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

/s/

Parinda Jani
6/15/2007 10:56:16 AM

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, May 09, 2007 3:03 PM
To: 'filomena.gesek@novartis.com'
Cc: Tornetta, Lauren
Subject: NEW Info.Request/Clinical/NDA 22122/5.9.07
Importance: High

Dear Filomena:

The Clinical Team has the following information/clarification requests for NDA 22-122:

1. Clarify whether the **Special Dermal Safety Studies (VOSG-PN-108, VOSG-PN-111 and VOSG-PE-112)** were performed with the to-be-marketed formulation of DSG1%.
2. Clarify if a **Photosensitivity Study** was performed as part of the developmental program of DSG 1%.

Please provide responses to the above requests as soon as possible; however, not later than Friday, May 11, 2007. Provide the response to me via email and as an official submission to the NDA.

Kindly confirm receipt of this email.

Best,

Lauren

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Div. of Anesthesia, Analgesia and Rheum. Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Phone: (301) 796-2246
Fax: (301) 796-9722 / 9723
Email: lauren.tornetta@fda.hhs.gov

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

/s/

Lauren Tornetta
6/15/2007 01:26:42 PM
CSO



NDA 22-122

INFORMATION REQUEST LETTER

Novartis Consumer Health, Inc.
200 Kimball Drive
Parsippany, New Jersey 07054-0622

Attention: Filomena Gesek
Director, Regulatory Affairs, U.S., Therapeutic Areas

Dear Ms. Gesek:

Please refer to your December 19, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Voltaren® (diclofenac sodium), Topical Gel.

We are reviewing the label provided in your submission for adherence to the format proposed by the Physician's Labeling Rule. Provided below is a list of comments based upon Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review Divisions. We request a prompt written response in order to continue our evaluation of your NDA.

The following issues/deficiencies have been identified in your proposed labeling.

1. Delete the — throughout the entire label.
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. Under Highlights the drug name must be followed by the drug's dosage form and route of administration and should be written as follows:

Voltaren® (diclofenac sodium), Topical Gel

4. Under Highlights the Initial U.S. Approval date should be the date of the first diclofenac approval in the U.S.
5. The below statement under Highlights **DOSAGE AND ADMINISTRATION** should be changed as follows: Total — dose should not exceed 32 g per day, over all affected joints.

6. The first statement under Highlights **DOSAGE AND ADMINISTRATION**,
_____ should be deleted due to redundancy.
7. The following statements under _____ should be moved and bulleted under the
corresponding _____ **INDICATION AND USAGE** sections:

/ / / / /
 - Not evaluated for use on joints of the spine, hip, or shoulder.
8. The statement _____ (3)" should be bulleted under Highlights **DOSAGE FORMS AND STRENGTHS** for format consistency.
9. Under both Highlights and FPI **ADVERSE REACTIONS**, do not refer to adverse reactions as _____." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at <http://www.fda.gov/cder/guidance>.
10. Under both FPI: Contents and FPI **DRUG INTERACTIONS**, subsection 7.2 must be changed. Create subsection headings that identify the content. Avoid using the word _____ for a subsection heading.
11. Under both the FPI: Contents and FPI **CLINICAL PHARMACOLOGY**, the Pharmacokinetics sub-section should be labeled 12.3 not 12.2.
12. Under FPI: Contents **NONCLINICAL TOXICOLOGY**, subsection 13.1 must be changed as follows:

13.1 Carcinogenesis, Mutagenesis, Impairment of _____ fertility
13. Under FPI: Contents and FPI, delete section 15 References, since none are listed.
14. A horizontal line must separate the FPI: Contents and FPI. [See 21 CFR 201.57(d)(2)]
15. Under FPI **PATIENT COUNSELING INFORMATION**, the heading must be changed to include the section number, 17. Also, the heading statement must appear in **bold-faced type** and in the same font size as other FPI headings.

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions, call Lauren Tornetta, Regulatory Project Manager, at (301) 796-2246.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Parinda Jani
5/25/2007 11:42:00 AM

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anesthesia, Analgesia and Rheumatology Products

Application Number: NDA 22-122
Name of Drug: Voltaren® (diclofenac topical sodium gel) 1%
Applicant: Novartis Consumer Health, Inc.

Material Reviewed:

Submission Date(s): December 19, 2006

Receipt Date(s): December 20, 2006

Submission Date of Structure Product Labeling (SPL): December 19, 2006

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

1. Delete the — throughout the entire label.
2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3. Under Highlights the drug name must be followed by the drug's dosage form and route of administration and should be written as follows:

Voltaren® (diclofenac sodium), Topical Gel

4. Under Highlights the Initial U.S. Approval date should be the date of the first diclofenac approval in the U.S.
5. The below statement under Highlights **DOSAGE AND ADMINISTRATION** should be changed as follows:

Total dose should not exceed 32 g per day, over all affected joints.

6. The first statement under Highlights **DOSAGE AND ADMINISTRATION** should be deleted due to redundancy.
7. The following statements should be moved and bulleted under the corresponding **INDICATION AND USAGE** sections:

- Not evaluated for use on joints of the spine, hip, or shoulder.

8. The statement should be bulleted under Highlights **DOSAGE FORMS AND STRENGTHS** for format consistency.
9. Under both Highlights and FPI **ADVERSE REACTIONS**, do not refer to adverse reactions as " ". Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at <http://www.fda.gov/cder/guidance>.
10. Under both FPI: Contents and FPI **DRUG INTERACTIONS**, subsection 7.2 must be changed. Create subsection headings that identify the content. Avoid using the word " " as the title for a subsection heading.
11. Under both the FPI: Contents and FPI **CLINICAL PHARMACOLOGY**, the Pharmacokinetics sub-section should be labeled 12.3 not 12.2.

12. Under FPI: Contents **NONCLINICAL TOXICOLOGY**, subsection 13.1 must be changed as follows:
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of — . fertility
13. Under FPI: Contents and FPI, delete section 15 References, since none are listed.
14. A horizontal line must separate the FPI: Contents and FPI. [See 21 CFR 201.57(d)(2)]
15. Under FPI **PATIENT COUNSELING INFORMATION**, the heading must be changed to include the section number, 17. Also, the heading statement must appear in **bold-faced type** and in the same font size as other FPI headings.

Recommendations

Labeling revisions, deficiencies and issues should be communicated to the Sponsor with a request that updated labeling be submitted to the application.

Lauren P. Tornetta, M.S.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

NDA 22-122
PM label review-PLR
Page 4 of 4

Drafted: LPT 05/09/07

Revised/Initialed:
PJani: 05/14/07

Finalized: LTornetta: 05/21/07
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Lauren Tornetta
5/21/2007 10:38:27 AM
CSO

Please Sign

Parinda Jani
5/21/2007 01:52:00 PM
CSO

From: Tometta, Lauren
Sent: Monday, April 23, 2007 1:54 PM
To: 'filomena.gesek@novartis.com'
Subject: NEW INFO.REQUEST/NDA 22-122
Importance: High

Filomena,

The Division has made the following information requests for NDA 22-122:

- Please provide a sample of the actual dosing card that will be enclosed with each tube of Voltaren Gel. The actual configuration of the dosing card is needed so that the review team can see how it will be used by patients.
- Also, please provide an acknowledgement that the proposed container labels and carton labeling submitted in December 2006 which say "Voltaren , are the labels and labeling that you want reviewed by DMETS for the proposed proprietary name "Voltaren Gel".

Kindly confirm receipt of the above requests and provide a response 1) to me via email; 2) to the NDA via official submission as soon as possible. However, it should not be later than Monday, April 30, 2007.

Thanks,
Lauren

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Phone: 301-796-2246
Email: lauren.tornetta@fda.hhs.gov

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Lauren Tornetta
4/24/2007 11:07:38 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Friday, March 23, 2007 11:20 AM
To: 'filomena.gesek@novartis.com'
Cc: Tornetta, Lauren
Subject: New Clinical Request/NDA 22-122/3.23.07

Importance: High

Dear Filomena:

We acknowledge your response to our request to provide detailed information on how the severity of skin AE's were determined and classified into mild, moderate and severe.

You responded that "No explicit instructions were provided to investigators regarding the severity grading of adverse events and that it was left to the investigator's clinical judgment to assign a grade".

Our follow up question and requests are as follows:

- 1) Was any *named* dermatological AE classification system used in characterizing the skin AE's ?
- 2) Please provide further information on the occurrence of skin infections and /or skin breakdowns in response to application of DSG or vehicle.
- 3) Please provide any photographic documentation of severe skin AE's, subjects diagnosed with application site dermatitis who discontinued treatment, and additionally those identified as blister/bullous lesions of any severity occurring in response to the application of DSG or vehicle.

We appreciate your prompt response to this request. Please send your response to me via email, followed by an official submission to the NDA.

Best,
Lauren

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

/s/

Lauren Tornetta
3/23/2007 11:25:35 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Monday, March 19, 2007 11:39 AM
To: 'filomena.gesek@novartis.com'
Cc: Tornetta, Lauren
Subject: Info.Request #5/Clinical/NDA 22122

Importance: High

Dear Filomena:

The Clinical Team would like to thank you for the timely response for information regarding the "All skin AE's in the major safety population".

A follow up request:

Please provide detailed information on how the severity of skin AE's were determined and classified into mild, moderate and severe.

Your prompt response to this request is appreciated. Please respond to me *via email* followed by an official, archival submission no later than Monday, March 26th, 2007.

Best,
Lauren

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Lauren Tornetta
3/19/2007 11:45:27 AM
CSO

B

7 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, March 07, 2007 2:33 PM
To: Tornetta, Lauren
Subject: FW: NEW: Info.Request/Clinical/NDA 22-122
Importance: High

Filomena,

As requested by the Clinical Team, please populate the following table:

1) TABLE SHOWING THE INCIDENCE OF *ALL SKIN AE's* IN THE POOLED MAJOR SAFETY POPULATION

Frequency of all skin AE's @ 0 to < 3 months exposure (N=)		Frequency of all skin AE's @ 3 to < 6 months exposure (N=)		Frequency of all skin AE's @ 6 to <9 months exposure (N=)		Frequency of all skin AE's @ 9-12 months exposure (N=)	
DSG (n, %)	VEHICLE (n, %)	DSG (n, %)	VEHICLE (n, %)	DSG (n, %)	VEHICLE (n, %)	DSG (n, %)	VEHICLE (n, %)

Response to this request is appreciated at your earliest convenience but, no later than **Wednesday, March 14, 2007**.

Kindly send me the response via email in addition to sending an official, archival submission.

Thank You,
 Lauren

Lauren P. Tornetta, M.S.
 Regulatory Project Manager
 Division of Anesthesia, Analgesia and Rheumatology Products
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research
 10903 New Hampshire Ave.
 Bldg. 22 Room 3119
 Silver Spring, MD 20993-0002
 Phone: (301) 796-2246
 Fax: (301) 796-9722 / 9723
 Email: lauren.tornetta@fda.hhs.gov

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Lauren Tornetta
3/7/2007 02:35:55 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Wednesday, February 28, 2007 11:12 AM
To: 'filomena.gesek@novartis.com'
Cc: Tornetta, Lauren
Subject: Info.Request#4/Clinical/NDA 22-122
Importance: High

Hi Filomena:

Request #4/Clinical:

1. Please provide or direct us to the location in the NDA submission where we can find the list of all study centers and investigators that enrolled patients into the studies (by study), and the number of patients enrolled from each site.

The medical officer would greatly appreciate any responses that you can provide at your earliest convenience. Please provide response via email to me followed by electronic archival submission.

Also, please **EMAIL** me your response to information requests #1 & #2 by COB today.

