CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-470

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	May 11, 2009
To:	Andrea Leonard-Segal, M.D., M.S. Director, Division of Nonprescription Clinical Evaluation Office of Nonprescription Products
Through:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	(b) (4) (Ketoprofen) (b) (4) 12.5 mg
Application Type/Number:	NDA #22-470
Applicant/sponsor:	Novartis
OSE RCM #:	2009-195

EXECUTIVE SUMMARY

This review was written in response to the submissions from Novartis, dated January 23, 2009 and April 2, 2009, for assessment of the labels and labeling for the product (b) (4) (ketoprofen) NDA #22-470, to identify areas that could lead to medication errors. The proprietary name (b) (4) was reviewed in OSE review #2009-194.

This product is an "oral (b) (4) and the Applicant submitted (b) (4) as the finished dosage form. Although the Division of Medication Error Prevention and Analysis (DMEPA) is aware of other over-the-counter products that are available in a similar dosage form, this dosage form represents a novel dosage form for products managed under the NDA process. All the other currently marketed over-the-counter (b) (4) products are unapproved products. As such the CDER Labeling and Nomenclature Committee (LNC) was contacted to determine the appropriate dosage form designation for this product. This determination has not been finalized prior to the completion of this review.

Using Failure Mode and Effects Analysis,[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling to identify vulnerabilities that could lead to medication errors. Our findings indicate that the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We provide recommendations below that aim at reducing the risk of medication errors. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Darrell Jenkins, project manager, at 301-796-0558.

1 MATERIALS REVIEWED

For this product the Applicant submitted labels and labeling on January 23, 2009 and April 2, 2009 (see Appendices A and B).

2 RECOMMENDATIONS

2.1 COMMENTS TO THE DIVISION

The Agency has not made a final determination on the dosage form of the proposed product. Once the Agency makes a final determination the dosage form (b) (4) will need to be revised to reflect the dosage form designation.

We request the following recommendations be communicated to the Applicant prior to approval.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.2 COMMENTS TO THE APPLICANT

A. General Comments on container labels and carton labeling

1. The word (b) (4) is not part of the dosage form. Delete the word (b) (4) from the statement (b) (4)

2. The statement "From the Makers of Excedrin" is distracting. Patients may interpret this statement to mean that the proposed product contains the same active ingredients as Excedrin. Reduce the size of the statement (b) (4) on the top of the primary display panel of the container label and carton labeling and relocate the statement away from the proprietary name for the proposed product.

B. Carton labeling

1. As presented, "Drug Facts" does not list the alcohol warning as stated in 21 CFR 201.322. Revise "Drug Facts" to include the following warning per 21 CFR 201.322:

   "Alcohol Warning" [heading in boldface type]: "If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take ketoprofen or other pain relievers/fever reducers. Ketoprofen may cause stomach bleeding."

C. Container Labels

No additional comments beyond those provided in general comments.

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/s/

Zachary A Oleszczuk
5/11/2009 12:34:54 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
5/13/2009 09:29:56 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/13/2009 11:14:31 AM
DRUG SAFETY OFFICE REVIEWER

Labeling Review for Nexcede (NDA 22-470)

Division of Nonprescription Regulation Development
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATES:	January 23, 2009 April 2, 2009 June 16, 2009
REVIEW DATE:	August 27, 2009
NDA/SUBMISSION TYPE:	22-470/N000
SPONSOR:	Novartis Consumer Health, Inc. 200 Kimball Drive Parsippany, NJ 07054-0622 Michael Kenny North American Regional Liaison Global Regulatory Affairs 973-503-7855 973-503-8486 (FAX)
DRUG PRODUCT:	Nexcede
ACTIVE INGREDIENT:	Ketoprofen, 12.5 mg
INDICATIONS:	Fever reducer; pain reliever
PHARMACOLOGICAL CATEGORY:	Internal analgesic
REVIEWER:	Michael L. Koenig, Ph.D.
TEAM LEADER:	Matthew R. Holman, Ph.D.

I. BACKGROUND

The sponsor submitted draft labeling bearing the proposed trade name (b) (4) on January 23, 2009. The submitted labeling included both outer carton and immediate container (pouch) labeling for 20-count cinnamon and peppermint flavored product. The labeling was identified as "representative of the labeling for all proposed marketed sizes." On March 13, 2009, the project manager contacted the sponsor and told the representative that we required draft labeling for all sizes and flavors intended for marketing. On April 2, 2009, the sponsor submitted outer carton and immediate container labeling for 10- and 40-count cinnamon and peppermint-flavored product.

