CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-122

CHEMISTRY REVIEW(S)

NDA 22-122

Voltaren® Gel
(diclofenac sodium topical gel)

Novartis Consumer Health, Inc.

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science
Branch V

CMC REVIEW OF NDA 22-122
For the Division of Anesthesia, Analgesia, and Rheumatology Products (HFD-170)

Table of Contents

CMC Review Data Sheet

1. NDA 22-122

2. REVIEW #: 2

3. REVIEW DATE: 15-Oct-2007

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed in CMC Review #1	Document Date
Original NDA Submission	19-Dec-2006
Amendment (BC) (information regarding manufacturing sites)	12-Jan-2007
Amendment (BC) (drug product samples)	27-Feb-2007
Amendment (BZ) (proposed trade names)	04-Apr-2007
Amendment (BL) (revised package insert in response to FDA 5/25/07 physician labeling rule comments)	11-Jun-2007
Amendment (BC) (fragrance composition from manufacturer)	01-Jul-2007
Amendment (BC) (response to 7/2/07 CMC IR)	12-Jul-2007
Amendment (BP) (response to 6/15/07 CMC and pharm/tox IR about impurities)	13-Jul-2007
Revised package insert in response to 7/12/07 CMC IR	27-Aug-2007*
Revised container labels and carton labeling in response to 7/12/07 CMC IR	07-Sep-2007*
Revisions to drug product specification (———) in response to 9/14/07 CMC IR	17-Sep-2007*
Revisions to drug product specification (tightened acceptance criteria for ——— and a statement for reduced frequency tests) in response to 9/18/07 CMC and pharm/tox IR	19-Sep-2007*

*These revisions were received by e-mails during CMC review #1. These revisions have been officially included in the 9/27/07 amendment (see below).

6. SUBMISSION(S) BEING REVIEWED (in this review):

Subject of this Review	Document Date
Amendment (BZ)	27-Sep-2007
Revisions to container labels and carton labeling	11-Oct-2007*

*Received by e-mail.

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Consumer Health, Inc.
Address:	200 Kimball Drive Parsippany, New Jersey 07054-0622
Representative:	Filomena Gesek Director, Regulatory Affairs US Therapeutic Areas 200 Kimball Drive Parsippany, New Jersey 07054-0622
Telephone:	(973) 503-7645

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Voltaren® Gel
b) Non-Proprietary Name: diclofenac sodium topical gel
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (new formulation, per the new MAPP 7500.3)
- Submission Priority: S

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

Referenced Listed Drug: NDA 21-005, Solarez (diclofenac sodium topical gel) 3%, Bradley Pharmaceuticals, Inc., for information on data pertaining to dermal carcinogenicity and photocodermal carcinogenicity.

10. PHARMACOL. CATEGORY: anti-inflammatory agent

11. DOSAGE FORM: gel

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

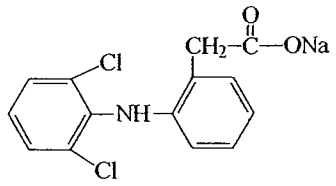
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__ Not a SPOTS product

CMC Review Data Sheet

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

Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, monosodium salt



$C_{14}H_{10}Cl_2NNaO_2$ MW 318.13

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	IV			4*	N/A		See note below*
/	III			4	N/A		**
	III			4	N/A		**

[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)

CMC Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,334	diclofenac sodium topical gel
NDA	19-201, 20-254, 20-142	diclofenac sodium drug substance

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1/29/07	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	The nonproprietary name "diclofenac sodium topical gel" is acceptable.	7/13/07	See note below*
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	The proposed proprietary name "Voltaren Gel" is acceptable	7/13/07	Walter Fava
EA	Categorical exclusion (see review)		Sue-Ching Lin
Microbiology	N/A		

* The nonproprietary name of the drug product is "diclofenac sodium topical gel" as the expression of the strength is based on the amount of the salt form (diclofenac sodium). The nonproprietary name should include the route of administration (refer to the established names in the USP). This nonproprietary name has been concurred by Dr. Rik Lostritto, Division Director and Chair of CDER Labeling and Nomenclature Committee, Dr. Ravi Harapanhalli, Branch Chief, and Ms. Yana Mille, Regulatory Director of Office of Pharmaceutical Science.