Kindly confirm receipt of this email and subsequent requests.

Thank You,

Lauren

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Thursday, February 22, 2007 9:49 AM
To: 'filomena.gesek@novartis.com'
Subject: Info.Request#3/Chemistry/NDA 22-122
Importance: High

Dear Filomena:

The Chemistry team has made the below request regarding NDA 22-122:

- Provide drug product samples packaged in the proposed container closure systems. These samples are for the reviewers to examine the drug product only, not for method validation purpose.

Please provide a response to this request as soon as possible, but no later than **Friday, March 2, 2007**.

Also, kindly provide an update on Information Requests #1(Clinical) and #2 (Pharm/Tox).

Best,
Lauren

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg. 22 Room 3119
Silver Spring, MD 20993-0002
Phone: (301) 796-2246
Fax: (301) 796-9722 / 9723
Email: lauren.tornetta@fda.hhs.gov

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

/s/

Lauren Tornetta
2/22/2007 09:53:20 AM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Tuesday, February 20, 2007 3:43 PM
To: 'filomena.gesek@novartis.com'
Cc: Tornetta, Lauren
Subject: Info.Request #2/NDA 22-122/Pharm-Tox
Importance: High

Dear Filomena:

The Division has the below request for pharmacology/toxicology information regarding NDA 22-122:

1. For the pharmacology and toxicology studies of Module 4 provide a listing that identifies which studies were submitted to support the previous NDAs (19-201 for Voltaren[®], NDA 20-142 for Cataflam[®], and NDA 20-254 Voltaren-XR[®]) and IND 64,334.

Please respond to this request as soon as possible, but no later than **Tuesday, February 27, 2007**. Kindly confirm receipt of this email.

Best Regards,
Lauren

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg. 22 Room 3119
Silver Spring, MD 20993-0002
Phone: (301) 796-2246
Fax: (301) 796-9722 / 9723
Email: lauren.tornetta@fda.hhs.gov

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

/s/

Lauren Tornetta
2/20/2007 03:48:32 PM
CSO

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Friday, February 16, 2007 2:24 PM
To: 'filomena.gesek@novartis.com'
Subject: Info. Request/NDA 22-122
Importance: High

Dear Filomena:

The Division has the below requests for information regarding NDA 22-122:

Please inform us of the state of **Trial VOSG-PN-316**, including the following:

- 1) Number of subjects randomized to each treatment group thus far.
- 2) What is your anticipated date for completion of enrollment?
- 3) What is your anticipated date for completion of the study?
- 4) When do you anticipate submitting the study results to the Agency?

Please respond to these requests as soon as possible but, no later than **Friday, Feb. 23, 2007**.

Best Regards,
Lauren

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg. 22 Room 3119
Silver Spring, MD 20993-0002
Phone: (301) 796-2246
Fax: (301) 796-9722 / 9723
Email: lauren.tornetta@fda.hhs.gov

2/16/2007

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

/s/

Lauren Tornetta
2/16/2007 04:19:41 PM
CSO



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

NDA FILING REVIEW

NDA: 22-122

Drug Name: Voltaren (Diclofenac Sodium Topical Gel 1%)

Indication(s): _____

Applicant: Novartis

Stamp Date: December 19, 2006

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Ruthanna Davi

Concurring Reviewer: Dionne Price

Medical Division: Division of Anesthesia, Analgesia, and Rheumatology Products

Medical Reviewer: Neville Gibbs, Medical Officer
Ellen Fields, Medical Team Leader

Project Manager: Lauren Tornetta

Keywords: NDA filing review

Introduction

The sponsor has submitted the results of two key studies (VOSG-PH-310 and VOSG-PE-315, hereafter referred to as 310 and 315, respectively) in support of the efficacy of Voltaren for _____

_____ Study 310 was a randomized, double-blind, placebo-controlled, parallel group, multi-center study of the efficacy and safety of Voltaren for osteoarthritis of the knee. Study 315 was the same such study for osteoarthritis of the hand.

Study 310

According to the sponsor, the purpose of study 310 was to demonstrate the efficacy and safety of Voltaren to treat the symptoms of osteoarthritis of the knee. Efficacy was defined as superiority compared to vehicle on all three primary endpoints at the week 12 (hence no multiplicity correction is required). The primary efficacy outcomes were the following.

- (1.) WOMAC 3.1 Likert scale pain index at visit 6
- (2.) WOMAC 3.1 Likert scale physical functioning index at visit 6
- (3.) VAX on global disease rating at visit 6

The sponsor provided statistical analyses of these endpoints utilizing the modified efficacy subpopulation (MES) which was defined as a subset of the intent-to-treat group. According to the sponsor, the MES analysis population was defined and designated to be used for the primary efficacy analysis prior to unblinding. However, it appears that the proportion of ITT subjects excluded from the MES population is quite large (about 50%) and therefore the integrity of the random treatment assignment may be compromised in the MES analysis population. This issue is not a filing issue but it will be examined further in the course of the statistical review of the application.

Statistical methods used for the primary efficacy analysis include implementation of an analysis of covariance model with the change from baseline in each of the endpoints described above as the response variable. On its face, this is not objectionable and is acceptable for filing. This issue will be further assessed as part of the statistical review of the application. The sponsor also provides sensitivity analyses to assess the impact of missing data in the primary efficacy analysis and other issues. Subgroup analyses by gender, age, and race are also provided.

The electronic data sets including the efficacy data for study 310 that are provided in the submission appear adequate for review of the study.

Study 315

According to the sponsor, the purpose of study 310 was to demonstrate the efficacy and safety of Voltaren to treat the symptoms of osteoarthritis of the hand. Efficacy was defined as superiority compared to vehicle on all three primary endpoints at weeks 4 and 6 using a hierarchical approach. The primary efficacy outcomes were the following.

- (1.) OA pain intensity in the target hand
- (2.) Total AUSCAN score in the target-hand (unweighted mean of all 15 questions)
- (3.) Global rating of disease activity

The sponsor provided statistical analyses of these endpoints utilizing the intent-to-treat group, the protocol specified analysis group for the primary efficacy analysis. Statistical methods used for the primary efficacy analysis include implementation of an analysis of covariance model with the change from baseline in each of the endpoints described above as the response variable. On its face, this is not objectionable and is acceptable for filing. This issue will be further assessed as part of the statistical review of the application. The sponsor also provides additional analyses which according to the sponsor help to validate the final ANCOVA model used in the efficacy analysis and address the impact of certain decisions regarding the study which were made

prior to unblinding. These issues will be further evaluated as part of the statistical review. Subgroup analyses by gender, age, and race are also provided.

The electronic data sets including the efficacy data for study 310 that are provided in the submission appear adequate for review of the study.

Reviewer's Conclusion

From a statistical perspective the application is sufficient for filing.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Ruth Davi
2/8/2007 04:48:09 PM
BIOMETRICS

Dionne Price
2/8/2007 05:07:45 PM
BIOMETRICS
concur

Tornetta, Lauren

From: Tornetta, Lauren
Sent: Monday, January 08, 2007 2:17 PM
To: 'filomena.gesek@novartis.com'
Subject: Info.Request/Chemistry/NDA 22-122
Importance: High

Dear Filomena:

As per my voicemail, the Division has requested the following information regarding manufacturing sites:

1. Please provide an identical table to Table 1-1 entitled "Sites of manufacturing, packaging, quality control and stability testing" on page 3 of the "Drug Product Manufacturers" (3.2.P.3.1 section) for the **DRUG SUBSTANCE** (3.2.S). Ensure to indicate activities performed at each site, i.e. Manufacturing, Packaging, Quality Control, Stability, as done in Table 1-1 of the Drug Product manufacturers.
2. Provide a detailed list of contacts (as done in section 3 "Contact persons" in the Drug Product Section (3.2.P.3.1) for the **Drug SUBSTANCE**.

Kindly provide this information as soon as possible but, no later than C.O.B Friday, January 12, 2007. If you have any questions, do not hesitate to contact me.

Thanks,
Lauren

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Bldg. 22 Room 3119
Silver Spring, MD 20993-0002
Phone: (301) 796-2246
Fax: (301) 796-9722 / 9723
Email: lauren.tornetta@fda.hhs.gov

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

/s/

Lauren Tornetta
1/8/2007 03:42:53 PM
CSO



Filomena Gesek
Associate Director
Regulatory Affairs

Novartis Consumer Health, Inc.
200 Kimball Drive
Parsippany, NJ 07054-0622

Tel (973) 503-7645
Fax (973) 503- 8428

December 11, 2006

Food and Drug Administration (360909)
Mellon Client Service Center- Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

USER FEE ID # PD3006785

Sir/Madam:

Please find a check in the amount of \$896,200, the user fee for NDA 22-122.

If you have questions regarding this information, please contact the undersigned at 973-503-7645.

Regards,

Novartis Consumer Health, Inc.

A handwritten signature in black ink, appearing to read 'Filomena Gesek', written over a horizontal line.

Filomena Gesek
Director, Regulatory Affairs

Enclosures:

PDUFA User Fee Cover Sheet

Check # 15903253

Cc: L. Malandro via facsimile (301-796-9723)

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

NOVARTIS CONSUMER HEALTH INC
Filomena Gesek
200 KIMBALL DR
PARSIPPANY NJ 070540622
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-122

2. TELEPHONE NUMBER
973-503 7645

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

3. PRODUCT NAME

Voltaren → diclofenac sodium topical gel, 1%)

6. USER FEE I.D. NUMBER
PD3006785

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO

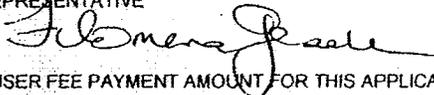
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director
Regulatory Affairs

DATE

11 DEC 06

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION
\$896,200.00

Form FDA 3397 (12/03)

(IBE_PRMT_CLOSE_G) (Print Cover sheet)

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

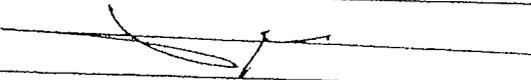
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached lists	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Jorge Insuasty, MD	TITLE Head, Global OTC, R&D
FIRM / ORGANIZATION Novartis Consumer Health, Inc.	
SIGNATURE 	DATE 10/17/06

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,334

Novartis Consumer Health, Inc.
200 Kimball Drive
Parsippany, NJ 07054-0622

Attention: Filomena Gesek
Associate Director, Regulatory Affairs

Dear Ms. Gesek:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for diclofenac sodium gel 1%.

We also refer to the meeting between representatives of your firm and the FDA on July 21, 2006. The purpose of the meeting was to discuss Novartis Consumer Health's proposals for the content, format, and organization of an NDA for the topical use of diclofenac sodium gel 1%.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2246.

Sincerely,

(See appended electronic signature page)

Lauren P. Tornetta, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 21, 2006

TIME: 1:30 p.m. to 2:30 p.m.

LOCATION: CDER White Oak 1315 Conference Room, Bldg. 22

APPLICATION: IND 64,334

DRUG NAME: Diclofenac Sodium Gel 1%

TYPE OF MEETING: Type B (Pre-NDA)

MEETING CHAIR: Rigoberto Roca, M.D.