On April 27, 2009, in response to a January 26, 2009, request from the sponsor to review the proposed proprietary name (b) (4) we informed the sponsor that the name is unacceptable. We also informed the sponsor that we had no promotional concerns with the proposed alternate proprietary name Nexcede and asked the sponsor to submit a request for review of the alternate proprietary name if they would like us to formally evaluate "Nexcede." The sponsor submitted this request on June 16, 2009, along with labeling bearing the proposed trade name Nexcede. The submitted labeling included both outer carton and immediate container (pouch) labeling for 20-count cinnamon and peppermint flavored product.

On July 7, 2009, we sent the sponsor preliminary comments on the Drug Facts part of the outer carton labeling via e-mail. These preliminary comments are listed in section II.A of this review. Additional comments (section II.B) are based, in part, on discussions at a team meeting on August 17, 2009, and a meeting between the DNCE director, ONP ADRA, and the project manager on August 24, 2009.

Submitted Labeling	**Representative of Following SKUs**
20-count carton & pouch, cinnamon flavor	10-, 20-, and 40-count
20-count carton & pouch, peppermint flavor	10-, 20-, and 40-count

II. REVIEWER'S COMMENTS

A. Preliminary Comments on Labeling Submitted June 16, 2009

The following 3 preliminary comments on the outer carton ***Drug Facts*** label were sent to the sponsor via e-mail on July 7, 2009:

1. Include the bulleted statement "asthma" under the "***Warnings***" subheading "**Ask a doctor before use if you have**".

2. Revise the current bulleted statement (b) (4) (b) (4) 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 in the April 29, 2009, final rule (*Federal Register* vol. 74, pages 19385 - 19409) and make the appropriate revisions.

B. **Additional Comments on Labeling Submitted June 16, 2009**

We have not received revised labeling based on the preliminary comments, but have identified additional issues that the sponsor must address. These comments should be forwarded to the sponsor as soon as possible so that the additional labeling revisions can be made.

1. Outer Carton Label Outside Drug Facts

a. Principal Display Panel (PDP)

i. Remove the promotional statement (b) (4) This product contains none of the active ingredients in any of the (b) (4) products currently on the market. Therefore, comparing the product to (b) (4) (b) (4) may be confusing to consumers. This statement would be allowed if a label comprehension study demonstrated that consumers are not misled by the statement.

ii. Decrease the font size and amend the phrase (b) (4) to read something other than (b) (4) According to the CMC reviewer, ONDQA has identified the correct dosage form as "soluble oral film" (e-mail dated August 5, 2009). In it's current font size and shape, (b) (4) looks like part of the trade name. We do not want this product identified as (b) (4) because this dosage form exists in the CDER DATA Standards manual and is distinct from a soluble film (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm).

NOTE: As of the date of this review, the CMC reviewer has not yet filed her review. Therefore, we do not feel it is appropriate to send this dosage form revision to the sponsor at this time.

iii. Remove or revise the word (b) (4) in the phrase (b) (4) (b) (4) does not provide useful information to consumers. If the sponsor wants to indicate that the product dissolves quickly, it must provide data showing how quickly the films dissolve and express the mean dissolution time in seconds or minutes. As indicated above, (b) (4) is not the appropriate dosage form for this product.

NOTE: As of the date of this review, the CMC reviewer has not yet filed her review. Therefore, we do not feel it is appropriate to send the dosage form revision to the sponsor at this time.

iv. Change the dosage form from (b) (4) to "Soluble Oral Films" to be consistent with the CDER Data Standards Manual (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/ucm071666.htm).

NOTE: As of the date of this review, the CMC reviewer has not yet filed her review. Therefore, we do not feel it is appropriate to send this dosage form revision to the sponsor at this time.

v. Add "See new warnings information" per 21 CFR 201.326(b) (74 FR 19385 at 19409).

b. No designated space for expiration date
Expiration date must be included on the outer package (21 CFR 201.17).

c. No designated space for lot/control number
Lot/control number must be included on the outer package (21 CFR 201.10(i)(iii)).

2. Outer Carton Drug Facts Label

a. ***Active ingredients/Purpose***
The submitted labeling is acceptable.

b. ***Warnings***
With the exception of the changes recommended in an e-mail dated July 7, 2009 (section II.A of this review), the submitted labeling is acceptable.

c. ***Directions***

i. 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.

ii. Change the bulleted statement "children: do not give to children under age 16 unless directed by a doctor" to "children under 16 years: ask a doctor." We believe this statement is easier to understand and is consistent with other labels for NSAID-containing products.

d. Other Sections/Issues

i. ***Inactive ingredients***
Change "sodium phosphate dibasic" to "dibasic sodium phosphate" (USP name).

ii. Change the word (b) (4) wherever it appears to the word “film(s).”
NOTE: As of the date of this review, the CMC reviewer has not yet filed her review. Therefore, we do not feel it is appropriate to send this dosage form revision to the sponsor at this time.