The CMC Review for NDA 22-122

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, this NDA is recommended for approval.

The following comments are requested to be added in the action letter:

1. The revised comparability protocol as amended on July 12, 2007 may be used in the proposed post-approval changes described in the NDA and the changes may be reported in an annual report.
2. An expiration dating period of 36 months is granted for the drug product when stored at controlled room temperature.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The diclofenac sodium drug substance used in the drug product (diclofenac sodium topical gel, 1%) is the same active pharmaceutical ingredient that is used in Voltaren® (diclofenac sodium delayed-release tablets), a prescription drug product marketed in the United States and approved by FDA in 1988 under NDA 19-201. CMC information for the diclofenac sodium drug substance is provided by cross-reference to the relevant CMC drug substance information contained in NDA 19-201 for Voltaren® (diclofenac sodium delayed-release tablets).

The applicant's specification for the drug substance includes all USP requirements for diclofenac sodium plus additional Novartis' tests for _____ tests. The acceptance criteria for the impurities are tighter than those required in USP for diclofenac sodium drug substance.

However, based on the chemical structures for the related substances, it was found that, except — all the impurities — contain structure alert — for genotoxicity. The NDA had provided some, but insufficient, genotoxicity study results for the impurities (negative Ames test results for — and negative Ames test or chromosome aberration assay results for —. Therefore, the applicant was requested in the 6/15/07 joint CMC and pharm/tox letter that such impurities be controlled to — total daily intake or be toxicologically qualified with negative findings in two in-vitro genotoxicity studies (point mutation and clastogenicity assays). In response to the FDA request, the 9/27/07 amendment provided additional in-vitro genotoxicity test results for the impurities. Dr. Leshin, the pharm/tox reviewer, has indicated during the telephone discussions and the 10/11/07 team meeting that the submitted genotoxicity data are deemed acceptable. Refer to the pharm/tox review for details. Based on the long history (nearly 20 years) of use of the oral tablets and the submitted genotoxicity data in the original NDA and its amendments, the qualification of these impurities are deemed acceptable.

(2) Drug Product

The drug product is a topical gel containing 1% of diclofenac sodium. It is packaged in aluminum tubes with a — screw cap (100-g and 20-g). —

All of the excipients are USP/NF ingredients, with the exception of the following two excipients: cocoyl caprylocaprate, which meets the Ph. Eur. requirements, and fragrance / —

Cocoyl caprylocaprate and — have not been used in FDA approved drugs. Adequate controls and toxicology data are provided in the NDA to support the use of these two excipients in this drug product.

One of the critical parameters in the manufacturing process is —

—. Therefore, an in-process control is performed to ensure —

— Other in-process control testing includes —

. The in-process tests are appropriate for a topical gel.

A comparability protocol was proposed for process changes related to — The protocol includes a description of planned changes, specific studies to be performed, specific

tests to be performed and acceptance criteria, and data to be reported. In response to the FDA request, the protocol was revised to include an in-vitro release test to compare the release rate of the product prepared by the proposed changes with the product prepared by the prechange process as described in section VII of the "Guidance for Industry, SUPAC-SS Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; in Vitro Release Testing and In Vivo Bioequivalence Documentation."

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

Voltaren® Gel is a topical nonsteroidal anti-inflammatory drug (NSAID) indicated for the [redacted] joints amendable to topical treatment, such as the hands and knees. The drug product will be dispensed by prescription only. It is intended to be applied to the affected area at a dose of 2 grams for the hands or 4 grams for the knees 4 times daily.

The submitted drug product stability data include 36-month stability data at 25°C/60%RH and 30°C/60%RH storage conditions and 6-month data at 40°C/75%RH storage conditions on three primary stability batches manufactured at the proposed commercial manufacturing site. The stability data support the proposed 36-month expiration period for the drug product stored at controlled room temperature. The drug product should be kept from freezing because a phase separation of the drug product was observed in aluminum tubes when subjected to freeze/thaw cycles.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information for the drug substance was entirely referenced to NDA 19-201. The specification is deemed acceptable to support the use of the drug substance in this NDA.