MEETING RECORDER: Lisa Malandro

FDA Attendee	Title
Curtis Rosebraugh, M.D.	Deputy Director ODE II
Bob Rappaport, M.D.	Director, Division of Anesthesia, Analgesia and Rheumatology Products (DAARP)
Rigoberto Roca, M.D.	Deputy Division Director (Addiction & Rheumatology)
Ali Al-Hakim, Ph.D.	Chemistry Reviewer
Dan Mellon, Ph.D.	Pharmacology/Toxicology Team Leader
Lawrence (Steve) Leshin, Ph.D.	Pharmacology/Toxicology Reviewer
Jeffrey Siegel, M.D.	Medical Team Leader
Joel Schiffenbauer, M.D.	Medical Team Leader
Tatiana Oussova, M.D.	Medical Officer
Dionne Price, Ph.D.	Statistical Team Leader
Yongman Kim, Ph.D.	Statistical Reviewer
Lauren Tornetta, M.S.	Regulatory Project Manager (DAARP)
Lisa Malandro	Regulatory Project Manager (DAARP)
Cherye Milburn	Regulatory Project Manager, Office of Drug Safety (ODS)
David Lee, Ph.D.	Clinical Pharmacology Reviewer

Novartis Consumer Health (NCH) Attendee	Title
Florian Bieber, M.D.	Head, Clinical Development & Drug Safety
Donatus Dreher, M.D.	Senior Manager, Clinical Research
Filomena Gesek	Associate Director, Regulatory Affairs
	Expert Statistician
Inna Kissen, Ph.D.	Director, Regulatory Affairs
Hongchun Qui, Ph.D.	Associate Director, Regulatory Affairs
Jacob Zijlstra, Ph.D.	Head, PreClinical Development/Toxicology
Soraya Madani, Ph.D.	Associate Director, Regulatory Affairs
	NCH Consultant

MEETING OBJECTIVES:

The primary objective for this meeting is to discuss and gain Agency concurrence with Novartis Consumer Health, Inc. (NCH's) proposals for the content, format and organization of an NDA for the topical use of diclofenac sodium gel 1%, four times a day, for the

ACTION ITEMS:

1. The Sponsor will submit a document to support the appropriateness of their post-hoc analysis of the modified efficacy population for review by the Division (see Question 7).
2. The Division will clarify the requirements for the location of the ISS and ISE in the CTD modules (see DISCUSSION under Question 10 for a detailed response to this action item).
3. The Division will review recommendations made by previous reviewers regarding carrying forward the mean values of either the placebo or the treatment group (see Question 13).

DISCUSSION POINTS:

The Sponsor's position and questions are presented below in *italicized* text. Agency responses, prepared and forwarded to the Sponsor prior to the meeting, are **bolded**. Following introductions, the discussion focused on Questions 4, 7, 10b, 13, and bullet 3 under "Additional FDA Comments." Discussion related to these questions is presented in normal text.

Chemistry, manufacturing and controls

[Handwritten scribbles and lines]

C

 1 Page(s) Withheld

 ✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

NCH Position for Question 3:

DSG is applied topically and in comparison to oral administration, results in lower systemic exposures. The proposed limits for the impurities for DSG are lower or similar to the specifications for diclofenac sodium delayed-release tablet (), any individual impurity not more than (), sum of all impurities not more than () in the USP Monograph. The (), not described in previous diclofenac oral formulations, has been qualified. () was found to be non-toxic ($LD50 > 2,000$ mg/kg), not mutagenic in the Ames assay and did not have potential to cause skin sensitization.

Question 3: With respect to impurities, the limits of () not more than () not more than () not more than () any other individual impurity not more than () and sum of all impurities not more than () will be applied to DSG. Does the agency agree with our impurity limits for DSG?

FDA Response:

The proposed impurity limits are acceptable. However, we expect future manufacturing capability and experience may result in the reduction of these impurities and subsequent improvement of the drug product quality.

We encourage you to include toxicity study reports of these impurities, if available, even though these compounds may be within regulatory limits.

Additional CMC Comments

- a. Provide a well documented Pharmaceutical Development Report. Refer to ICH Q8 guideline
- b. Provide adequate amount of stability data to cover the proposed expiration dating
- c. Provide complete names, addresses and CFN numbers for all the sites involve in manufacturing, testing and packaging of the drug substance and the drug product

Nonclinical

NCH Position for Question 4:

As described in Appendix 2, a series of safety studies were performed with DSG to ascertain the absence of an irritating, sensitizing, or phototoxic potential for this formulation. An extensive series of preclinical safety tests have been performed with its active ingredient, diclofenac

sodium, in many species. Acute toxicity, mid-term and long-term toxicity, in vitro and in vivo mutagenicity, teratogenicity, fertility, peri- and post-natal toxicity, carcinogenicity and special safety pharmacology studies were performed in rats, mice, rabbits, dogs and baboons. The results from these toxicity studies have been submitted in the NDA for diclofenac sodium enteric-coated tablets, NDA 19-201. Based upon these data, NCH believes that the nonclinical toxicology of the product is supported and that additional nonclinical toxicology data are unnecessary.

Question 4: The DSG NDA will contain results from the skin and eye irritation studies, sensitization and phototoxicity studies. In addition, a review and CTD-type summary tables of the nonclinical safety studies submitted in NDA 19-201, and a review of the published literature on diclofenac sodium will be included. Does the Agency agree that this information is adequate to support the nonclinical requirements for the filing of a NDA?

FDA Response:

Studies to characterize the potential for dermal carcinogenicity and dermal photocarcinogenicity for this topical product are missing from your nonclinical development program. It is not clear if you intend to submit the NDA as a 505(b)(1) or 505(b)(2) application. If you plan to submit a 505(b)(1) application, then you would need to conduct your own studies in appropriate animal models or obtain a right of reference to such studies. If you are considering submission of a 505(b)(2) application, then you may be able to rely on studies not conducted by or for you and to which you have not obtained a right of reference or use (i.e., published literature or the Agency's finding of safety and/or effectiveness for a listed drug) to support your nonclinical development program in these areas. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54 and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/guidance.htm> for further information.

With the above exception, your nonclinical development program appears to be adequate; however, final determination of adequacy will be determined upon review of the study reports. In addition to the summary tables, please include in the NDA submission an appendix containing copies of the cited study reports and published literature.

DISCUSSION:

The Sponsor stated that they are planning to submit a 505(b)(2) application. Drs. Leshin and Mellon explained that the Sponsor should research what other similar drugs are approved. The applicant should include justification for the appropriateness of the previously approved data. The Sponsor will need to obtain Right of Reference to this data, if used in their application. Dr. Mellon explained the Sponsor should also examine patent issues with these other approved products and address any patent issue conflicts prior to submission of the application.

NCH Position for Question 5:

The anti-inflammatory activity of systemically administered diclofenac sodium has been demonstrated in a variety of nonclinical studies that were submitted in the NDA for diclofenac sodium enteric-coated tablets, NDA 19-201. The anti-inflammatory activity of topically applied diclofenac sodium and a topical diclofenac diethylamine product was shown in several animal models including carrageenin induced edema in rats, ultraviolet erythema in guinea pigs, and adjuvant arthritis in rats. The DEA product is marketed outside the US and differs from DSG only in that it contains 1.16% diclofenac diethylamine salt instead of 1% diclofenac sodium. Very similar absorption of diclofenac was observed in the clinical pharmacokinetic studies comparing DSG with DEA. Based on this information, NCH proposes that the nonclinical PK studies of the product are sufficiently supported and that no new nonclinical PD studies are necessary.

Question 5: The nonclinical pharmacodynamics section of the DSG NDA will contain a review and CTD-type summary tables of the relevant studies already submitted in NDA 19-201, of the published literature on topically applied diclofenac sodium and of the studies conducted with the topical diclofenac diethylamine 1.16% product marketed in other countries. No new nonclinical pharmacodynamic studies will be submitted. Does the Agency agree that the proposed information will be sufficient to support the filing of a NDA?

FDA Response:

See the response to Question 4.

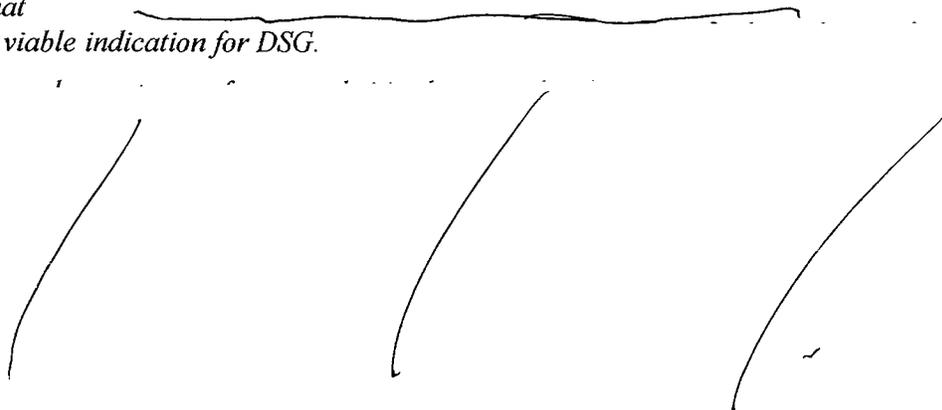
Clinical/Safety

NCH Position for Question 6:

NCH believes that

_____ is a viable indication for DSG.

“D.S.G. . . .”



Question 6: Does the FDA concur that DSG could be evaluated and approved for the indication

FDA Response:

The Division has previously granted the indication _____
_____ This is consistent with our previous recommendation
provided you in a letter dated 12/17/04. Alternatively, _____ joints
amendable to _____ treatment, such as the hands and knees” might be considered.
However a statement regarding the fact that certain joints, such as the hips and shoulders,
are not included in the indication would need to be added to the label.

NCH Position for Question 7:

As described in Section 2.4, NCH has two independent studies providing replicated evidence of efficacy of DSG for _____

Two studies in osteoarthritis of the superficial joints of the extremities, one in osteoarthritis of the knee (VOSG-PN-310) and one in osteoarthritis of the hand (VOSG-PE-315) show positive results in all three primary efficacy endpoints and thus provide replicate evidence of efficacy of the product in the target indication.

These results are supported by two further studies in the target indication. VOSG-PN-304, a knee osteoarthritis study, was designed identically to VOSG-PN-310. Numerical superiority of DSG over placebo was achieved on all three primary endpoints in the ITT efficacy population. Statistically significant and clinically relevant superiority was achieved on all three primary endpoints in an a posteriori analysis in the modified efficacy population. This population of patients without significant pain at baseline in the non-treated knee and whose pain did not decrease during the washout period was then defined a priori for VOSG-PN-310 as the primary efficacy population. Ultimately, positive results were obtained in both knee studies (VOSG-PN-304 and VOSG-PN-310) in all three primary endpoints in the modified efficacy population.

Hand OA study VOSG-PE-314 was designed in identical fashion to VOSG-PE-315. Efficacy was demonstrated in this study on two out of the three primary efficacy variables at 2 weeks, which thereby also supports the efficacy of DSG.

An additional study with the diclofenac diethylamine product in knee osteoarthritis also supports the efficacy of the diclofenac sodium product. In study VOSG-PE-303, diclofenac diethylamine demonstrated statistically and clinically significant improvements versus placebo on assessments of pain symptoms and function. The results of this study are applicable to the diclofenac sodium product due to the similarity of the formulations as established by in-vitro studies showing that these two products have essentially the same skin penetration rate.

NCH believes that the replicated evidence of efficacy in the target indication and the supportive evidence of efficacy from additional studies with DSG and the diethylamine formulation support submission and review of an NDA for DSG in the indication of _____

NCH further believes that the body of evidence consisting of the diethylamine post-marketing adverse event reports and the DSG skin safety and Phase 3 studies adequately supports the safety of the DSG product.

