

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-470

CHEMISTRY REVIEW(S)

NDA 22-470

**Nexcede
(ketoprofen oral soluble films)
12.5 mg**

Novartis Consumer Health, Inc.

Jane L. Chang, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III**

**For Division of Nonprescription Clinical Evaluation
HFD-560**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-470
2. REVIEW #: 1
3. REVIEW DATE: 15-SEP-2009
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
2/6/2007 Pre-IND Meeting Minutes	05-Mar-2007

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	23-JAN-2009
Amendment (Labeling)	26-JAN-2009
Amendment (Labeling)	02-APR-2009
Amendment (Labeling)	16-JUN-2009
Amendment (Quality)	03-AUG-2009
Amendment (Quality)	02-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Consumer Health, Inc.
Address:	200 Kimball Drive Parsippany, NJ 07054-0622
Representative:	Suzanne LoGalbo, R.Ph., JD
Telephone:	973-503-8095

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nexcede
- b) Non-Proprietary Name: ketoprofen
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):

Chemistry Review Data Sheet

- Chem. Type: 3 (New Dosage Form)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: internal analgesic

11. DOSAGE FORM: oral soluble film

12. STRENGTH/POTENCY: 12.5 mg

13. ROUTE OF ADMINISTRATION: Oral

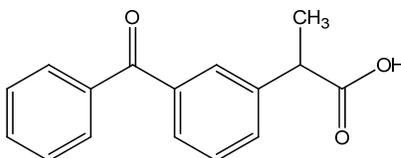
14. Rx/OTC DISPENSED: ___Rx ___Y___OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

___SPOTS product – Form Completed

___Y___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



3-Benzoyl- α -methylbenzeneacetic acid

CAS Number: [22071-15-4] $C_{16}H_{14}O_3$ MW = 254.28

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	6/16/2009	By J. Chang
	IV	(b) (4)	(b) (4)	1	Adequate	6/3/2009	By J. Chang
	III	(b) (4)	(b) (4)	1	Adequate	6/26/2009	By J. Chang
	II	(b) (4)	Ketoprofen	1	Adequate	6/26/2009	By J. Chang

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74,282	ketoprofen 12.5 mg oral (b) (4)
NDA	18-754*	Orudis
NDA	20-429*	Orudis KT, 12.5 mg

*Application Holder: Wyeth Consumer Healthcare. Novartis Consumer Health, Inc. does not have a right of reference.

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending*		
Pharm/Tox	N/A		
Biopharm	Granted the biowaiver request for ketoprofen oral soluble film, cinnamon flavor	8/31/2009	Albert (Tien-Mien) Chen
Methods Validation	N/A, according to the current ONDQA policy		
Office of Drug Safety	Unacceptable for (b) (4) as the tradename	4/24/2009	K. Taylor and C. Holquist
	Acceptable for "Nexcede" as the tradename	8/28/2009	Z. Oleszczuk, K. Taylor and D. Toyer
EA	Categorical exclusion (see review)	2/27/2009	J. Chang
Microbiology	N/A		

*As of the date of this review, a site recommendation from the Office of Compliance has not been made for the drug substance manufacturer, (b) (4). All other manufacturing and testing facilities are acceptable.

Executive Summary Section

The Chemistry Review for NDA 22-470

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product

Ketoprofen oral soluble film contains 12.5 mg of ketoprofen for immediate release oral administration. It is a transparent, thin film of approximate dimensions of 22 mm x 32 mm, imprinted with an identifying mark "NTPI" in white ink on one side. It is available in two flavors, peppermint (Formulation 1588-02) and cinnamon (Formulation 1589-01). The peppermint flavor drug product is aqua blue and has a peppermint aroma. The cinnamon flavor drug product is light red and has a cinnamon aroma. The drug products are indicated for the temporary relief of minor aches and pains due to: headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pains of arthritis; temporarily reduces fever. This dosage form lends itself for use with or without water.