All the inactive ingredients are USP/NF materials except cocoyl caprylocaprate and [redacted] The specifications of the non-compendial excipients are adequate. The pharm/tox reviewers have concluded that the submitted toxicology information is adequate to support the use of these two excipients. Refer to the pharm/tox review for details.

The manufacture process and the specification are adequate to ensure consistency in the quality of the drug product. The packaging materials were found to be adequate.

The Office of Compliance has issued an "acceptable" recommendation for each facility used for manufacturing and control of the drug substance and drug product.

Executive Summary Section

The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proposed proprietary name, Voltaren® Gel. The container and carton labeling that was submitted in the original NDA had a large graphic design located to the right of the proprietary name. In response to the DMETS 8/15/07 comments, the prominence of the graphic design has been decreased. The revised graphic design was deemed acceptable by DMETS.

The nonproprietary name of the drug product is "diclofenac sodium topical gel" as the expression of the strength is based on the amount of the salt form (diclofenac sodium). The nonproprietary name should include the route of administration (refer to the established names in the USP). This nonproprietary name has been concurred by Dr. Rik Lostritto, Division Director and Chair of CDER Labeling and Nomenclature Committee, Dr. Ravi Harapanhalli, Branch Chief, and Ms. Yana Mille, Regulatory Director of Office of Pharmaceutical Science.

The revised container labels and carton labeling, as provided in the 10/11/07 e-mail, have responded adequately to the CMC comments, including the prominence (boldness) of the nonproprietary name and the addition of a "keep from freezing" statement.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Ravi Harapanhalli, Ph.D., Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DFS

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Sue Ching Lin
10/15/2007 05:25:23 PM
CHEMIST

Ravi Harapanhalli
10/16/2007 09:12:21 AM
CHEMIST

NDA 22-122

Voltaren® Gel
(diclofenac sodium topical gel)

Novartis Consumer Health, Inc.

Sue-Ching Lin

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-marketing Assessment and Manufacturing Science
Branch V

CMC REVIEW OF NDA 22-122
For the Division of Anesthesia, Analgesia, and
Rheumatology Products (HFD-170)

Table of Contents

CMC Review Data Sheet

1. NDA 22-122

2. REVIEW #: 1

3. REVIEW DATE: 19-Sep-2007

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 64,334 Pre-NDA meeting	21-Jul-2006
IND 64,334 CMC End-of-Phase 2 meeting	01-June-2005
IND 64,334 CMC review of original IND	05-Dec-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	19-Dec-2006
Amendment (BC) (information regarding manufacturing sites)	12-Jan-2007
Amendment (BC) (drug product samples)	27-Feb-2007
Amendment (BZ) (proposed trade names)	04-Apr-2007
Amendment (BL) (revised package insert in response to FDA 5/25/07 physician labeling rule comments)	11-Jun-2007
Amendment (BC) (fragrance composition from manufacturer)	01-Jul-2007
Amendment (BC) (response to 7/2/07 CMC IR)	12-Jul-2007
Amendment (BP) (response to 6/15/07 CMC and pharm/tox IR about impurities)	13-Jul-2007
Revised package insert in response to 7/12/07 CMC IR	27-Aug-2007*
Revised container labels and carton labeling in response to 7/12/07 CMC IR	07-Sep-2007*
Revisions to drug product specification (— in response to 9/14/07 CMC IR	17-Sep-2007*
Revisions to drug product specification (tightened acceptance criteria for — and a statement for reduced frequency tests) in response to 9/18/07 CMC and pharm/tox IR	19-Sep-2007*

*These revisions were received by e-mails. Official amendments for these revisions are to be submitted by the end of September.

CMC Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Novartis Consumer Health, Inc.
Address:	200 Kimball Drive Parsippany, New Jersey 07054-0622
Representative:	Filomena Gesek Director, Regulatory Affairs US Therapeutic Areas 200 Kimball Drive Parsippany, New Jersey 07054-0622
Telephone:	(973) 503-7645

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Voltaren® Gel
b) Non-Proprietary Name: diclofenac sodium topical gel
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 5 (new formulation, per the new MAPP 7500.3)
- Submission Priority: S

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

Referenced Listed Drug: NDA 21-005, Solarez (diclofenac sodium topical gel) 3%, Bradley Pharmaceuticals, Inc., for information on data pertaining to dermal carcinogenicity and photocodermal carcinogenicity.