Question 7: Does the FDA agree (pending NDA review) that the combined evidence of safety and efficacy in NCH's knee and hand osteoarthritis studies supports the indication _____

FDA Response:

As stated above, hand and knee OA represent different aspects of OA. This concept is supported by the differences in trial design and endpoints. Therefore, you will need to provide replicate evidence in at least one model to support any indication. Based on the data submitted, it is not clear that you have achieved this level of evidence. As stated in

your package, superiority was achieved in the knee OA trial in a post-hoc analysis in the MODIFIED efficacy population, and a modified population was then defined for the second trial. However, the use of a modified population might not be generalizable to the intended or general population of patients with knee OA. If so, an additional study in the defined INTENDED population would be needed to support an indication.

DISCUSSION:

With respect to the modified efficacy population, the Sponsor feels that this population is generalizable to the broader knee population. Dr. Schiffenbauer explained that this population excluded approximately 50% of patients treated with the drug. Due to the exclusion, the Sponsor does not have data to support use of this product in patients with bilateral OA, which makes up a large percentage of the population with OA. The Sponsor clarified that the only patients who were excluded were those with significant pain in the non-target knee because it was difficult to discern differences in pain in the signal knee. Other patients who experienced less severe disease in the non-target knee were included. In the second study, the population was defined up front, and the results of the modified ITT population replicated those of the original intent-to-treat population.

Dr. Rappaport requested that the Sponsor submit a document developed specifically to address the issue regarding the population studied, the generalizability of their results, and including a rationale for why this is appropriate to support an application. All pertinent information, including European data, should be included. The Division will review this document and reassess their position (see post-meeting comments below).

Post meeting comments:

We have reviewed your submission and discussion regarding the generalizability of Trial 310 in reference to the study of pain in one versus two knees. We accept your argument that demonstration of efficacy in one knee would be generalizable to the population of OA patients with pain in both knees, and that the modified efficacy population is representative of the larger OA population. Further, the use of a flare design is also acceptable. Therefore, the results of Study VOSG-PN-310 can be used to demonstrate efficacy in OA patients.

NCH Position for Question 8:

Tolerability of DSG was very good over the various double-blind studies in knee OA and hand OA and the single-arm long-term extension study in knee OA. The incidence of cutaneous AEs was low. No serious application site AEs were reported. The systemic AE profile was not different from placebo. DSG was safe in prolonged use.

The tolerability observed in these studies in patients with OA of the superficial joints is consistent with the low systemic exposure found in the PK studies and the absence of irritation or sensitization potential in the special skin safety studies.

There is an extensive post-marketing safety database for DEA derived from twenty years of worldwide spontaneous reports in an exposed population of millions of patients. This data

indicates that DEA has a very favorable safety profile. Based on the similarity of the skin penetration and PK profiles of DSG and DEA, this data supports the safety of the DSG formulation as well.

Question 8: NCH proposes to submit safety data from the DSG clinical program, including up to 12 months of safety data from open label knee OA study VOSG-PE-309, and post-marketing safety data from the DEA (serious and unexpected adverse events) in support of safety for use of DSG. Does the agency agree with this proposal?

FDA Response:

Yes

Regulatory

NCH Position for Question 9:

Paper CTD

The information and data necessary to file an NDA has been collected in various media including paper and is not generally available in a format conducive to electronic filing. Also, with the exception of product labeling, the submission of applications in electronic format is suggested but not currently required. Therefore, NCH proposes to submit the NDA for DSG in paper, CTD format.

SAS transport files

It is common practice to submit the SAS transport files on CD ROM. NCH wishes to confirm that submission of this information in this manner continues to be acceptable. We will comply with specifications given in the FDA Guidance on Providing Regulatory Submissions in Electronic Format – General Considerations.

Drug substance referencing

In support of our NDA in CTD format, NCH proposes to cross-reference the drug substance sections of NDA 19-201 for Voltaren Tablets, which is not in CTD format. We plan to provide a detailed table with cross-references to locate the specific information under Section 3.2.S, without including other documents behind the tab of each Section of Module 3.2.S.

Question 9 (a-c):

- a. *NCH proposes to submit the NDA for DSG in paper CTD format. Labeling will be provided in electronic format in accordance with Structured Product Labeling requirements and as Word documents on CD ROM. Does the Agency agree that this is acceptable?*
- b. *NCH plans to provide the Agency with SAS transport files of the raw and derived study data in CDISC format electronically on CD ROM. Does the Agency agree?*
- c. *NCH plans to cross-reference the drug substance sections of NDA 19-201 which is not in CTD format. A detailed table will be provided to locate cited information. No documents will be provided in Module 3.2.S. Does the Agency agree with this proposal?*

FDA Response:

- a. **Yes. The Division prefers electronic format for as much of the submission as possible. However, you cannot submit both for any single part of the NDA.**
- b. **Yes. However, a detailed description for variables and variable values must accompany the SAS data.**
- c. **Yes**

NCH Position for Question 10:

ISS/ISE

NCH believes that the required elements of the ISS and ISE may be incorporated into the Summaries in CTD Module 2.7. If needed, integrated analyses (statistical output) presentations will be presented in a separate report in Module 5.3.5.3.

Case Report Tabulations

NCH believes that the Case Report Tabulations requirement will be satisfied by the comprehensive listings of patient data that are appended to each individual clinical trial report.

Question 10(a & b):

- a. *NCH proposes to include the required elements of the ISS and ISE within the Summaries in Module 2.7. No separate ISS and ISE will be included in the NDA. Does the Agency agree with this proposal?*
- b. *NCH proposes that the requirement in Section 5.3.7 for Case Report Tabulations will be satisfied by the comprehensive listings of patient data that are appended to each*

individual clinical trial report. No tabulations will be supplied specifically in Section 5.3.7. Does the Agency agree with this proposal?

FDA Response:

- a. Separate ISS and ISE are required. The ISS and ISE belong in section 5.3.5.3 (see also below for additional recommendations when submitting the NDA)**
- b. No. You will need to provide Case Report Tabulations that integrates AEs across all studies. Please define what you mean by comprehensive listing of patient data.**

DISCUSSION:

The following provide further clarification of question 10b:

The CRTs are now termed tabulated data sets and are found located under each study in Module 5. For example, section 5.3.5 will provide a folder titled "Reports of Efficacy and Safety Studies" followed by section 5.3.5.1 which identifies a folder titled "Study Reports of Controlled Clinical Trials." Each study can be placed under this section and numbered in order. Under each study in this section (for example 5.3.5.1.1 Study ID #XXX) you can locate the following folders:

5.3.5.1.1 Individual Subject Data Listing

Data Tabulation

Data Listings

Annotated CRFs

The above is just an example. However, we strongly recommend contacting Ken Edmunds, the Agency IT specialist involved with CTD submissions, for additional details and clarification.

NCH Position for Question 11:

There is no reported incidence of osteoarthritis of the superficial joints in subjects below the age of 18 years. Therefore NCH proposes that the DSG product is not likely to be used in a substantial number of pediatric patients and will request a full waiver from the requirements of 21 CFR 314.55 for data on the safety and efficacy of the drug product in pediatric subpopulations.

Question 11: NCH expects to request a full waiver from the requirements for safety and efficacy data in pediatric subpopulations at the time of NDA submission. Will this preclude the acceptance of the NDA for review?

FDA Response:

A request for a waiver for pediatric studies would not preclude acceptance of submission of the NDA.

NCH Position for Question 12:

Appendix 5 includes proposed labeling structured in accord with the Final Rule for Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products dated 24 January 2006. NCH believes that the labeling structure (exclusive of formatting requirements) conforms to the requirements of the Final Rule.

Question 12: Does the Agency agree that the structure of the proposed product labeling is acceptable?

FDA Response:

Yes.

Statistics

NCH Position for Question 13:

NCH proposes that the analyses of efficacy and safety parameters described in Sections 2.7.1 and 2.7.2 of this document will adequately demonstrate the efficacy and safety of DSG in the relevant indication. NCH believes that these analyses reflect the traditional process by which studies in this category are analyzed.

Question 13: Does the Agency agree that the analyses of efficacy and safety parameters described in Sections 2.7.1 and 2.7.2 of this document are adequate for the demonstration of efficacy and safety of DSG in the relevant indication?

FDA Response:

In general, the statistical methodology is acceptable; however, we have the following additional comments/recommendations.

- a. In study VOSG-PN-304, the analyses conducted on the modified intent-to-treat population were post-hoc. To ensure the validity of the results, confirmatory analyses should be pre-specified.**
- b. Sensitivity analyses are mentioned but not specified in the briefing document. We recommend that you include a continuous responder analysis and a baseline observation carried forward analysis as strategies for handling missing data.**

- c. **We also recommend that you conduct a rigorous assessment of rescue use.**

DISCUSSION:

Dr. Price clarified that a continuous responder analysis is analogous to a cumulative distribution function. In a continuous responder analysis, the proportion of responders is calculated using multiple definitions (or cut-offs) of treatment response ranging from 0% to 100% improvement. All discontinuations or drop-outs should be classified as non-responders in the analysis. A plot of the proportion of responders against the multiple cut-offs allows for a comparison of the curves for the placebo and drug groups. Dr. Rappaport suggested that the Sponsor look at the label for Lyrica or Cymbalta as examples.

The Sponsor stated that, previously reviewers recommended that the mean of either the placebo or treatment group be carried forward for any drop-outs. Dr. Price stated that, when using an imputation method such as last-observation-carried-forward (LOCF), the Division's concern is that a good score could be carried forward for a patient who drops out due to an adverse event. Any proposed imputation strategy would need to address this concern. Since the Division was unaware of the previous recommendation, the statistical review team agreed to re-evaluate previous recommendations and to provide comments in a post-meeting note.

Post meeting note:

The Division reviewed previous meeting minutes and did not find any documentation of a recommendation for an imputation strategy carrying forward mean values. Alternate strategies to handle missing data may be employed; however, the methodology will need to appropriately address the concern conveyed at the meeting.

The Sponsor's proposal for evaluating use of rescue medication seems appropriate at this time.

NCH Position for Question 14:

In the open-label safety study VOSG-PN-309, 583 subjects were exposed in total; 355 treated one knee and 228 treated both knees. The number of subjects who treated for a duration of 6 and 12 months was 354 and 186, respectively.

NCH proposes that the analysis of safety described in Section 2.7.3 appropriately addresses safety of DSG in long-term use.

Question 14: Does the Agency agree that analysis of the long-term safety study VOSG-PN-309, as described in Section 2.7.3 of this document, is adequate to evaluate the safety of DSG in long-term use?

FDA Response:

Yes.

FDA COMMENTS: OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY (OSE)

- If you believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then you are encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.
- You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

ADDITIONAL FDA COMMENTS:

- Provide narratives for all SAEs in addition to deaths and withdrawals due to AEs
- Provide an integrated safety dataset that includes a unique patient identifier, treatment assignment, dosing at time of event, dosing prior to event if different, duration of event or start and stop dates, days on study drug at time of event, outcome of event, marker
- For serious adverse events, verbatim term, preferred term, (if MedDRA, include higher level term), gender, age, race, concomitant medications.
 - Include all studies in the ISS. If there are studies of different design or duration, please discuss the safety dataset with the division to determine the most appropriate studies to integrate.
 - Use the SAS transport format
 - Dates should be formatted as dates
- Provide all of the CRFs for patients discontinued from all studies due to:
 - Investigator opinion
 - Sponsor request
 - Withdrawn Consent
 - Other

DISCUSSION:

With respect to bullet 3, the ISS should present adverse events separately by:

1. Controlled studies
2. Open-label studies
3. European formulation

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Lauren Tornetta
8/21/2006 02:24:17 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,334

Novartis Consumer Health, Inc.
200 Kimball Drive
Parsippany, NJ 07054-0622

Attention: Rich Cuprys
Global Head, Regulatory Affairs

Dear Mr. Cuprys:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for diclofenac sodium topical gel.