The excipients in the peppermint flavor drug product include Hypromellose (b) (4) (b) (4) USP, sucralose NF, polyethylene glycol 400 NF, xylitol NF, maltodextrin NF, peppermint flavor, sodium hydroxide NF, acesulfame potassium NF, dibasic sodium phosphate NF, FD&C blue #1, and white imprint ink. The same excipients are used for the manufacture of the cinnamon flavor drug product except that the peppermint flavor and FD&C blue #1 are replaced with cinnamon flavor and FD&C red #40. The white imprint ink is used in trace amount and is

Executive Summary Section

composed

(b) (4)

An earlier peppermint formulation (1588-01) was used for human PK studies (EDFT-PN-101, Parts I and II). Subsequently, the commercial formulation (Formulation 1588-02) was used in a bridging bioequivalence study (EDFT-PN-101, Part II and EDKT-PN-102). In vitro comparative dissolution data for the clinical batch of the peppermint flavor (1588-02) and the cinnamon flavor (1589-01) showed similar dissolution profile, and therefore, support the biowaiver request for the cinnamon flavor (see the review by Biopharmaceutics reviewer, Dr. Tien-Mien Chen on 8/31/2009).

(b) (4)

Acceptable specifications have been provided to ensure product identity, strength, purity, and quality. The specifications includes description, identification (by RP-HPLC and UV), assay (RP-HPLC), uniformity of dosage units (RP-HPLC), dissolution (RP-HPLC), disintegration, related substances (RP-HPLC), water activity, and microbial limits. In addition, testing for residual (b) (4) is performed as in-process controls in-lieu of finished product test.

Acceptable information was provided for the single-use, multi-layer flexible laminated pouch as the primary packaging container. Multiple individual pouches are packaged together in a non-protective, standard folding carton as a secondary container.

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Acceptable stability data were provided for three primary batches each for the peppermint flavor and the cinnamon flavor drug products (b) (4)

One of these peppermint flavor batches was used in the bridging bioequivalence study. The data included up to 6 months at 40°C/75%RH and 18 months at 30°C/75%RH and 5°C. Except for the microbiological testing, the data showed little change and insignificant variability. (b) (4)

Stability data from special storage conditions including freeze/thaw, 50°C/ambient RH for one month, and photostability testing were provided. Except for the photostability study on the unpackaged samples, all other samples met the proposed specifications. The data support the proposed expiration dating period of 24 months when stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

Up to 6 months long-term and accelerated stability data were provided for the peppermint flavor and the cinnamon flavor drug products, one batch each at the commercial scale (b) (4)

The results showed little change and insignificant variability.

(2) Drug Substance

Ketoprofen is a well-established compendial drug substance whose structure has been fully elucidated. Ketoprofen has been approved in various formulations since 1986. These formulations include oral capsules (25 mg, 50 mg, and 75 mg, NDA 18-754), oral extended release capsules (100 mg, 150 mg, and 200 mg, NDA 19-816), and oral tablets (12.5 mg, NDAs 20-429 and 20-499). All of these products have been discontinued.

The drug substance is manufactured by (b) (4). Details of the manufacturing process and control of materials and ketoprofen are provided in (b) (4). This DMF has been reviewed by this reviewer and found to be adequate to support the NDA. The drug substance complies with the USP monograph. Testing for residual toluene and benzene are also included in the drug substance specification.

B. Description of How the Drug Product is Intended to be Used

For adult and children 16 years and over, allow 1 oral soluble film to dissolve on tongue every 4 to 6 hours while symptoms persist. If pain or fever do not get better in 1 hour, 1 more soluble film may be taken. Do not take more than 2 soluble films in any 4 to 6 hours period and 6 films in any 24 hour period. The smallest effective dose should be used. Do not give to children under age 16 unless directed by a doctor. Do not take longer than 10 days, unless directed by a doctor.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until all issues are resolved.