10. PHARMACOL. CATEGORY: anti-inflammatory agent

11. DOSAGE FORM: gel

12. STRENGTH/POTENCY: 1%

13. ROUTE OF ADMINISTRATION: topical

14. Rx/OTC DISPENSED: __√__ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__√__ Not a SPOTS product

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,334	diclofenac sodium topical gel
NDA	19-201, 20-254, 20-142	diclofenac sodium drug substance

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	1/29/07	S. Adams
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMETS	The proposed proprietary name "Voltaren Gel" is acceptable	7/13/07	Walter Fava
EA	Categorical exclusion (see review)		Sue-Ching Lin
Microbiology	N/A		

The CMC Review for NDA 22-122

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, this NDA is recommended for approval pending resolution of remaining labeling issues (more prominence (boldness) of nonproprietary name, addition of "keep from freezing" caution statement, and revisions on SPL information), which are expected to be resolved during the upcoming labeling negotiation with the applicant. The stability data support the proposed 36-month expiration period for the drug product stored at controlled room temperature. However, the drug product should be kept from freezing because a phase separation of the drug product was observed in aluminum tubes when subjected to freeze/thaw cycles.

The applicant is expected to submit additional in-vitro genotoxicity test results for the impurities at the end of September. However, these results are not approvability issues. In discussions with the pharm/tox reviewers, the qualification of the impurities in the drug substance and drug product is deemed acceptable.

All of the manufacturing, control, and packaging facilities are acceptable as recommended by the Office of Compliance.

The following comments are requested to be added in the action letter:

1. The revised comparability protocol as amended on July 12, 2007 may be used in the proposed post-approval changes described in the NDA and the changes may be reported in an annual report.
2. An expiration dating period of 36-months is granted for the drug product when stored at controlled room temperature.
3. You are reminded of your agreement in the amendment dated July 13, 2007 to submit the results of in vitro genotoxicity assessment of impurities and revised specification sheet for the drug product by the end of September, 2007.

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

None

II. Summary of CMC Assessments

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

(1) Drug Substance

The diclofenac sodium drug substance used in the drug product (diclofenac sodium topical gel, 1%) is the same active pharmaceutical ingredient that is used in Voltaren® (diclofenac sodium delayed-release tablets), a prescription drug product marketed in the United States and approved by FDA in 1988 under NDA 19-201. CMC information for the diclofenac sodium drug substance is provided by cross-reference to the relevant CMC drug substance information contained in NDA 19-201 for Voltaren® (diclofenac sodium delayed-release tablets).

The applicant's specification for the drug substance includes all USP requirements for diclofenac sodium plus additional Novartis' tests for [redacted] tests. The acceptance criteria for the impurities are tighter than those required in USP for diclofenac sodium drug substance.

However, based on the chemical structures for the related substances, it was found that, except [redacted], all the impurities [redacted] contain structure alert [redacted], for genotoxicity. The NDA had provided some, but insufficient, genotoxicity study results for the impurities (negative Ames test results for [redacted] and negative Ames test or chromosome aberration assay results for [redacted]. Therefore, the applicant was requested in the 6/15/07 joint CMC and pharm/tox letter that such impurities be controlled to [redacted] total daily intake or be toxicologically qualified with negative findings in two in-vitro genotoxicity studies (point mutation and clastogenicity assays). In response to the FDA request, the applicant agreed in the 7/13/07 amendment to provide additional in-vitro genotoxicity study results for the structural alert impurities. However, in discussions with pharm/tox reviewers on 9/14/07, the pharm/tox reviewers had concluded that, based on the long history (nearly 20 years) of use of the oral tablets and the available genotoxicity data in the NDA, the additional genotoxicity study results, which are expected to be submitted at the end of September, are not required for the approval of this NDA. This is documented in the Pharm/Tox review in the DFS.