3. Immediate Container (Pouch) Label
The same comments made in II.A.1. apply to the immediate container labels.

RECOMMENDATIONS

Advise the sponsor to make the following revisions to the labeling for all SKUs submitted on June 16, 2009. Further advise the sponsor that our review is ongoing and additional labeling revisions may be necessary.

1. Revisions that need to be made, as identifed in an e-mail to the sponsor dated July 7, 2009:

Outer Carton Drug Facts Label

1. Include the bulleted statement "asthma" under the *"**Warnings**"* subheading "**Ask a doctor before use if you have**".

2. Revise the current bulleted statement (b) (4) (b) (4) 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 in the April 29, 2009, final rule (*Federal Register* vol. 74, pages 19385 - 19409) and make the appropriate revisions.

2. Additional revisions that need to be made based on further review of labeling:

1. Outer Carton Label Outside Drug Facts

a. Principal Display Panel (PDP)

i. Remove the promotional statement (b) (4) This product contains none of the active ingredients in any of the (b) (4) products currently on the market. Therefore, comparing the product to (b) (4) (b) (4) may be confusing to consumers. This statement would be allowed if a label comprehension study demonstrated that consumers are not misled by the statement.

ii.. Remove or revise the word (b) (4) in the phrase (b) (4) (b) (4) does not provide useful information to consumers. If you want to indicate that the product dissolves quickly, provide data showing how quickly the films dissolve and express the mean dissolution time in seconds or minutes.

iii. Add "See new warnings information" per 21 CFR 201.326(b) (74 FR 19385 at 19409).

b. No designated space for expiration date

Expiration date must be included on the outer package (21 CFR 201.17).

c. No designated space for lot/control number

Lot/control number must be included on the outer package (21 CFR 201.10(i)(iii).

2. Outer Carton Drug Facts Label

a. ***Directions***

i. 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.

ii. Change the bulleted statement (b) (4) (b) (4) to "children under 16 years: ask a doctor." We believe this statement is easier to understand and is consistent with other labels for NSAID-containing products.

b. ***Inactive ingredients***

Change "sodium phosphate dibasic" to "dibasic sodium phosphate" (USP name)

3. Immediate Container (Pouch) Label

Revise according to comments provided for Outer Carton Label Outside Drug Facts.

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/s/

MICHAEL L KOENIG
08/27/2009

MATTHEW R HOLMAN
08/27/2009

Labeling Review Addendum for Nexcede (NDA 22-470)

Division of Nonprescription Regulation Development
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATES:	January 23, 2009 April 2, 2009 June 16, 2009 September 24, 2009
REVIEW DATE:	October 2, 2009
NDA/SUBMISSION TYPE:	22-470/N000
SPONSOR:	Novartis Consumer Health, Inc. 200 Kimball Drive Parsippany, NJ 07054-0622 Michael Kenny North American Regional Liaison Global Regulatory Affairs 973-503-7855 973-503-8486 (FAX)
DRUG PRODUCT:	Nexcede
ACTIVE INGREDIENT:	Ketoprofen, 12.5 mg
INDICATIONS:	Fever reducer; pain reliever
PHARMACOLOGICAL CATEGORY:	Internal analgesic
REVIEWER:	Michael L. Koenig, Ph.D.
TEAM LEADER:	Matthew R. Holman, Ph.D.

I. BACKGROUND

This is an addendum to the review filed on August 27, 2009. On September 4, 2009, we sent the sponsor a discipline review letter identifying the following deficiencies that needed correction:

- Remove the promotional statement (b) (4)
- Change dosage form from "oral (b) (4) to "oral soluble film."
- Decrease the font size and remove the word (b) (4) from the statement (b) (4)
- Remove or revise the statement (b) (4)
- Add "See new warnings information"statement.
- Designate spaces for the expiration date and lot/control number.
- Revise the word (b) (4) wherever it appears in Drug Facts.
- Make the following revisions under the heading ***Directions***
  - 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.
  - Revise the bulleted statemen (b) (4) (b) (4)

In response to the discipline review letter, the sponsor submitted revised labeling for all SKUs except the pouch containing the cinnamon-flavored product.