We also refer to the meeting between representatives of your firm and the FDA on June 1, 2005. The purpose of the meeting was to present CMC specific information and to reach concurrence with the Agency regarding the acceptability of Novartis's proposals submitted in the briefing package.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

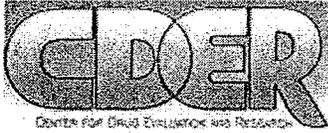
If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

(See appended electronic signature page)

John L. Smith, PhD
Chemistry Team Leader for
Division of Anesthesia, Analgesia
and Rheumatology Products
DNDCIII, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 1, 2005

TIME: 10a-11a

LOCATION: S300, 9201 Corporate Boulevard, Rockville, MD

APPLICATION (DRUG): IND 64,334 (diclofenac sodium topical gel 1%)

SPONSOR: Novartis Consumer Health, Inc.

TYPE OF MEETING: CMC End of Phase 2 Meeting

MEETING CHAIR: James Witter, MD, PhD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. James Witter, MD, PhD	Medical Team Leader	ODEII/DAARP
2. John Smith, PhD	Chemistry Team Leader	ONDC/DNDCIII, HFD-830
3. Sue Ching Lin, MS, RPh	Chemistry Reviewer	ONDC/DNDCIII, HFD-830
4. Josie Yang, PhD	Pharm/Tox Team Leader	ODEII/DAARP
5. Hamid Amouzadeh, PhD	Pharm/Tox Reviewer	ODEII/DAARP
6. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor
1. Filomena Gesek	Associate Director, Regulatory Affairs	Novartis
2. Hongchun Qiu, PhD	Associate Director, Pharmaceutical Development	Novartis
3. Jeffrey T. Needels	Associate Director, Research Stability Services	Novartis
4. Cynthia Rappana	Senior Scientist, Global R&D Analytical Develop.	Novartis
5. Jacob Zijlstra, PhD	Head, Preclinical Development/Toxicology	Novartis
6. Claude Chieze, DMV	Head, EU Global Project Management	Novartis
7. Pierre Humbert-Droz, PhD	Global Head CMC, Global Regulatory Affairs	Novartis
8. Chin Koerner	DEV-Regulatory Liaison	Novartis

PURPOSE OF THE MEETING: To present CMC-specific information for diclofenac sodium topical gel 1% and to reach concurrence regarding the acceptability of the Novartis Consumer Health, Inc. (hereafter referred to as Novartis) proposals for _____ excipient acceptability _____ and stability requirements for a _____

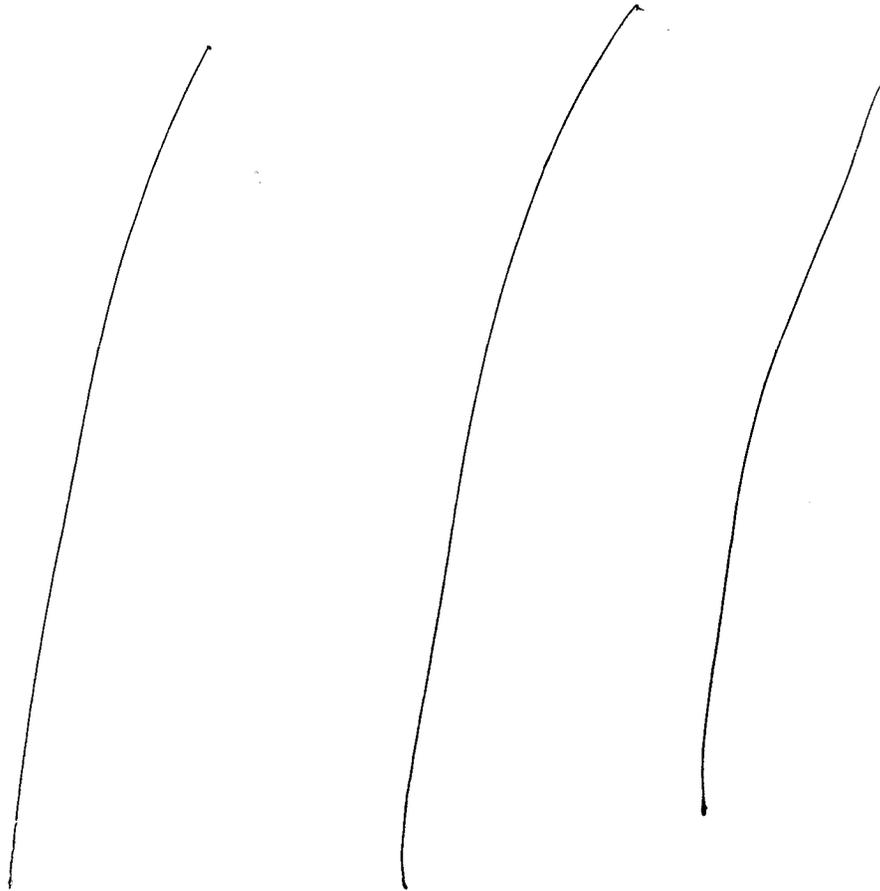
4. **Does the FDA concur that the information provided in this document along with that being collected in the ongoing clinical studies mentioned, will be sufficient to support approval for the use of _____ the diclofenac sodium gel, 1 % product?**

FDA Preliminary Response: From the Pharm/Tox perspective, the information presented is adequate to support the NDA filing.

From the CMC perspective, the names of the ingredients should be provided in English, along with their CAS numbers.

Meeting Comments: Novartis stated they would provide submit to the IND the English translation of the ingredient names and CAS numbers for _____

- 5.



nt

6. **Does the Agency agree that acceptable data from one site-specific batch will be sufficient for approval of the _____**

FDA Preliminary Response: It is not clear as to what the "site-specific" means in this question. Three batches of the drug product packaged in _____ should be placed on stability and the results submitted in the NDA. An additional "site-specific" batch is acceptable, provided stability data for three batches of the drug product packaged in _____ have been submitted for a different site.

Meeting Comments: Novartis clarified that stability data will be provided for three batches of drug product: one manufactured in _____ and two manufactured in _____. The packaging would be done by the _____ only. The FDA agreed that it is acceptable.

7. **Does the Agency agree that stability data from _____ as acceptable to support packaging this product at the _____ facility as long as the same packaging components are used and seal integrity is confirmed?**

FDA Preliminary Response: Yes.

Meeting Comments: Novartis accepted the response and no further discussion was required.

Additional Comments Discussed During the Meeting: Regarding the non-proprietary name of the drug product, the chemistry reviewer indicated that the non-proprietary name should include the route of administration in order to be in line with the current USP nomenclature convention for topical drug products. Therefore, the non-proprietary name for this drug product should be "diclofenac sodium topical gel." On the label, the strength, 1%, should be placed outside of parentheses and it is not a part of the non-proprietary name.

Minutes Preparer: Jane A. Dean, RN, MSN
Chair Concurrence: James Witter, MD, PhD
Drafted by: JAD/6-24-05
Revised by: sl/6-24-05, js/6-28-05
Initialed by:
Final:

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

/s/

Jane Dean
7/1/05 03:36:46 PM
For John Smith



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,334

Novartis Consumer Healthcare, Inc.
Attention: Filomena Gesek
Associate Director Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Ms. Gesek:

Please refer to your Investigational New Drug Application (IND) file for diclofenac sodium gel 1%.

We also refer to the meeting between representatives of your firm and the FDA on December 7, 2004. The purpose of the meeting was to discuss Phase 3 clinical development plans for hand osteoarthritis.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

(See appended electronic signature page)

Sharon Hertz, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 7, 2004

TIME: 11:05 am- 11:30am

LOCATION: S300, 9201 Corporate Boulevard, Rockville, MD

APPLICATION (DRUG): IND 64,334 (diclofenac sodium gel 1%)

SPONSOR: Novartis Consumer Healthcare, Inc.

TYPE OF MEETING: Guidance

MEETING CHAIR: Sharon Hertz, MD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Sharon Hertz, MD	Deputy Director	ODEV/DAAODP, HFD-550
2. James Witter, MD, PhD	Primary Medical Team Leader	ODEV/DAAODP, HFD-550
3. Carmen DeBellis, RPh	Chief Project Manager	ODEV/DAAODP, HFD-550
4. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
5. Joel Schiffenbauer, MD	Medical Team Leader	ODEV/DAAODP, HFD-550
6. Atiar Rahman, PhD	Statistics Reviewer	OB/DBIII, HFD-725
7. Lei K. Zhang, PhD	Clinical Pharmacology Reviewer	OCPB/DPEIII, HFD-880
8. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Angela Browne, PharmD	Director Regulatory Affairs	Novartis
2. Claude Chieze, DVM	Senior Project Manager	Novartis
3. Donatus Stefan Dreher, MD, PhD	Senior Manager, Clinical Dev.	Novartis
4. Francois Elki, MD	Head Clin. Research Europe	Novartis
5. Filomena Gesek	Assoc. Director Reg. Affairs	Novartis
6. Morris Gold, ScD	Director Biostatistics	Novartis
7. Andrew Snoddy, PhD	Director Clinical Research	Novartis
8. Kaj Martensson, MD	Head Clin. Res. & Operations	Novartis
9.		

PURPOSE OF THE MEETING: To discuss Phase 3 clinical development plans for _____

MEETING OBJECTIVE: To reach concurrence regarding the adequacy of the proposed protocol which, if positive, will support the indication of _____

BACKGROUND: Novartis Consumer Healthcare, Inc., hereafter referred to as Novartis, is developing a prescription, topical dosage form of diclofenac sodium gel 1% for _____

On June 29, 2004, an End of Phase 2 meeting was held between Novartis and the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, hereafter referred to as the Division, to obtain feedback on the clinical program. Novartis has modified the protocol, submitted as part of this meeting package, incorporating recommendations made during that meeting.

QUESTIONS: The meeting began with general comments and introductions. Draft responses to the questions had been provided the day before and are identified as "Original FDA Response." Discussion during the meeting is captured in the "Meeting Comments" section as follows:

Question 1: In both of the Phase 3 clinical studies of hand OA, Novartis intends to designate the dominant hand as the target hand and include patients with appreciably greater pain in their dominant hand. All patients will treat both hands. **Does the FDA agree with our proposal?**

Original FDA Response: Treatment of both hands is acceptable. However, we suggest you perform a full set of evaluations (Total AUSCAN Index and Pain VAS) on both hands; a single patient global is sufficient. Given the variability in symptoms of hand OA, in joints involved at any particular time, and in the duration of pain cycles this would provide for a more robust assessment of response. Your studies must reach statistical significance and support the conclusion that there is a clinically meaningful difference on the target hand only, with the second hand trending in the same direction.

Meeting Comments: *Novartis acknowledged and accepted the response.*

Question 2: It is proposed to conduct at least one, or if possible both, of the pivotal hand OA studies in European countries. **Will this affect the acceptability for use of these studies for registration in the US?**

Original FDA Response: The clinical trials must include concomitant medications available in the US. If both trials permit medications not available in the US, the generalizability of the results may be questionable and may limit applicability of these studies for sole support of efficacy. It is also unclear that use of hands (e.g., time spent on computers, heavy lifting) is comparable across cultures also limiting generalizability.

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

/s/

Sharon Hertz
12/17/04 05:46:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 64,334

Novartis Consumer Health, Inc.
Attention: Angela Browne, PharmD
Manager, Regulatory Affairs
200 Kimball Drive
Parsippany, NJ 07054-0622

Dear Dr. Browne:

Please refer to your Investigational New Drug Application IND file for diclofenac sodium gel 1%.