(2) Drug Product

The drug product is a topical gel containing 1% of diclofenac sodium. It is packaged in aluminum tubes with a [redacted] screw cap (100-g and 20-g) [redacted]

All of the excipients are USP/NF ingredients, with the exception of the following two excipients: cocoyl caprylocaprate, which meets the Ph. Eur. requirements, and fragrance ——

Cocoyl caprylocaprate and —— , have not been used in FDA approved drugs. Adequate controls and toxicology data are provided in the NDA to support the use of these two excipients in this drug product.

One of the critical parameters in the manufacturing process is ——

—— Therefore, an in-process control is performed to ensure ——

. Other in-process control testing includes ——

. The in-process tests are appropriate for a topical gel.

A comparability protocol was proposed for process changes related to ——

The protocol includes a description of planned changes, specific studies to be performed, specific tests to be performed and acceptance criteria, and data to be reported. In response to the FDA request, the protocol was revised to include an in-vitro release test to compare the release rate of the product prepared by the proposed changes with the product prepared by the prechange process as described in section VII of the "Guidance for Industry, SUPAC-SS Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; in Vitro Release Testing and In Vivo Bioequivalence Documentation."

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

Voltaren® Gel is a topical nonsteroidal anti-inflammatory drug (NSAID) indicated for the —— oints, such as the hands and knees. The drug product will be dispensed by prescription only. It is intended to be applied to the affected area at a dose of 2 grams for the hands or 4 grams for the knees 4 times daily.

The submitted drug product stability data include 36-month stability data at 25°C/60%RH and 30°C/60%RH storage conditions and 6-month data at 40°C/75%RH storage conditions on three primary stability batches manufactured at the proposed commercial manufacturing site. The stability data support the proposed 36-month expiration period for the drug product stored at controlled room temperature. The drug product should be kept from freezing because a phase separation of the drug product was observed in aluminum tubes when subjected to freeze/thaw cycles.

C. Basis for Approvability or Not-Approval Recommendation

The CMC information for the drug substance was entirely referenced to NDA 19-201. The specification is deemed acceptable to support the use of the drug substance in this NDA.

All the inactive ingredients are USP/NF materials except cocoyl caprylocaprate and [redacted]. The specifications of the non-compendial excipients are adequate. The pharm/tox reviewers have concluded that the submitted toxicology information is adequate to support the use of these two excipients. Refer to the pharm/tox review for details.

The manufacture process and the specification are adequate to ensure consistency in the quality of the drug product. The packaging materials were found to be adequate.

The Office of Compliance has issued an "acceptable" recommendation for each facility used for manufacturing and control of the drug substance and drug product.

The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proposed proprietary name, Voltaren® Gel. The labeling deficiencies that were identified by this reviewer have been conveyed to the applicant. The remaining issues (more prominent nonproprietary name, addition of "keep from freezing" statement due to phase separation observed in the temperature cycling studies, and revisions on SPL information) will need to be resolved during the upcoming labeling negotiation with the applicant.

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Ravi Harapanhalli, Ph.D., Branch Chief, Branch V, ONDQA

C. CC Block: entered electronically in DFS

63 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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

/s/

Sue Ching Lin
9/20/2007 12:18:56 PM
CHEMIST

Ravi Harapanhalli
9/20/2007 12:44:13 PM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment
Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170)

OND Division:	Anesthesia, Analgesia and Rheumatology Products
NDA:	22-122
Applicant:	NOVARTIS
Stamp date:	December 20, 2006
PDUFA Date:	October 20, 2007
Trademark:	Voltaren —
Established Name:	Diclofenac Sodium topical gel 1%
Dosage Form:	Gel
Route of Administration:	Topical
Indication:	—
	—
Pharmaceutical Assess. Lead:	Ali Al-Hakim, Ph.D.
ONDQA Fileability:	YES √ NO___
Comments for 74-Day Letter:	YES ___ NO √

Summary, Critical Issues and Comments

A. Summary

This application is submitted under 505 (b) (2) regulations based on the fact that diclofenac sodium, the active ingredient for this NDA, has been used in various formulations in many approved drug products. However, the sponsor listed Voltaren (diclofenac sodium) Enteric Coated Tablets as the referenced drug. The NDA described the drug product as a diclofenac sodium topical gel, 1%, in an opaque, white gel base. The proposed product will be indicated for use by adults, for — joints amenable to — treatment, such as the hands and knees.