Submitted Labeling	**Representative of Following SKUs**
10-, 20-, and 40-count carton, cinnamon flavor	Not applicable
10-, 20-, and 40-count carton & pouch, peppermint flavor	Not applicable

The sponsor agreed with all labeling revisions except one. The sponsor did not agree to remove the promotional statement (b) (4) and proposed alternative labeling. The following comments are based, in part, on discussions at the Label Review team meeting held on September 30, 2009.

II. REVIEWER'S COMMENTS

1. We did not receive a copy of the label for a pouch containing cinnamon-flavored film and, therefore, cannot evaluate the labeling for this SKU.

2. The sponsor argued that it should not have to remove the statement (b) (4) (b) (4)" because the statement:
   - Provides reassurance to consumers that the product is produced by a well-known company
   - Is similar to statements on "other legacy and newly introduced OTC products"
   - Is mitigated by the placement of a note at the bottom of the PDP stating that the products do "not contain any of the active ingredients found in (b) (4) producst"

   The team determined that the sponsor must remove the promotional statement (b) (4) (b) (4) for the following reasons:

- The font style for (b) (4) and NEXCEDE are identical and some consumers may believe that (b) (4) is part of the trade name.
- Consumers may assume NEXCEDE is a novel dosage form of (b) (4)
- We do not believe the "note" at the bottom of the PDP is sufficient to prevent consumers from being misled into believing Nexcede contains the same active ingredients in (b) (4)

3. The sponsor must increase the font size of the statement "See new warnings information." 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. The inactive ingredient "dibasic sodium phosphate" is not in alphabetical order under the heading ***Inactive ingredients*** as required in 21 CFR 201.66(c)(8).

III. RECOMMENDATIONS

Send a discipline review letter to the sponsor advising the sponsor that it must 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 "does not contain any of the active ingredients found in (b) (4) products" for all labels. The submitted labeling is potentially misleading because many consumers will mistakenly believe that Nexcede contains the same active ingredients as (b) (4) Reference to (b) (4) can be included in labeling only if acceptable studies demonstrate that consumers are not misled by this statement.

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).

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/s/

MICHAEL L KOENIG
10/02/2009

MATTHEW R HOLMAN
10/02/2009

Labeling Review Addendum for Nexcede (NDA 22-470)

Division of Nonprescription Regulation Development
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION DATES:	January 23, 2009 April 2, 2009 June 16, 2009 September 24, 2009 October 29, 2009
REVIEW DATE:	November 9, 2009
NDA/SUBMISSION TYPE:	22-470/N000
SPONSOR:	Novartis Consumer Health, Inc. 200 Kimball Drive Parsippany, NJ 07054-0622 Michael Kenny North American Regional Liaison Global Regulatory Affairs 973-503-7855 973-503-8486 (FAX)
DRUG PRODUCT:	Nexcede
ACTIVE INGREDIENT:	Ketoprofen, 12.5 mg
INDICATIONS:	Fever reducer; pain reliever
PHARMACOLOGICAL CATEGORY:	Internal analgesic
REVIEWER:	Michael L. Koenig, Ph.D.
TEAM LEADER:	Matthew R. Holman, Ph.D.

I. BACKGROUND

This is an addendum to the review originally filed on August 27, 2009 and amended on October 2, 2009. On October 5, 2009, we sent comments on the labeling submitted on September 24, 2009, to the sponsor. In the e-mail message, we identified the following deficiencies that needed correction:

- Provide labeling for all SKUs
- Remove the statement (b) (4) and the statement "does not contain any of the active ingredients found in (b) (4) products."
- Increase the font size of the statement "See new warnings information."
- Ensure that "dibasic sodium phosphate" is in alphabetical order in the section ***Inactive ingredients***.

In response to the e-mail message, the sponsor submitted revised labeling for all SKUs:

Submitted Labeling	**Representative of Following SKUs**
10-, 20-, and 40-count carton & pouch, cinnamon flavor	Not applicable
10-, 20-, and 40-count carton & pouch, peppermint flavor	Not applicable

The sponsor agreed with all labeling revisions.

II. REVIEWER'S COMMENTS

The sponsor made all of the requested changes. The labeling is acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Nexcede labeling and request final printed labeling. The final printed labeling (FPL) must be identical to the submitted labeling: Nexcede pouch labels (cinnamon and peppermint flavors) and carton labels for 10-, 20-, and 40-count films (cinnamon and peppermint flavors) submitted on October 29, 2009.