III. Administrative

- A. Reviewer's Signature**
electronically signed in DFS
- B. Endorsement Block**
electronically signed in DFS
- C. CC Block**
entered electronically in DFS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22470	ORIG-1	NOVARTIS CONSUMER HEALTH INC	KETOPROFEN ORAL-ORAL (b) (4)
NDA-22470	ORIG-1	NOVARTIS CONSUMER HEALTH INC	KETOPROFEN ORAL-ORAL (b) (4)
NDA-22470	ORIG-1	NOVARTIS CONSUMER HEALTH INC	KETOPROFEN ORAL-ORAL (b) (4)
NDA-22470	ORIG-1	NOVARTIS CONSUMER HEALTH INC	KETOPROFEN ORAL-ORAL (b) (4)
NDA-22470	ORIG-1	NOVARTIS CONSUMER HEALTH INC	KETOPROFEN ORAL-ORAL (b) (4)
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/

JANE L CHANG
09/15/2009

MOO JHONG RHEE
09/15/2009
Chief, Branch III

NDA 22-470

**Nexcede
(ketoprofen oral soluble films)
12.5 mg**

Novartis Consumer Health, Inc.

Jane L. Chang, Ph.D.

Review Chemist

**Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III**

**For Division of Nonprescription Clinical Evaluation
HFD-560**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 22-470
2. REVIEW #: 2
3. REVIEW DATE: 13-NOV-2009
4. REVIEWER: Jane L. Chang
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	23-JAN-2009
Amendment (Labeling)	26-JAN-2009
Amendment (Labeling)	02-APR-2009
Amendment (Labeling)	16-JUN-2009
Amendment (Quality)	03-AUG-2009
Amendment (Quality)	02-SEP-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (Labeling)	25-SEP-2009
Amendment (Labeling)	29-OCT-2009
Amendment (Labeling)	11-NOV-2009

7. NAME & ADDRESS OF APPLICANT:

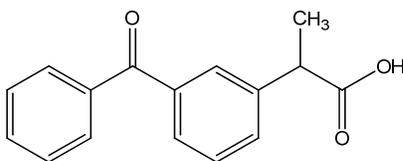
Name:	Novartis Consumer Health, Inc.
Address:	200 Kimball Drive Parsippany, NJ 07054-0622
Representative:	Suzanne LoGalbo, R.Ph., JD
Telephone:	973-503-8095

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Nexcede
- b) Non-Proprietary Name: ketoprofen

Chemistry Review Data Sheet

- c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3 (New Dosage Form)
 - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: nonsteroidal anti-inflammatory drug
11. DOSAGE FORM: oral soluble film
12. STRENGTH/POTENCY: 12.5 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: ___Rx___ ___Y___ OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
___ ___ SPOTS product – Form Completed
___Y___ Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



3-Benzoyl- α -methylbenzeneacetic acid
CAS Number: [22071-15-4] $C_{16}H_{14}O_3$ MW = 254.28

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	Natural Peppermint Flavor WONF 699170	1	Adequate	6/16/2009	By J. Chang
	IV	(b) (4)	(b) (4)	1	Adequate	6/3/2009	By J. Chang
	III	(b) (4)	(b) (4)	1	Adequate	6/26/2009	By J. Chang
	II	Boehringer Ingelheim	Ketoprofen	1	Adequate	6/26/2009	By J. Chang

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74,282	ketoprofen 12.5 mg oral (b) (4)
NDA	18-754*	Orudis
NDA	20-429*	Orudis KT, 12.5 mg

*Application Holder: Wyeth Consumer Healthcare. Novartis Consumer Health, Inc. does not have a right of reference.

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	11/13/2009	M. Stock
Pharm/Tox	N/A		
Biopharm	Granted the biowaiver request for ketoprofen oral soluble film, cinnamon flavor	8/31/2009	Albert (Tien-Mien) Chen
Methods Validation	N/A, according to the current ONDQA policy		
Office of Drug Safety	Unacceptable for (b) (4) as the tradename	4/24/2009	K. Taylor and C. Holquist
	Acceptable for "Nexcede" as the tradename	8/28/2009	Z. Oleszczuk, K. Taylor and D. Toyer
EA	Categorical exclusion (see review)	2/27/2009	J. Chang
Microbiology	N/A		

Executive Summary Section

The Chemistry Review for NDA 22-470

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The labels have adequate information as required. The Office of Compliance has made an "Acceptable" site recommendation. Therefore, from a CMC perspective, this NDA is recommended for "Approval".