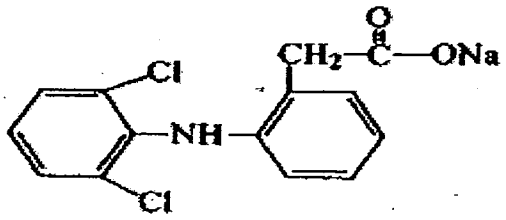
The sponsor reported that drug product has been developed based on the approved drug product, Voltaren® 1% Emulgel® which contains 1.16% of diclofenac diethylamine. Voltaren® 1% Emulgel® (Voltaren® is approved for marketing in more than 100 countries worldwide)

The mechanism of action of diclofenac is thought to be related to prostaglandin synthetase inhibition. Prostaglandins act as messenger molecules in the process of inflammation. This is a similar mechanism to other nonsteroidal anti-inflammatory drugs (NSAID).

B. Review, Comments and Recommendations

Drug Substance Synthesis/Manufacturing Process

Diclofenac sodium drug substance is 2-[2, 6-dichlorophenyl] amino] benzeneacetic acid, monosodium salt. Chemical structure of the drug substance is shown below



The applicant reported that diclofenac sodium drug substance (benzene-acetic acid derivative) used in diclofenac sodium topical gel, 1% is the same active pharmaceutical ingredient that is used in Voltaren (diclofenac sodium) Enteric Coated Tablets, approved under NDA 19-201. Therefore, the applicant referenced NDA 19-201 for all CMC drug substance information. Hence, the reviewer needs to examine and review the referenced NDA, related DMF (s) and any subsequent amendments, supplements and updates for any new and significant CMC information related to the drug substance. Particular attention should be paid to any changes in the approved manufacturing process, tests and acceptance criteria.

Drug Product

The following table contains composition/components of the drug product

	[illegible]		
Diclofenac sodium *(Diclofenac sodium)*	USP/Ph. Eur.	Active ingredient	1.00
Isopropyl alcohol *(Isopropyl alcohol)*	USP/Ph. Eur.		
Propylene glycol *(Propylene glycol)*	USP/Ph. Eur.		
Cocoyl caprylocaprate	Ph. Eur.		
Mineral oil	USP/Ph. Eur.		
Polyoxyl 20 cetostearyl ether	NF/Ph. Eur.		
Carbomer Homopolymer Type C	NF/Ph. Eur.		
Strong ammonia solution	NF/Ph. Eur.		
Perfume	In-house standard		
Purified water *(Water, purified)*	USP/Ph. Eur.		

[1] Component names in italics are the names referenced in European Pharmacopoeia.

The reviewer should examine and evaluate the excipients especially the [illegible] ingredients.

Evaluation should focus on grade (e.g. USP, GRAS, etc), manufacturing, composition, process controls and sources. The reviewer may also need to examine any new/novel excipients with respect to FDA approved excipients or if they have been used for different route of administration). In this case, details of the manufacturing process and safety qualification limit need to be assessed in collaboration with the pharmacology reviewer.

Manufacturing process

The maior step of the manufacturing process of the drug product involves [illegible]

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Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		All sites were entered in the EES
6	Has an environmental assessment report or categorical exclusion been provided?	√		
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?			To be determined by the reviewer
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			References were provided to previous NDAs
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		Validation Report
15	Is a separate microbiological section included?	√		l l
16	Have all consults been identified and initiated?			Pharm/Tox Biopharm Statistics OCP/CDRH/CBER LNC √ DMETS/ODS Microbiology

Have all DMF References been identified? Yes (√) No ( )

DMF Number	Holder	Description	LOA Included	Status
l	l	l	√	
			√	

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/s/

Ali Al-Hakim
1/30/2007 01:08:21 PM
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Ravi Harapanhalli
2/2/2007 06:39:31 PM
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