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/

MICHAEL L KOENIG
11/08/2009

MATTHEW R HOLMAN
11/09/2009

Labeling Review Addendum for Nexcede (NDA 22-470)

Division of Nonprescription Regulation Development
Center for Drug Evaluation and Research • Food and Drug Administration

SUBMISSION (RECEIVED) DATES:	January 23, 2009 (January 26, 2009) April 2, 2009 (April 3, 2009) June 16, 2009 (June 17, 2009) September 25, 2009 (September 28, 2009) October 29, 2009 (October 30, 2009) November 11, 2009 (November 12, 2009)
REVIEW DATE:	November 15, 2009
NDA/SUBMISSION TYPE:	22-470/N000
SPONSOR:	Novartis Consumer Health, Inc. 200 Kimball Drive Parsippany, NJ 07054-0622 Michael Kenny North American Regional Liaison Global Regulatory Affairs 973-503-7855 973-503-8486 (FAX)
DRUG PRODUCT:	Nexcede
ACTIVE INGREDIENT:	Ketoprofen, 12.5 mg
INDICATIONS:	Fever reducer; pain reliever
PHARMACOLOGICAL CATEGORY:	Internal analgesic
REVIEWER:	Michael L. Koenig, Ph.D.
TEAM LEADER:	Matthew R. Holman, Ph.D.

I. BACKGROUND

This is an addendum to the review originally filed on August 27, 2009 and amended on October 2 and November 9, 2009. After we posted our addendum review in DARRTS on November 9, 2009, the CMC reviewer noticed that the ***Inactive ingredients*** section on the cinnamon-flavored products was incorrect. On November 10, 2009, the PM informed the sponsor in an e-mail message that it should change the coloring agent in peppermint-flavored 10-, 20-, and 40-count films from FD&C red#40 to FD&C blue#1.

In response to the e-mail message, the sponsor submitted revised labeling for the peppermint-flavored 10-, 20-, and 40-count film cartons.

In addition, the sponsor identified an "unintentional hairline" between the Allergy alert and Stomach bleeding warnings on both peppermint- and cinnamon-flavored 40-count film cartons. The sponsor removed the hairline.

Submitted Labeling	**Representative of Following SKUs**
10-, 20-, and 40-count carton, peppermint flavor	Not applicable
40-count carton, cinnamon flavor	Not applicable

II. REVIEWER'S COMMENTS

The sponsor corrected the deficiency on 10-, 20-, and 40-count film cartons (peppermint flavor). The sponsor also removed the unintentional hairline separating the Allergy alert and Stomach bleeding warnings on 40-count film cartons (peppermint and cinnamon flavors). The submitted labeling is acceptable.

III. RECOMMENDATIONS

Issue an **APPROVAL** letter to the sponsor for the submitted Nexcede labeling and request final printed labeling. The final printed labeling (FPL) must be identical to the submitted labeling: Nexcede pouch labels (cinnamon and peppermint flavors) and carton labels for 10- and, 20-count films (cinnamon flavor) submitted on October 29, 2009 and the carton labels for 10-, 20-, and 40-count films (peppermint flavor) and 40-count films (cinnamon flavor) submitted on November 11, 2009.

SUBMITTED LABELING

All approved labeling is appended. The pouch (peppermint and cinnamon flavor) and 10- and 20-count carton (cinnamon flavor) labeling was submitted on October 29, 2009. The 10- and 20-count carton (peppermint flavor) and the 40-count carton (peppermint and cinnamon flavor) labeling was submitted on November 11, 2009.

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/

MICHAEL L KOENIG
11/16/2009

MATTHEW R HOLMAN
11/17/2009

LABELING FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-470	Applicant: Novartis	Stamp Date: January 26, 2009
Drug Name: Trade name TBD **Primary:** (b) (4) **Alternate: Nexcede**	**NDA Type: Original submission**	

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comments
1	Is Index sufficient to locate necessary labeling?	X		
2	Has labeling for all SKUs been submitted (e.g., blister card, pouch, immediate container, carton label and package insert labeling, etc)?		X	The sponsor has provided representative labels for the 20-count cinnamon- and peppermint flavored products only. Request the sponsor provide labels for all SKUs it intends to market.
3	Does the submission contain the annotated specifications for the "Drug Facts" label?	X		
4	Is a new trade name being proposed? If multiple trade names, is the RLD trade name identified?	X		A trade name is being reviewed by DMEPA. RLD trade name is pending.

Any Additional Comments:
1. Request labels for all SKUs.