We also refer to the meeting between representatives of your firm and the FDA on June 29, 2004. The purpose of the meeting was to obtain FDA's input for an End of Phase 2 meeting.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

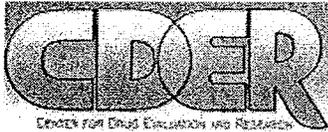
If you have any questions, please call Ms. Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

(See appended electronic signature page)

Sharon Hertz, MD
Deputy Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 29, 2004

TIME: 10:08 am – 11:25 am

LOCATION: 9201 Corporate Boulevard, Rockville, MD

APPLICATION (DRUG): IND 64,334 (diclofenac sodium gel 1%)

SPONSOR: Novartis Consumer Health, Inc.

TYPE OF MEETING: End of Phase 2 Meeting

MEETING CHAIR: Sharon Hertz, MD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Name of FDA Attendee	Title	Division Name & HFD#
1. Sharon Hertz, MD	Deputy Director	ODEV/DAAODP, HFD-550
2. James Witter, MD, PhD	Medical Team Leader	ODEV/DAAODP, HFD-550
3. Jonca Bull, MD	Director	ODEV, HFD-105
4. Carmen DeBellis, RPh	Chief Project Manager	ODEV/DAAODP, HFD-550
5. Dennis Bashaw, PharmD	Clinical Pharmacology Team Leader	OCPB/DPEIII, HFD-880
6. Terri Rumble	ADRA	ODEV, HFD-105
7. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
8. Sue Ching Lin, MS	Chemistry Reviewer	ODEV/DAAODP, HFD-550
9. Lei Zhang, PhD	Clinical Pharmacology Reviewer	OCPB/DPEIII, HFD-880
10. Conrad Chen, PhD	Pharm/Tox Reviewer	ODEV/DAAODP, HFD-550
11. Atiar Rahman, PhD	Statistics Reviewer	OB/DBIII/HFD-725
12. Joel Schiffenbauer, MD	Medical Team Leader	ODEV/DAAODP, HFD-550
13. Dianne Tesch, RN	Consumer Safety Officer	DSI, HFD-046
14. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Angela Browne, PharmD	Manager, Regulatory Affairs	Novartis
2. Henry Weidmuller	Director, Regulatory Affairs	Novartis
3. Helmut Albrecht, MD	Head, Clinical & Medical Development	Novartis
4. Jean-Luc Kienzler, MD	Head, Clinical Pharmacology	Novartis
5. Selim Rachidi, MS	Assoc. Dir., Clinical Operations	Novartis
6. Morris Gold, ScD	Director, Biostatistics	Novartis
7. Jacob Zilstra, PhD	Head, Preclinical Development	Novartis
8. Jorge Insuasty, MD	Sr. VP, Research & Development	Novartis

External Attendee	Title	Sponsor/Firm Name
9. Claude Chieze, DVM	Sr. Project Manager	Novartis
10. _____	_____	Consultant
11. Linda Carter	Executive Director, Regulatory Affairs	Novartis
12. Eluice Franjro	Head, Clinical Research	Novartis

PURPOSE OF THE MEETING: To discuss plans with the FDA for developing a prescription, topical dosage form of diclofenac sodium gel 1% for _____

MEETING OBJECTIVES:

1. To reach concurrence regarding the adequacy of the proposed clinical development plan for the stated indication for diclofenac sodium gel, 1%

BACKGROUND: Novartis Consumer Health (hereafter referred to as Novartis) has developed a topical anti-inflammatory analgesic, diclofenac sodium gel, 1% (DSG, 1%) to be used to _____ On November 18, 2003, Novartis met with the Division to obtain guidance on the clinical development plan at which time, the Division agreed with Novartis that they could proceed with the established dosing regimen of 4 grams of DSG, 1% applied four times a day.

Based on the existing body of knowledge regarding the diclofenac molecule and the experience of a similarly formulated topical diclofenac diethylamine gel, 1.16% (DDG, 1.16%), the During the meeting between the Division and Novartis on November 18, 2003, the Division accepted Novartis's proposal that total long term exposure to DSG, 1% in the clinical program be focused to include at least 450 patients exposed for three months, 225 exposed for six months and 75 exposed for one year.

Additional preclinical studies of 12 weeks duration were submitted to the Division on January 23, 2004 to support the safety of 12 week dosing in human clinical trials. In response to concerns from the Division regarding heat, exercise and maximal dosing on systemic availability, additional Phase 1 protocols were submitted to the Division for review on March 15, 2004.

Novartis would like input from the Division on their clinical development plans to evaluate the efficacy of DSG, 1% in _____ and to determine if the generated efficacy and safety databases would support the _____ indication of _____

QUESTIONS:

The meeting opened with general comments and introductions. Because draft responses to the questions had been provided the day before (labeled "Original FDA Response"), discussion began immediately with the questions (bolded) as follows:

Question 1: Will protocol VOSG-PE-107 satisfy the request from the Agency for evaluation of the “effect of moderate exercise and local heat in its influence on drug absorption through the skin?”

Original FDA Response: Yes.

Meeting Comments: None.

Question 2: Will Protocol VOSG-PE-113 satisfy the request from the Agency for information on “the use of maximal topical dosing (i.e. dose and surface area – number of joints treated) to determine the degree of systemic availability?”

Original FDA Response:

Yes, as it relates to the knee — 2. However, we have the following two comments:

1. Please explain why a “14-day washout period” will be used in this study, while in Study VOSG-PE-107, a “7-day washout period” will be used.
2. Please also conduct full PK sampling for Regimen B (application to both knees) on Day 1. We would like to determine PK on Day 1 for this treatment arm because people may use this drug for single day application.

Should you desire _____ I need to evaluate the systemic absorption of diclofenac following application to both hands and both knees at day 1 and at steady-state. The objective of this trial would be to assess dermal absorption under “maximal use” conditions.

Meeting Comments: Novartis stated that a “14-day washout period” used in Protocol VOSG-PE-113 was according to the OGD guidance for in vivo bioequivalence evaluation for oral diclofenac (Post meeting note: This guidance, along with most of the drug specific OGD guidances, was withdrawn by the Agency in mid 2002). A “7-day washout period” in Protocol VOSG-PE-107 was based on previous PK experience with another topical diclofenac in which a “7-day washout period” was adequate. This clarification is acceptable to the Agency.

In response to the Division’s draft responses, Novartis further proposed that Regimen A would be changed to study both knees (instead of one knee) and Regimen B would be changed to study both knees and both hands. The Division stated that we would prefer seeing one knee versus both knees and both hands to cover both extremes, but we would accept Novartis’ proposal. Novartis also stated that they would collect Day 1 full PK blood samples for Regimen B but not for Regimen A. Because of the amount of blood that would be collected, it is acceptable to collect Day 1 full PK samples for Regimen B only.

The Division reminded Novartis that whether additional PK studies are needed to determine exposure of the drug under “maximal dosing conditions” would depend upon the final approved indication and the results obtained in Study VOSG-PE-113 and our evaluation of these results.

Question 3: Does the Agency agree that the Phase 3 protocols VOSG-PE-304 and VOSG-PE-310 are adequately designed to support registration of DSG, 1%, for _____

Original FDA Response:

Yes, overall the design is acceptable. The ability of these studies to support registration will also depend on the adequacy of the results.

In particular, the duration of studies (12 weeks) and the primary endpoints (WOMAC pain, function, and a patient global) chosen are appropriate. We would encourage you to also include a patient global that seeks to characterize the risk: benefit ratio of the product as a secondary endpoint.

We continue to recommend the use of the maximum daily dose of rescue medication for 3-4 consecutive days before a patient is considered a failure. For non-OA conditions, the duration of use of rescue medication could be extended up to 7 days although the doses should be lower than 4 grams daily. You should consider using rescue medication as an endpoint in this trial and in the extension study. A responder analysis incorporating pain and rescue use as variables can be very informative. In any case, patients who fail therapy because of excess rescue should continue in the trial for the safety evaluation and their efficacy results will be included in the ITT analysis.

We are concerned about patients electing to treat their non-study knee should it become painful during the trial. Please describe how the efficacy data from such patients will be managed.

We are also concerned about possible concomitant use of NSAIDs since they are so widely available. We suggest you treat patients who have taken a certain amount of NSAID rescue as a treatment failure rather than as a protocol violator.

We suggest that at least one study include use of the daily patient diary for 2 weeks instead of one in case the onset of action is delayed and is not seen within 1 week.

Meeting Comments:

Novartis accepted the Division's recommendations including the addition of a global question to assess the risk: benefit ratio of the product as a secondary endpoint.

Novartis also agreed with the Division's recommendations about use of rescue medication.

Concerning patients electing to treat their non-study knee with study drug or systemic medication, Novartis noted that if that should happen, the data would be captured. The Division suggested that Novartis plan how to address the potential problem of confounding the results with the use of systemic medications and how subjects will be instructed to manage nonstudy knee pain during the trial.

Novartis was encouraged to explore responder analyses early in development, using more than descriptive analysis. Novartis replied that a responder analysis is planned in the protocol.

Question 4: Does the Agency agree that the Phase 3 protocols VOSG-PE-314 and VOSG-PE-315 are adequately designed to support registration of DSG, 1%,

Original FDA Response:

No. Two longer (6-12-week) duration studies in hand OA may be sufficient to support an indication of _____ We recommend that you begin with a 4-week trial as a POC trial employing the 3 co-primary endpoints -pain,

function, and patient global. Based on these results the feasibility of a longer study can be better assessed.

Meeting Comments:

Novartis stated that they would prefer not to do a proof of concept trial because the duration of time required for such an effort was not optimal. Hand OA is different from knee OA with pain often lasting only up to four weeks, and if they use eight weeks as an end point, they would miss the treatment benefit seen at four weeks, hence their rationale for proposing the four week protocol. The Division stated that they would still prefer to see a longer trial than four weeks. Novartis offered a proposal to look at the data generated at four weeks as a primary end point and then at six weeks and finally at eight weeks. The Division said we would need to see the proposal. Novartis said they would submit a proposal with different times as endpoints as well as address the issue of measuring function. Novartis asked if pain and global were okay, if we would

_____ ie Division stated _____

Question 5: Does the Agency agree that the combined osteoarthritis of the knee and osteoarthritis of the hand clinical studies would support registration of DSG, 1%, for _____

Original FDA Response:

We do not agree. Please clarify how labeling that would _____

Meeting Comments:

Question 6: Does the Agency agree that the proposed program of studies provides sufficient extent of exposure to support the claim that diclofenac sodium gel, 1% (DSG, 1%) is safe and effective when used at the proposed dose and regimen for _____

Original FDA Response:

Yes, pending review, this appears to be sufficient for _____

Meeting Comments:

Question 7: As DSG, 1% is anticipated to have a safety profile very similar to DDG, 1.16%, NCH proposes submitting the NDA for this product after the safety database for patients treated through 6 months is available, and commits to submission of data on patients treated through 12 months as soon as it is available (and prior to NDA approval). Does the Agency agree with this proposal?

Original FDA Response:

The application should be complete at the time of submission.