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

(1) Drug Product

Ketoprofen oral soluble film contains 12.5 mg of ketoprofen for immediate release oral administration. It is a transparent, thin film of approximate dimensions of 22 mm x 32 mm, imprinted with an identifying mark "NTPI" in white ink on one side. It is available in two flavors, peppermint (Formulation 1588-02) and cinnamon (Formulation 1589-01). The peppermint flavor drug product is aqua blue and has a peppermint aroma. The cinnamon flavor drug product is light red and has a cinnamon aroma. The drug products are indicated for the temporary relief of minor aches and pains due to: headache, the common cold, toothache, muscular aches, backache, menstrual cramps, and minor pains of arthritis; temporarily reduces fever. This dosage form lends itself for use with or without water.

The excipients in the peppermint flavor drug product include Hypromellose (b) (4) (b) (4) USP, sucralose NF, polyethylene glycol 400 NF, xylitol NF, maltodextrin NF, peppermint flavor, sodium hydroxide NF, acesulfame potassium NF, dibasic sodium phosphate NF, FD&C blue #1, and white imprint ink. The same excipients are used for the manufacture of the cinnamon flavor drug product except that the peppermint flavor and FD&C blue #1 are replaced with cinnamon flavor and FD&C red #40. The white imprint ink is used in trace amount and is composed of (b) (4)

Executive Summary Section

An earlier peppermint formulation (1588-01) was used for human PK studies (EDFT-PN-101, Parts I and II). Subsequently, the commercial formulation (Formulation 1588-02) was used in a bridging bioequivalence study (EDFT-PN-101, Part II and EDKT-PN-102). In vitro comparative dissolution data for the clinical batch of the peppermint flavor (1588-02) and the cinnamon flavor (1589-01) showed similar dissolution profile, and therefore, support the biowaiver request for the cinnamon flavor (see the review by Biopharmaceutics reviewer, Dr. Tien-Mien Chen on 8/31/2009).

(b) (4)

Acceptable specifications have been provided to ensure product identity, strength, purity, and quality. The specifications includes description, identification (by RP-HPLC and UV), assay (RP-HPLC), uniformity of dosage units (RP-HPLC), dissolution (RP-HPLC), disintegration, related substances (RP-HPLC), water activity, and microbial limits. In addition, testing for residual (b) (4) is performed as in-process controls in-lieu of finished product test.

Acceptable information was provided for the single-use, multi-layer flexible laminated pouch as the primary packaging container. Multiple individual pouches are packaged together in a non-protective, standard folding carton as a secondary container.

Acceptable stability data were provided for three primary batches each for the peppermint flavor and the cinnamon flavor drug products (b) (4)

Executive Summary Section

(b) (4) One of these peppermint flavor batches was used in the bridging bioequivalence study. The data included up to 6 months at 40°C/75%RH and 18 months at 30°C/75%RH and 5°C. Except for the microbiological testing, the data showed little change and insignificant variability. (b) (4)

Stability data from special storage conditions including freeze/thaw, 50°C/ambient RH for one month, and photostability testing were provided. Except for the photostability study on the unpackaged samples, all other samples met the proposed specifications. The data support the proposed expiration dating period of 24 months when stored at 25°C (77°F), excursions permitted to 15-30°C (59-86°F).

Up to 6 months long-term and accelerated stability data were provided for the peppermint flavor and the cinnamon flavor drug products, one batch each at the commercial scale (b) (4)

The results showed little change and insignificant variability.

(2) Drug Substance

Ketoprofen is a well-established compendial drug substance whose structure has been fully elucidated. Ketoprofen has been approved in various formulations since 1986. These formulations include oral capsules (25 mg, 50 mg, and 75 mg, NDA 18-754), oral extended release capsules (100 mg, 150 mg, and 200 mg, NDA 19-816), and oral tablets (12.5 mg, NDAs 20-429 and 20-499). All of these products have been discontinued.