Michael L. Koenig, Ph.D. — March 13, 2009
Reviewing Interdisciplinary Scientist — Date

Matthew R. Holman, Ph.D. — March 13, 2009
Supervisor/Team Leader — Date

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/s/

Michael Koenig
3/13/2009 10:48:49 AM
INTERDISCIPLINARY

Matthew Holman
3/13/2009 12:19:43 PM
INTERDISCIPLINARY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 09, 2009

TO: Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation (DNCE)
Office of Nonprescription Products

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (DSI)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 9/10/09
Associate Director (Bioequivalence)
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-470 Ketoprofen 12.5 mg orally-[redacted (b) (4)] from Novartis Consumer Health, Inc.

At the request of DNCE, DSI audited the clinical and analytical portions of the following bioequivalence study:

Study Number: EDKT-PN-101 (Protocol Amendment 3)

Study Title: A Randomized, Open-Label, Crossover, Single-Center, Two Part Sequential Pharmacokinetic Study in Healthy Volunteers under Fasting Condition: Part I to demonstrate bioequivalence between one ketoprofen 12.5 mg orally-[redacted (b) (4)] and one ketoprofen 12.5 mg immediate release tablet and Part II to investigate dose proportionality properties of (one and two) ketoprofen orally-[redacted (b) (4)] and demonstrate bioequivalence between the Clinical Service Form and Final Market Image following single oral dose administration.

The audit of the clinical and analytical portions of this study was conducted at [redacted (b) (4)]. Following the clinical site inspection, (May 18-June 12,2009), and the analytical site inspection (August 24-28, 2009), Form FDA 483 was issued at each site(Attachments 1 and 2). Our evaluation of the significant findings are as follows:

Clinical Site: (b) (4)

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, for Part I of the protocol the following were noted:

a. Screening Subject 112/GLA was excluded from participating in the study due a high supine blood pressure (Inclusion Criteria # 6). The protocol section entitled "Inclusion Criteria for Part I and Part IT" documents normal vital signs as follows:
- Supine systolic blood pressure between 90 and 140 mmHg inclusive
- Supine diastolic blood pressure between 50 and 90 mmHg inclusive
The subject's screening supine blood pressure was 129/89 which did not exclude this subject from study participation.

b. Due to a laboratory accident, 19 out of 82 subjects had a re-collection of the final visit Hematology laboratory blood samples during the periods of 14 August 2007 to and including 16 August 2007. According to the protocol section entitled "Changes to the protocol" the Institutional Review Board (IRB) should be informed within 10 working days of a change to the protocol for subject safety. The IRB was not informed.

c. A repeat screening CBC was performed on Subject 1019IEOA 11 July 2007. According to the protocol section entitled "Changes to the protocol" the Institutional Review Board (IRB) should be informed within 10 working days of a change to the protocol for safety reasons. The IRB was not informed.

d. For Subject 1071IYO, repeat screening labs were performed 24 July 2007 as the subject's screening labs done on 5 July 2007 were out of the 21 day window for eligibility assessment. The study start date was 28 July 2007. The protocol section entitled "Description of study visits for Part I Visit 1 (Screening. Day -21 to -2)" documents the following: *"Subjects will be assessed/or eligibility within 21 days prior to study start."* According to the protocol section entitled "Changes to the protocol" the Institutional Review Board (IRB) should be informed

within 10 working days of a change to the protocol for safety reasons. The IRB was not informed.

Although the above observations represent protocol violation, with respect to subject exclusion (observation 1a) and failure to inform the IRB regarding protocol changes (observation 1b, 1c and 1d), these findings did not compromise subject safety and should not impact study integrity. Nevertheless, the firm should take corrective action such that the above issues are not repeated for future studies.

Analytical Site: (b) (4)

1. Analytical batches were accepted even when > 50% of the low QC samples (15 ng/ml) failed.

In bioequivalence study EDKT-PN-101 (Part-I), the analytical runs for analysis of plasma samples collected from subjects 1016, 1020 (8/19/07), 1023, 1025 (8/20/07), 1053, 1054 (8/24/07) and 1071, 1072 (8/20/07), had two of three QCs (66.7%) at 15 ng/mL failed the acceptance criteria (>15% deviation from the actual concentration. Except for these four runs in bioequivalence study EDKT-PN-101 (Part-I), all other runs were accepted properly.

2. Failure to conduct Incurred Sample Reproducibility (ISR) experiment for bioequivalence study EDKT-PN-101.

The reason for not conducting ISR experiment was not documented at the time when the study was conducted. Part I of the study was conducted between August 17-September 26, 2007 and Part II was conducted between April 11-22, 2008. As the firm had an active SOP (effective April 1, 2008) for ISR, ISR assessment should have been conducted.

3. Failure to provide proper criteria to analyst for selection of initial integration parameters used in all analytical runs.