Chemistry Comments:

The following comments pertain to the drug product specification:

- 1. The acceptance criteria for each test should be established as the clinical studies progress into Phase 3.*
- 2. Testing of $\overline{\text{---}}$ should be included in the drug product specification and this test should be performed for every batch at release.*

Statistical Comments:

- 1. For sensitivity analysis, you should analyze the data by imputing the missing values in more than one way e.g. simple LOCF, worst possible scenario, best possible scenario, and inter group exchange (selecting a random value from the other treatment group).*
- 2. In the three studies used to calculate sample size, the WOMAC score was evaluated using a 0 to 100 mm VAS scale. In the proposed study the evaluation of WOMAC was done using a categorical scale. The sponsor should justify the calculation of sample size based on a VAS scale to be applied to a categorical scale. Specifically, what does a difference of 6.4 mm in VAS means in terms of categorical change? What is the eventual power?*
- 3. The Division suggests that you start with a full model (including the interaction term) and then reduce the model if the interaction is found to be not significant. In case a significant interaction is found, look for the causes of such significant interaction and perform appropriate analysis.*
- 4. For the time-weighted average, you calculated the weights of 1:4:7:8:4 for observations at Weeks 0, 1, 4, 8, and 12, respectively. These weights were determined by calculating the area under curve using the trapezoidal rule. In the FDA's proposal, the time weighted average was defined as the total area under curve divided by length of treatment. Using this rule the weights are variables and are $1/L_j$, $4/L_j$, $7/L_j$, $8/L_j$, $4/L_j$, where L_j is the length of time patient j was in the study. The FDA suggests only one such analysis.*
- 5. It is recommended that you specify the pooling rules in the protocol.*

Meeting Comments:

Novartis expressed their wish to submit six month safety data and the Division emphasized that the NDA submission needs to include the 12 month safety data at the time of submission. The

Division stated that unforeseen circumstances could occur, such as patient dropout and that it is important for the Division to have all of the data and that the submission should be able to stand on its own. Novartis stated understanding that 12 month data would need to be submitted with the NDA.

Novartis asked if the European safety reports were useful and what information did the Division want to see from the alternative formulation. The Division requested that Novartis report any unexpected events, such as deaths, that we would not expect, rather than a whole, separate database, the focus should be on anything that could affect labeling.

Novartis stated they would incorporate the chemistry comments. The Division asked if they planned on having a separate End of Phase 2 CMC meeting. Novartis stated they would be sending updated CMC information with the NDA. The Division strongly suggested they ask for an End of Phase 2 CMC meeting.

Novartis clarified that the time-weighted average was using the area under the curve for every patient divided by the amount of time the patients was in the study. The Division suggests that the time weighted average analysis be only as a secondary analysis. The primary efficacy analysis should be an end-of-trial (landmark) analysis at 12 weeks.

Minutes Preparer: Jane A. Dean, RN, MSN

Chair Concurrence: Sharon Hertz, MD

Drafted by: JD/6-29-04

Revised by: SCL/7-1-04;

LZ/7-8-04

JW/7-14-04

SH/7-26-04

Initialed by: JS/7-6-04

DB/7-12-04

TO/7-12-04

AR/7-13-04

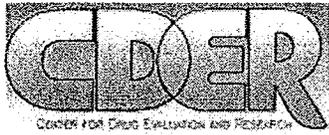
SH/7-26-04

Final: SH/7-26-04

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

/s/

Sharon Hertz
7/27/04 12:37:31 PM



MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 18, 2003

TIME: 10 am

LOCATION: S300 Corporate

APPLICATION (DRUG): PreIND 64334 (diclofenac sodium gel 1%)

SPONSOR: Novartis Consumer Health

TYPE OF MEETING: Guidance Meeting

MEETING CHAIR: James Witter, MD, PhD

MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Brian E. Harvey, MD, PhD	Deputy Director	ODEV/HFD-105
2. James Witter, MD, PhD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
3. Joel Schiffenbauer, MD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
4. Josie Yang, PhD	Pharm/Tox Team Leader	ODEV/DAAODP, HFD-550
5. John L. Smith, PhD	Chemistry Team Leader	ONDC/DNDCIII/HFD-830
6. Terri Rumble	Assoc. Dir. Regulatory Affairs	ODE V/HFD-105
7. Conrad Chen, PhD	Pharm/Tox Reviewer	ODEV/DAAODP, HFD-550
8. Carolyn L. Yancey, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
9. Tatiana Oussova, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
10. Michael Yao, MD	Medical Reviewer	ODEV/DAAODP, HFD-550
11. Chandra Churasia, PhD	Biopharm Reviewer	DPS/DPEIII, HFD-880
12. Suktae Choi, PhD	Statistical Reviewer	OB/DBIII/HFD-725
13. Diane Tesch	Consumer Safety Officer	OMP/DSI/HFD-046
14. Carmen DeBellis, RPh	Chief, Project Management	ODEV/DAAODP, HFD-550
15. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor Name</u>
1. Angela Browne, PharmD	Project Manager	Novartis
2. Jacob Zijlstra, PhD	Head, Clinical Development	Novartis
3. Morris Gold, ScD	Biostatistics	Novartis
4. Geoffrey Ross, MD	Global Medical Affairs	Novartis
5. Francois Elkik, MD	Head, Clinical Research, EU	Novartis
6. Lincy Thomas, PharmD	Post-Doc Fellow, Regulatory Affairs	Novartis
7. Henry Weidmuller	Director, Regulatory Affairs	Novartis
8. Claude Chieze, DVM	Senior Project Manager	Novartis
9. Gail Solomon, MS	Principal Scientist, Clinical Operations	Novartis
10. Linda Carter	Executive Director, FDA Liaison	Novartis
11. Helmut Albrecht, MD	VP, Clinical and Medical Development	Novartis

PURPOSE OF THE MEETING: To discuss the clinical development plan for diclofenac sodium gel, 1% and to reach concurrence regarding the adequacy of the proposed clinical development plan for the stated indication of a topical _____

MEETING OBJECTIVES:

Review of topics and FDA response:

1. Acceptability of the overall clinical development program
2. Acceptability of the design of the Phase 3 trials to support registration
3. Adequacy of the extent of exposure to support registration
4. Labeling, clinical studies section

QUESTIONS:

Question 1 (page 6 in briefing package)

Novartis Consumer Health, Inc. proposes that the program outlined below is adequate for registration. Does the Agency agree?

FDA Response: No. The acceptability of the phase I in vivo biopharmaceutics trial is dependent upon a number of issues including the use of maximal topical dosing (i.e. dose and surface area - number of joints treated, in this case, both knees) to determine the degree of systemic availability. In addition, the Sponsor should evaluate the effect of moderate exercise and local heat in its influence on drug absorption through the skin.

The Sponsor has conducted a skin irritation study in rabbits for up to 4 weeks. However, there is no animal study to support the safety of 8-week and 12-week human clinical trials. The Sponsor is advised to compare and to correlate the local toxicities of diclofenac sodium

gel and diclofenac diethylammonium gel from the existing animal data. Depending on the outcome of the analysis, additional animal toxicity studies may be required.

Additional Comments: The Sponsor clarified that they have conducted a three month study in rabbits with diclofenac diethylammonium and agreed to submit the information on the comparison of dermal toxicity of diclofenac sodium gel and diclofenac diethylammonium gel.

The Division cannot comment on three Phase I dermal studies without reviewing those protocols.

The proposed "pivotal" safety and efficacy studies (VOSG-PN-304 and VOSG-PN-310) are not adequate to support a claim for

such studies, because this is a new route of administration, should be 12 weeks in duration with three co-primary endpoints (of the target knee) of WOMAC pain, WOMAC function and a patient global that is intended to capture the patient's overall impression of the drug (i.e. in terms of efficacy and adverse events). The treatment effect for pain should be an improvement compared to baseline pain of at least 30%. These replicate studies should demonstrate superiority of the 1% gel over placebo gel at the landmark analysis of 12 weeks as in indicator of durability of response. These studies should also include a time-weighted-average approach for WOMAC pain which emphasizes the end of the trial and should be consistent with the treatment effect noted in the primary outcome.

The Sponsor was reminded of the problems associated with missing data when using the Last Observation Carried Forward (LOCF) statistical technique for analyzing data.

Question 2 (page 7 in briefing package)

NCH intends to conduct two randomized, double-blind, multicenter, placebo-controlled studies lasting 8 weeks in patients with osteoarthritis of the knee. Those patients satisfying baseline inclusion criteria will be randomized to one of two treatment arms: 4 grams diclofenac sodium gel, 1% (DSG, 1%) or placebo gel applied four times a day (QID). Each study will recruit 150 patients per treatment arm. Does the Agency agree that the two pivotal Phase 3 studies described will suffice to establish that 4 grams of DSG, 1%, applied QID is effective for

FDA Response: No. Please see answer to number one above. In addition, please explain why other dosing regimens of the 1% gel will not apparently be explored.

Please describe how a 4 gram dose can be accurately measured out by a consumer before application of the product. Over what size area will the drug be applied? Please, clarify what would be your approach to prevent consumers from misusing the product by increasing the amount per application.

The Sponsor is reminded that the target joint needs to be defined in the protocols; this same joint is the primary joint that is then treated and studied at each study visit. The Sponsor should consider including the contralateral joint as a secondary outcome in these trials, applying the same metrics as for the target joint. Labeling indication (assuming approval)

Additional Comments: The Sponsor noted that greater than four times application per day was not practical and that the current treatment regimen provides satisfactory results. Sponsor indicated that other joints (i.e. hand) could be studied in the future to meet unmet needs.

Question 3 (page 8 in briefing package)

Does the agency agree with the proposed duration and primary endpoint for the trial to achieve the claim

FDA Response: No. Please see answer to number one above. The phase 3 trials are to be 12 weeks in duration since this is a new route of administration.

On page 52, please change the wording of your question for the global rating of disease (#4) to "Considering all the ways this treatment has affected you, how well are you doing?"

Question 4 (page 9 in briefing package)

Does the agency agree that our proposed inclusion/exclusion criteria and monitoring for safety and tolerability is adequate?

FDA Response: The inclusion and exclusion criteria appear to be acceptable. However, it is unclear how rescue medication will be utilized in these studies. It is noted that patients may take acetaminophen up to 4 grams daily but what duration of this dosing will constitute an efficacy failure? The Division suggests that up to three consecutive days of rescue medication be administered and if a longer duration is needed, then this is a treatment failure. For analysis, the last observation carried forward (LOCF) should be that observation immediately prior to rescue medication.

Please, clarify whether those patients who took concomitant medications prohibited by the protocol, would be included in the final ITT analysis (p. 47 says "patients should not be discontinued for intake of disallowed treatment, unless there is a safety issue").

Additional Comments: The Sponsor is reminded to clarify rescue medication and concomitant medication in the protocol.

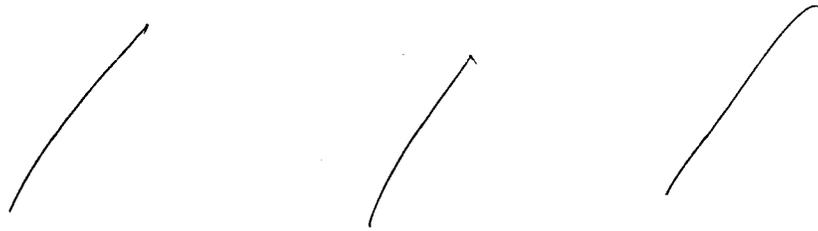
Question 5 (page 12 of briefing package)

NCH proposes that the outlined program of studies provides sufficient extent of exposure to support the claim that diclofenac sodium gel, 1% (DSG, 1%) is safe and effective when used at the proposed dose and regimen. Does the Agency agree?

FDA Response: For approval of a chronic-use therapy, it is expected that ICH numbers will be achieved for long-term safety assessment. Owing to the nature of this compound and the fact that a similar compound has been marketed overseas for an extended period of time, the projected number of patients at 75 (vs. 100) is acceptable. However, it is suggested that clinical chemistries be monitored at weeks 8 and 12 during the phase 3 trials. Also, the final

label is expected to contain language consistent with the current NSAID template.