The drug substance is manufactured by (b) (4). Details of the manufacturing process and control of materials and ketoprofen are provided in (b) (4). This DMF has been reviewed by this reviewer and found to be adequate to support the NDA. The drug substance complies with the USP monograph. Testing for residual (b) (4) are also included in the drug substance specification.

B. Description of How the Drug Product is Intended to be Used

For adult and children 16 years and over, allow 1 oral soluble film to dissolve on tongue every 4 to 6 hours while symptoms persist. If pain or fever do not get better in 1 hour, 1 more soluble film may be taken. Do not take more than 2 soluble films in any 4 to 6 hours period and 6 films in any 24 hour period. The smallest effective dose should be used. Do not give to children under age 16 unless directed by a doctor. Do not take longer than 10 days, unless directed by a doctor.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

All facilities have acceptable site recommendations. All labels have the required information.

III. Administrative

- A. Reviewer's Signature**
electronically signed in DFS
- B. Endorsement Block**
electronically signed in DFS
- C. CC Block**
entered electronically in DFS

(D) 7 pages of CMC has been withheld in full immediately following this page as B4(CCI/TS)



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/

JANE L CHANG
11/13/2009

MOO JHONG RHEE
11/16/2009
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division: Division of Nonprescription Clinical Evaluation
NDA: 22-470
Applicant: Novartis Consumer Health, Inc.
Stamp Date: Jan. 26, 2009
PDUFA Date: Nov. 26, 2009
Trademark: (b) (4) or Nexcede™
Established Name: Ketoprofen
Dosage Form: Oral (b) (4)
Route of Administration: Oral
Indication: Temporarily relieves of minor aches and pains and temporarily reduces fever

PAL: Shulin Ding, Ph.D.

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues

A. Summary

This NDA is submitted by Novartis Consumer Health under section 505(b)(2) of the Federal Food Drug and Cosmetic Act in support of the nonprescription marketing of (b) (4) (ketoprofen) 12.5 mg oral (b) (4) for temporary relief of minor aches and pains and reduction of fever. The referenced drugs are Orudis NDA 18-715 (ketoprofen capsules 25, 50 and 75 mg) for pre-clinical and clinical safety, and Orudis KT NDA 20-429 (ketoprofen tablets 12.5 mg) for efficacy. Novartis conducted two bioequivalence studies to support this (b)(2) submission.

The CMC information of the proposed drug substance (ketoprofen USP) is referenced to (b) (4) (b) (4) has not been reviewed for an NDA/ANDA.

The proposed drug product is a rapidly dissolving, immediately release, thin film with a dimension of 22mm x 32 mm. Two flavors are proposed: peppermint and cinnamon. The peppermint one is transparent, aqua blue. The cinnamon one is transparent, light red. The film, weighing 70 mg each, is imprinted with a white ink and individually packaged in a single use, multi-layer, laminated aluminum pouch.

The applicant evaluated the bioequivalence of the to-be-marketed, peppermint flavored formulation to Orudis KT in the pivotal BE studies. Although one part of the first BE study was done using a non-to-be-marketed peppermint formulation, the applicant has addressed this formulation issue by conducting a bridging study to demonstrate that the two peppermint formulations are bioequivalent.

The cinnamon flavored, to-be-marketed formulation was not used in the BE studies. The applicant provides comparative in-vitro drug release profile to support its marketing in the absence of clinical studies.

In addition to 12.5 mg of ketoprofen per film, the to-be-marketed formulations contains the following excipients: hypromellose (2910, 4-6 centipoise), USP, sucralose, NF; polyethylene glycol 400, NF; xylitol, NF; maltodextrin, NF; sodium hydroxide, NF; acesulfame potassium, NF, sodium phosphate dibasic, USP; FD&C blue #1; FD&C red #40; purified water, USP; acetone, NF; peppermint flavor, cinnamon flavor, and white imprint ink. There are no novel excipients except the two flavors.