During the study period, the site had no established criteria for selection of initial integration parameters for analytical runs. However, audit trail for each analytical run were available for audit electronically. The records in the audit trails confirmed that modifications made to initial integration parameters were used to process all chromatograms in each run. Moreover, no incidence suggesting attempts to bias acceptance of QC samples via changes in the initial integration parameters

were noted. During the inspection, the site was asked by DSI to re-integrate some of the passing analytical runs where initial integration parameters were different from other runs. No discrepancies were noted (i.e., modifications of initial integration parameters did not bias run acceptance). Thus, the above observation is not likely to have significant impact on outcomes of the studies.

Frontage Laboratories acknowledged the findings. They stated that they would implement corrective measures and introduce SOP incorporating use of initial integration parameters for analytical runs.

Conclusion:

Following the inspections at (b) (4), the Division of Scientific Investigations recommends the following:

1. The accuracy of the pharmacokinetic data from subjects 1016, 1020, 1023, 1025 1053, 1054, 1071 and 1072 in study EDKT-PN-101 (Part-I) cannot be assured (see Form 483 issued at analytical site- Item 1). Data from these subjects should be excluded from bioequivalence determination.

2. The firm should investigate and provide data to show that there is no ISR issue with the LC/MS/MS method used in study EDKT-PN-101 (see Form 483 issued at analytical site- Item 2).

At the close of the inspection, the firm indicated that they would provide a written response to all the Form 483 findings. As of the date of this memo, (b) (4) has not submitted a response. Upon receipt of the response, DSI will evaluate and forward a copy of our evaluation to DNCE.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

ADrugupta

Arindam Dasgupta, Ph.D.

Final Classifications:

VAI- (b) (4)

VAI- (b) (4)

cc: DARRTS
OND/ONP/DNCE/Leonard Segal/Patel
OC/DSI/Viswanathan/Dasgupta/Yau/Rivera-Lopez

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HFR-CE350/Harlan lisa.harlan@fda.hhs.gov
HFR-CE150/DIB

Draft: AD 9/09/09
Edits: MKY
DSI: (b) (4) O:\BE\EIRCOVER\22470nov.ket.doc
FACTS: (b) (4)

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/s/

ARINDAM DASGUPTA
09/11/2009
Dr. Martin Yau acting for Dr. Viswanathan

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 29, 2009

TO: Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation (DNCE)
Office of Nonprescription Products

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (DSI)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 9/30/09
Associate Director (Bioequivalence)
Division of Scientific Investigations (DSI)

SUBJECT: Review of [redacted] (b) (4) Response dated 09/17/09: Addendum to EIR Covering NDA 22-470 Ketoprofen 12.5 mg orally- [redacted] (b) (4) from Novartis Consumer Health, Inc.

At the request of DNCE, the Division of Scientific Investigations (DSI) audited the analytical portion of the following bioequivalence study at [redacted] (b) (4) Malvern, PA on August 24-28, 2009.

Study Number: EDKT-PN-101 (Protocol Amendment 3)

Study Title: A Randomized, Open-Label, Crossover, Single-Center, Two Part Sequential Pharmacokinetic Study in Healthy Volunteers under Fasting Condition: Part I to demonstrate bioequivalence between one ketoprofen 12.5 mg orally- [redacted] (b) (4) and one ketoprofen 12.5 mg immediate release tablet and Part II to investigate dose proportionality properties of (one and two) ketoprofen [redacted] (b) (4) and demonstrate bioequivalence between the Clinical Service Form and Final Market Image following single oral dose administration.

DSI's evaluation of the Form 483 items and our recommendation was forwarded to DNCE on 09/09/09. This addendum evaluate the response to the Form 483 provided by [redacted] (b) (4) on 09/17/09 (attachment 1).

Analytical Site: [redacted] (b) (4)

1. Analytical batches were accepted even when > 50% of the low QC samples (15 ng/ml) failed.

09/17/09 (b) (4) **Response:** (b) (4) acknowledges the finding but believes that there is little impact on study data.

09/29/09 DSI evaluation: DSI conclusion remains the same that the data from subjects 1016, 1020, 1023, 1025 1053, 1054, 1071 and 1072 in study EDKT-PN-101 (Part-I) should be excluded from bioequivalence determination.

2. Failure to conduct Incurred Sample Reproducibility experiment for bioequivalence study EDKT-PN-101.

09/17/09 (b) (4) **Response:** Although ISR SOP (SOP-510) was issued before the analysis of the Part II samples for study EDKT-PN-101 (April 41-22, 2008), it was not conducted as it was at the very beginning when (b) (4) began ISR testing.

