874A, Z214923A, and Z234838 (08386). Your drug product stability data for the three registration batches (i.e. Z214873A, Z214874A, and Z214923A) of Formulation 1589-01 do not support the proposed expiration dating period of 24 months. $(b) (4)$

$(b) (4)$

7. $(b) (4)$

8. Commit to place the first three commercial batches of the drug products of each flavor from each site, including $(b) (4)$ on long-term stability studies.
9. Provide updated stability data for both flavors of drug products.

To facilitate prompt review of your response, please also provide an electronic courtesy copy of your response to both Jeannie David, Regulatory Project Manager in the Office of New Drug Quality Assessment (jeannie.david@fda.hhs.gov), and Neel Patel, Regulatory Project Manager in the Office of New Drugs (neel.patel@fda.hhs.gov).

If you have any questions, contact Jeannie David, Regulatory Project Manager, at phone number 301-796-4247 or email at jeannie.david@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Division Pre-Marketing Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

Moo-Jhong Rhee
6/15/2009 04:25:19 PM
Chief, Branch III



FILING COMMUNICATION

NDA 22-470

Novartis Consumer Health, Inc.
Attention: Michael Kenny
Associate Director, Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Mr. Kenny:

Please refer to your new drug application (NDA) dated January 23, 2009, received January 26, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for 12.5 mg ketoprofen oral (b)(4).

We also refer to your submissions dated January 26, February 19, and April 2, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is November 26, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by November 2, 2009.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Neel Patel, Regulatory Project Manager, at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, MD
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Joel Schiffenbauer
4/10/2009 10:42:17 AM



NDA 22-470

NDA ACKNOWLEDGMENT

Novartis Consumer Health, Inc.
Attention: Suzanne LoGalbo, R.Ph, JD
Head, North American Region
Global Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Ms. LoGalbo:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: 12.5 mg ketoprofen oral (b) (4)

Date of Application: January 23, 2009

Date of Receipt: January 26, 2009

Our Reference Number: NDA 22-470

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 27, 2009 in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however,

it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-0970.

Sincerely,

{See appended electronic signature page}

Neel Patel, PharmD.
Regulatory Project Manager
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Neel Patel
2/26/2009 04:01:29 PM