The proposed commercial manufacturing scale is (b) (4) and (b) (4) for peppermint and cinnamon formulations, respectively. The designated commercial sites for manufacturing and packaging are (b) (4). The former is responsible for bulk film manufacturing. The latter is responsible for imprinting/cutting/packaging. These two sites are also the manufacturing/packaging sites of the clinical supplies and registration stability batches. The manufacturing process consists of the following steps (b) (4)

Stability data provided in the initial submission to support an expiration dating period of 24 months at storage temperature of 20-25°C in US and below 30°C for other countries include long term (30°C/75% RH) data of 12 months and accelerated temperature (40°C/75% RH) data of 6 months from (b) (4) batches for each formulation. To support (b) (4) as an alternative site for imprinting/cutting/packaging, one full scale batch for each formulation has been manufactured and put on stability, but only initial data have been provided in the NDA. The applicant also conducted special studies (freeze/thaw, 50°C, and photostability) to support storage/handling of the proposed product.

B. Critical issues for review

Drug Substance Impurity Profile

- This is the first time (b) (4) is referenced to support the approval of an NDA/ANDA. (b) (4) is not the same DMF referenced by Orudis KT tablets (NDA 20-429, DMF 3605) and Orudis capsules (NDA 18-754). It is possible that the impurity profile of (b) (4) may be different from that of Orudis NDAs.

Dosage Form Nomenclature

- The applicant proposes “oral (b) (4) as the dosage form, which is not recognized by CDER Data Standard Manual and the Orange Book.

The proposed product does not fit the definition of (b) (4) given in CDER Data Stand Standard Manual because it is not narrow. According to the Manual, (b) (4) is a long narrow piece of material. The proposed product fits the

Manual's definition for "soluble film" (a thin layer or coating which is susceptible to being dissolved when in contact with a liquid). The current version of Orange Book does not recognize "soluble film" although "extended release film" is enlisted. A buccal product with "soluble film" as the dosage form was approved last year by OND (NDA 22-266). (b) (4)
(b) (4) OGD has approved to-date only extended release films.

Drug Product Manufacturing

- The bulk film is manufactured by (b) (4). It is shipped to packaging sites located in Puerto Rico. (b) (4)
(b) (4). Note that the hold time of the bulk film in the clinical and registration stability batches was only 1-2 months. Therefore, one year of bulk hold time is not supported by registration stability data.
- It is unclear how the drug product manufacturing site receives and releases drug substance for drug product manufacturing. It is unclear how drug product packaging site receives and packaging site receives and release the bulk film for imprinting/cutting/packaging.

Drug Product Specification

- Microbiological test is proposed to be performed for the (b) (4)
(b) (4). The reduced testing may be acceptable if the proposal is site specific. This is because three different sites are involved in manufacturing and packaging. Microbiological property of a batch which is packaged at one site can not and should not be used to represent that of the batches packaged at a different site. A similar proposal exists in NDA 22-327 (Prevacid 24 HR) which is currently under review.

Drug Product Stability

- The applicant proposes two different laminated aluminum pouches for packaging but only one of them is evaluated in the registration stability studies. No stability batches have been made using the second pouch.
- The (b) (4) level in the product is reported as pass/fail without actual concentrations.

Potential Interference with Assay of Cinnamon formulation

(b) (4)

Biowaiver

- The applicant provides a dissolution comparison study report to justify the waiver of BE studies for the cinnamon flavored formulation. The report should be critically reviewed to make sure that biowaiver criteria are met. A consult request has been sent to ONDQA Biopharm review team.

C. Comments for 74-Day Letter

The following comments are to be conveyed to the applicant in the 74-day letter:

1. Provide representative samples [REDACTED] (b) (4) for dosage form evaluation.

D. Comments/Recommendation

This NDA is **fileable** from chemistry, manufacturing and controls (CMC) perspective. The major review issues include drug substance impurity profile, dosage form nomenclature, drug product manufacture, drug product specification, stability, specificity of assay method, and dissolution comparison for biowaiver.