09/29/09 DSI conclusion: The firm did not provide ISR data for ketoprofen. The firm needs to conduct ISR assessment to confirm the reproducibility of the LC/MS/MS method.

3. Failure to provide proper criteria to analyst for selection of initial integration parameters used in all analytical runs.

09/21/09 (b) (4) **Response:** The firm has implemented a new SOP (SOP-534, effective date April 20, 2009) which provides proper criteria to the analyst for selecting initial integration parameters.

09/29/09 DSI evaluation: The firm has implemented corrective action and the firm's response is acceptable.

Conclusions:

The firm did not provide ISR data for ketoprofen. The firm needs to conduct ISR assessment to confirm the reproducibility of the LC/MS/MS method.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Adasgupta

Arindam Dasgupta, Ph.D.

Final Classifications:

VAI- [redacted] (b) (4)

cc: DARRTS
OND/ONP/DNCE/Leonard Segal/Patel
OC/DSI/Viswanathan/Dasgupta/Yau/Rivera-Lopez
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OC/CDER/OTS/OCP/DCP2/suresh.doddapaneni@fda.hhs.gov

Draft: AD 9/29/09
Edits: MKY
DSI: [redacted] (b) (4) O:\BE\EIRCOVER\22470nov.ket.resp.doc
FACTS: [redacted] (b) (4)

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/s/

ARINDAM DASGUPTA
09/30/2009
Dr. Martin Yau acting for Dr. Viswanathan

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 2009

TO: Andrea Leonard Segal, M.D.
Director
Division of Nonprescription Clinical Evaluation (DNCE)
Office of Nonprescription Products

FROM: Arindam Dasgupta, Ph.D.
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 11/18/09
Acting Team Leader for Bioequivalence
GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations (DSI)

SUBJECT: 2nd Addendum to the Review of EIR Covering NDA 22-470 Ketoprofen 12.5 mg orally- (b) (4) sponsored by Novartis Consumer Health, Inc.

At the request of DNCE, the Division of Scientific Investigations (DSI) audited the analytical portion of a bioequivalence study (EDKT-PN-101) at (b) (4) (b) (4)

DSI's evaluation of the Form FDA-483 items and our recommendation was forwarded to DNCE on 09/09/09. A first addendum dated 09/29/09 evaluated the response to the Form 483 provided by (b) (4) on 09/17/09. This 2nd addendum evaluates the additional data submitted by the sponsor (11/17/09) in response to the request by DNCE (see attachment 1 for timeline and details of the above review activities).

DSI evaluation of data submitted by (b) (4) (b) (4)

At the request of the Agency, (b) (4) conducted Incurred Sample Reproducibility (ISR) assessment using 198 samples from study EDKT-PN-101 (Part II). The results demonstrate reproducibility (see data in Attachment 2) for the samples analyzed and the firm's response is acceptable. There were no stability issues with the samples analyzed.

Conclusion:

The analytical portion of the study EDKT-PN-101 can be accepted for review.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Arindam Dasgupta, Ph.D.

Final Classifications:

VAI- (b) (4)

cc: DARRTS
OND/ONP/DNCE/Leonard Segal/Patel
OC/DSI/Salewski/Dasgupta/Yau/Rivera-Lopez
OC/CDER/OTS/OCP/DCP2/suresh.naraharisetti@fda.hhs.gov
OC/CDER/OTS/OCP/DCP2/suresh.doddapaneni@fda.hhs.gov

Draft: AD 11/17/09
Edits: MKY
DSI: (b) (4); O:\BE\EIRCOVER\22470nov.ket.adden2.doc
FACTS: (b) (4)

Attachment 1

Analytical Site: (b) (4)

Form FDA-483 observation: Failure to conduct Incurred Sample Reproducibility (ISR) experiment for bioequivalence study EDKT-PN-101.

09/17/09 (b) (4) **Response:** Although ISR SOP (SOP-510) was issued before the analysis of the Part II samples for study EDKT-PN-101 (April 14-22, 2008), it was not conducted as it was at the very beginning when (b) (4) began ISR testing.

09/29/09 DSI conclusion: The firm did not provide ISR data for ketoprofen. The firm needs to conduct ISR assessment to confirm the reproducibility of the LC/MS/MS method.

10/16/09 Sponsor Response: (b) (4) would conduct an ISR experiment on Part II samples for study EDKT-PN-101 (April 14-22, 2008). (b) (4) would do the ISR assessment on 5% of study samples and also provide additional long term stability data.

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/

ARINDAM DASGUPTA
11/19/2009