Question 6 (page 14 of briefing package)

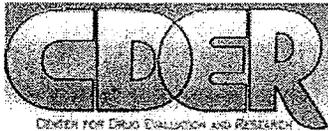


Minutes Preparer:	Jane A. Dean, RN, MSN
Chair Concurrence:	James Witter, MD, PhD
Drafted by:	JADean/12-15-03
Initialed by:	JWitter
Final:	12-17-03

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

/s/

James Witter
12/17/03 03:19:18 PM
Concur



MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 10, 2003
TIME: 1 pm – 2:30 pm
LOCATION: Corporate S300
APPLICATION (DRUG): PreIND 64334 (diclofenac sodium gel 1%)
SPONSOR: Novartis Consumer Health, Inc.
TYPE OF MEETING: Pre IND meeting
MEETING CHAIR: James Witter, MD, PhD
MEETING RECORDER: Ms. Jane A. Dean, RN, MSN

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name & HFD#</u>
1. Lee S. Simon, MD	Division Director	ODEV/DAAODP, HFD-550
2. James Witter, M.D., PhD	Medical Officer Team Leader	ODEV/DAAODP, HFD-550
3. Josie Yang, PhD	Pharmacology Team Leader	ODEV/DAAODP, HFD-550
4. Carmen DeBellis, RPh	Chief Project Manager	ODEV/DAAODP, HFD-550
5. David Hilfiker	Chief Project Manager	ODEV/DAAODP, HFD-560
6. Dennis Bashaw, PharmD	Biopharm Team Leader	OPS/OCPB/DPE3, HFD-880
7. John Smith, PhD	Chemistry Team Leader	ODEV/DAAODP, HFD-550
8. Laura Shay, RN, NP	Project Manager	ODEV/DAAODP, HFD-550
9. Charles Ganley, MD	Division Director	ODEV/DAAODP, HFD-560
10. Curtis Rosebraugh, M.D., M.P.H.	Deputy Director	ODEV/DAAODP, HFD-560
11. Andrea Leonard-Segal, M.D., M.S.	Medical Officer Team Leader	ODEV/DAAODP, HFD-560
12. Rosemarie Neuner, M.D., M.P.H.	Medical Officer	ODEV/DAAODP, HFD-560
13. Leah Cutter, Ph.D.	Project Manager	ODEV/DAAODP, HFD-560
14. Jane A. Dean, RN, MSN	Project Manager	ODEV/DAAODP, HFD-550

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. Angela Browne, PharmD	Manager, Regulatory Affairs	Novartis Consumer Healthcare
2. Cynthia Psaras, PhD	Assoc. Director, Regulatory Affairs	Novartis Consumer Healthcare
3. Chang Lee, MD, PhD	Director, Clinical Research	Novartis Consumer Healthcare
4. Gail Solomon, MS	Principal Scientist, Clinical Research	Novartis Consumer Healthcare
5. Morris Gold, ScD	Director, Biostatistics	Novartis Consumer Healthcare
6. Jacob Zijlstra, PhD	Dir., Preclinical Development & Tech.	Novartis Consumer Healthcare
7. Hongchun Qui, MS, PhD	Principal Scientist, Formulation Dev.	Novartis Consumer Healthcare
8. Dorothy Heidemann, MS	Prin. R&D Proj. Manager, Form. Dev.	Novartis Consumer Healthcare
9. Jeffrey Needels, MS	Principal Scientist, Prod. Dev. Stability	Novartis Consumer Healthcare
10. Claude Chieze	Project Manger, Project Management	Novartis Consumer Healthcare
11. Geoffrey Ross, MD	Medical Affairs	Novartis Consumer Healthcare
12. Helmut Albrecht, MD	VP, Research & Dev.	Novartis Consumer Healthcare

PURPOSE OF THE MEETING: To discuss with the agency the sponsor's plans for submitting an IND for diclofenac sodium gel, 1%.

MEETING OBJECTIVES:

1. Concurrence on the approach proposed for chemistry, manufacturing and control issues;
2. Concurrence on the adequacy of the preclinical program;
3. Concurrence on the adequacy of the clinical development plan for the stated indication.

QUESTIONS:

Chemistry, Manufacturing and Controls

Sponsor Question #1:-- Manufacturing/Packaging process

Is the manufacturing process, as presented, acceptable to establish both sites as potential manufacturers of the commercial product?

FDA Response: It is acceptable to manufacture the drug product at these sites, provided that the release analysis and the stability of the drug product manufactured at these sites show comparable and satisfactory data.

Sponsor Question #2: Stability -Does the Agency agree that the proposed stability plans (Appendix B and Appendix C) will provide sufficient data to allow both facilities _____, to manufacture commercial product:

- a) To be packaged at either manufacturing site in aluminum tubes within the 20-g to 100-g size?
- b) To be packaged in _____

FDA Response: The proposed stability plans are acceptable with the following comments:

1. Your stability protocol as shown on page 55 does not include testing on _____
Please revise it to reflect the frequency of _____ testing.
2. For the proposed regulatory specifications (pages 71 &72), include the acceptance criteria for _____

Please verify that all the proposed manufacturing and packaging facilities are cGMP compliant.

Comments Regarding Formulation: For each non-compendial ingredient (page 6), please provide the identity (i.e. the chemical name if is a single compound, the composition if it is a mixture) and specification, or a reference to an appropriate DMF.

Nonclinical

Sponsor Question #3: Adequacy of nonclinical program - Novartis Consumer Health, Inc. (NCH) feels that the nonclinical programs conducted with the active ingredient, diclofenac sodium, and the drug product, diclofenac sodium gel, 1 %, are adequate to support use of this drug product topically in humans.

Does the agency agree?

FDA Response: The studies conducted with the drug product, diclofenac sodium 1% gel, are adequate to support the proposed clinical studies in humans.

Clinical

Sponsor Question #4: Pharmacokinetic study – Study design – A plasma PK study (VOSG-PN-107) is proposed to establish the relative bioavailability and pharmacokinetic similarity between the new diclofenac sodium gel, 1%, and the well established diclofenac diethylammonium (DEA) gel, 1.16%. An oral diclofenac sodium arm is included. NCH believes that the study design is adequate to compare the two topical formulations and provide considerable evidence towards establishing their similar systemic safety profiles.

Does the Agency agree?

FDA Response: For topical products, we require that the doses, surface area of application, and dosing frequency in a definitive topical PK trial represent the upper limits of the proposed indication. Given that the sites of application used in this trial were on intact skin, we should limit the use of this product to such areas. As to the study itself, the study design seems adequate, but ultimately this is a review issue.

Sponsor Question #5: - Pharmacokinetic study – metabolites - The pharmacokinetic profile of diclofenac is well established. The major metabolite is 4'OH-diclofenac (DF); other metabolites (3'OH-DF and 5'OH-DF) account for 25% or less of total free and conjugated compounds (i.e., diclofenac and 3'OH, 4'OH, and 5'OH-DF metabolites) excreted in the urine. Currently, only the 4'OH-DF metabolite sample is commercially available for laboratory analysis. Therefore, the Sponsor does not plan to determine levels of 3'OH-1 and 5'OH-DF metabolites in its PK study.

Does the Agency agree?

FDA Response: We will require only the parent and primary metabolite be followed pharmacokinetically.

Sponsor Question #6: Proposed indication – In addition to the 31 previously conducted efficacy studies in diclofenac DEA gel, 1.16%, a well designed and adequately sized, double-blind, placebo-controlled study in patients with knee osteoarthritis (OA), VOSG-PE-303, has recently been completed.

_____ ng. NCH believes that the additional — proposed Phase 3 studies in _____,) osteoarthritis and _____) are adequate to demonstrate and confirm the efficacy of diclofenac sodium gel, 1%, for the proposed indication _____

Does the Agency agree?

FDA Response: The Agency has concerns related to the development of a topical NSAID product

[Handwritten signatures]

1 Page(s) Withheld

 ✓ Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Sponsor Question #7: Primary Endpoint - The Agency recently proposed the use of three primary endpoints (pain, function, and global evaluation) in analgesic studies. In its pivotal OA study, VOSG-PN-304, NCH plans to use the well-defined WOMAC index, which uses pain, stiffness, and physical function scores as the primary efficacy outcome.

Does the Agency agree?

FDA Response: The use of any primary efficacy endpoint at 2 weeks is

Sponsor Question #8: Safety – diclofenac sodium gel – In the proposed clinical development plan more than 800 patients in a total of nine studies will be exposed to diclofenac sodium gel, 1%. Three hundred (300) of these subjects will be treated with diclofenac sodium gel, 1%, for three months. NCH believes that this program, supported by the extensive safety information available for the diclofenac DEA gel, will adequately demonstrate safety of this formulation.

Does the Agency agree?

FDA Response: The use of the clinical trial safety data base and the spontaneous case reports of postmarketing adverse events associated with the use of the diclofenac DEA gel by the Sponsor in support of the proposed diclofenac sodium gel is directly dependent on the demonstration of bioequivalency between the 2 formulations in the proposed biopharm studies. Based on what is known about the metabolism of diclofenac it is not clear if the hepatotoxicity associated with the drug is truly dose dependent or a rare idiosyncratic reaction. If it is the latter, then the proposed safety database of 300 patients at 3 months may be inadequate to capture such an event. If hepatotoxicity risk is related to the dose, the Sponsor will also need to supply information regarding the following:

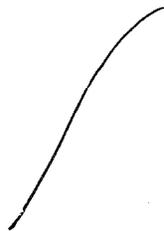
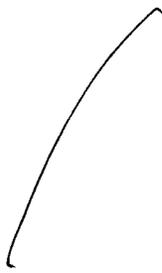
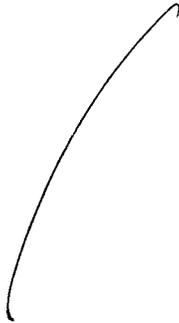
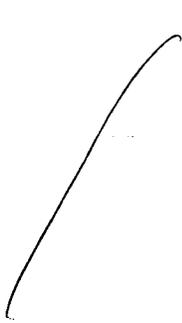
- how a 4 g dose can be accurately measured by a consumer before application of the product,*
- how to prevent consumers from misusing the product by increasing the amount per application (e.g. using on multiple sites simultaneously), preventing the concomitant use of heating pads and wraps/bandages which may lead to increase dermal absorption.*

Sponsor Question #9: Proposed marketing – Diclofenac DEA gel, 1.16%, (Voltaren® Emulgel®), was first marketed in Switzerland in 1985 and is currently available for OTC use in over 40 countries. Based on sales data through July 2002, it is estimated that _____ consumers have used this formulation. In addition, a total of 30,566 patients participated in five post-marketing studies and 2,158 subjects participated in 41 Phase 1, 2, and 3 clinical studies during this period. Diclofenac DEA gel, 1.16%, has been demonstrated to be safe for OTC use worldwide. Maximum plasma concentration of diclofenac after topical administration of diclofenac DEA gel, 1.16%, are significantly lower than plasma concentrations after oral administration of diclofenac sodium tablets. Pre-clinical data comparing the two diclofenac topical formulations (DEA vs. sodium salt) demonstrate there is no significant difference in the amount of diclofenac absorbed through the skin. Given the extraordinary safety data and extensive use of diclofenac and after conducting the proposed clinical program, NCH believes that diclofenac sodium gel, 1%, _____

Does the Agency agree?

FDA Response: The sponsor is referred to the Agency's responses to Questions 6, 7 and 8 regarding

Sponsor Question #10: _____



Minutes Preparer: Jane A. Dean, RN, MSN

Chair Concurrence: James Witter, MD, PhD

Drafted by: J. A. Dean

Initialed by: J. Witter

Final: 5/23/03

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Lee Simon

5/27/03 07:32:54 PM