GMP inspections have been requested. The drug substance manufacturing site is in Italy. The drug product manufacturing/packaging sites are in [REDACTED] (b) (4)

Shulin Ding, , Ph.D.
Pharmaceutical Assessment Lead, Branch III

Moo-Jhong Rhee, , Ph.D.
Chief, Branch III

Filing Checklists

A. Administrative Checklists

YES	NO		Comments
x		On its face, is the section organized adequately?	
x		Is the section indexed and paginated adequately?	
x		On its face, is the section legible?	
x		Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	
x		Has an environmental assessment report or categorical exclusion been provided?	

B. Technical Checklists

1. Drug Substance: Ketoprofen USP referenced to (b) (4)

	x	Does the section contain synthetic scheme with in-process parameters?	
	x	Does the section contain structural elucidation data?	
	x	Does the section contain specifications?	
	x	Does the section contain information on impurities?	
	x	Does the section contain validation data for analytical methods?	
	x	Does the section contain container and closure information?	
	x	Does the section contain stability data?	

2. Drug Product

x		Does the section contain manufacturing process with in-process controls?	
x		Does the section contain quality controls of excipients?	
x		Does the section contain information on composition?	
x		Does the section contain specifications?	
x		Does the section contain information on degradation products?	
x		Does the section contain validation data for analytical methods?	
x		Does the section contain information on container and closure systems?	
x		Does the section contain stability data with a proposed expiration date?	
x		Does the section contain information on labels of container and cartons?	
x		Does the section contain tradename and established name?	

C. Review Issues

x		Has all information requested during the IND phases, and at the pre-NDA meetings been included?	
	x	Is a team review recommended?	

x		Are DMFs adequately referenced?	
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/s/

Shulin Ding
3/19/2009 03:28:24 PM
CHEMIST

Moo-Jhong Rhee
3/20/2009 08:57:05 AM
CHEMIST
Chief, Branch III



Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22470/000	Sponsor:	NOVARTIS CONS
Org. Code:	560		200 KIMBALL DR
Priority:	3S		PARSIPPANY, NJ 070540622
Stamp Date:	26-JAN-2009	Brand Name:	KETOPROFEN ORAL (b) (4)
PDUFA Date:	26-NOV-2009	Estab. Name:	
Action Goal:		Generic Name:	KETOPROFEN ORAL (b) (4)
District Goal:	27-SEP-2009	Product Number; Dosage Form; Ingredient; Strengths	

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	J. CHANG	Review Chemist	301-796-1973
	S. DING	Team Leader	301-796-1349

Overall Recommendation: ACCEPTABLE on 13-NOV-2009 by M. STOCK (HFD-320) 301-796-4753

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:
 Responsibilities: (b) (4)

Profile: NOT ELSEWHERE CLASSIFIED OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-MAY-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: (b) (4) AADA:
 (b) (4)

Responsibilities: (b) (4)

Profile: (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-NOV-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION



Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)
 DMF No: AADA:
 Responsibilities: (b) (4)
 Profile: NOT ELSEWHERE CLASSIFIED OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 13-MAR-2009
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE

Establishment: CFN: (b) FEI:
 ()
 ()
 DMF No: AADA:
 Responsibilities: (b) (4)
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 17-MAR-2009
 Decision: ACCEPTABLE
 Reason: BASED ON PROFILE
 Profile: NOT ELSEWHERE CLASSIFIED OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 10-JUL-2009
 Decision: ACCEPTABLE
 Reason: DISTRICT RECOMMENDATION



Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: 1911445 FEI: 1911445
 NOVARTIS CONSUMER HEALTH INC
 10401 HWY 6
 LINCOLN, NE 685179626
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
 FINISHED DOSAGE RELEASE TESTER
 FINISHED DOSAGE STABILITY TESTER
Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-MAR-2009
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) FEI: (b) (4)
 (b) (4)
 (b) (4)
DMF No: AADA:
Responsibilities: (b) (4)
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-AUG-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
