CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BL 103772 / 5056

Trade Name: **Remicade**

Generic Name: **Infliximab**

Sponsor: **Centocor Inc.**

Approval Date: **September 3, 2003**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 5056

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 5056

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103772/5056

SEP 03 2003

Centocor, Inc.
Attention: Stella S. Jones, Ph.D.
Vice President, Worldwide Regulatory Affairs
200 Great Valley Parkway
Malvern, PA 19355-1307

Dear Dr. Jones:

Your request to supplement your biologics license application for Infliximab to revise the Patient Information Sheet has been approved.

This fulfills your commitment "to submit a labeling supplement in accordance with 21 CFR 601.12(f)(1) that provides for revisions to the Patient Information Sheet by April 15, 2003," as stated in commitment number 1 of the April 1, 2003 approval letter.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10 point font.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

FOR P.K.

Patricia Keegan, M.D.
Acting Director
Division of Clinical Trials Design and Analysis
Office of Therapeutics Research and Review
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
LETTER: Fulfillment of PMC (FPC)
Summary Text: Clinical Supplmt. – Labeling Only
REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:

- **Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).**

RIS Data Check:

- **Verify short summary – Ltr. & Submission screen should match.**
- **Check Letter for PMCs (if PMCs – add "PMCs – Approved With" special characteristic code.)**
- **Perform Review Completion Process**
- **Milestone: Confirm Approved Status**

cc: Keith Webber, HFM-555
Steven Kozlowski, HFM-561
Marc Walton, HFM-576
E. Unger, HFM-576
DARP BLA file, HFM-585
Karen Weiss, HFM-500
QAS, HFM-4
RIMS, HFM-110
B. Conner, HFM-588
T. Stifano, OCBQ, HFM-600
Eva Barrion, APLB, HFM-602 (with final draft PI)
M. Kiester, DDMAC, HFD-42 (with final draft PI)
D. Taub, ORP, DIDP, HFD-013
M. Dempsey, OPSS, HFD-400
E. Rivera-Martinez, IPCB, HFD-322
H. Brubaker, ORP/DIDP, HFD-013
T. Martin, OEP, HFD-006
P. Lincoln-Smith, HFM-570

History: HFM-588:B. Conner:7.29.03: K. Townsend: 8.1.2003: 9.3.2003

File Name: (S:\Conner\BLA\Letters\103772_5056AP)

Office	Name/Signature	Date
OTRR	B Conner	9/3/03
OTRR/OARP	Laura D Jones	9/3/03
DMRP	Dyc ha Jones	9-3-03
OCTOA	F.A.R.	9/3/03
SARP	Kelly Townsend	9/4/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 5056

LABELING

Rx Only

REMICADE® (infliximab)
Patient Information Sheet

You should read this information sheet before you start using REMICADE (pronounced rem-eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet does not take the place of talking with your doctor. You and your doctor should talk about your health and how you are feeling before you start taking REMICADE, while you are taking it and at regular checkups. If you do not understand any of the information in this sheet, you should ask your doctor to explain what it means.

What is REMICADE?

REMICADE is a medicine that is used to treat adults with moderate to severely active rheumatoid arthritis and Crohn's disease. Your doctor has decided to treat you with REMICADE because your disease is still active even though you have tried other treatments.

How does REMICADE work?

The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis or Crohn's disease, but blocking TNF with REMICADE may reduce the inflammation caused by too much TNF in your body. You should also know that REMICADE may help you feel better but can also cause serious side effects and can reduce your body's ability to fight infections (see below).

What should I know about the immune system, and taking REMICADE for Rheumatoid Arthritis or Crohn's Disease?

The immune system protects the body by responding to "invaders" like bacteria, viruses and other foreign matter that enter your body by producing antibodies and putting them into action to fight off the "invaders." In diseases like rheumatoid arthritis and Crohn's disease, your body's immune system produces too much TNF. Too much TNF can cause your immune system to attack healthy tissues in your body and cause inflammation. If this condition is left untreated, it can cause permanent damage to the body's bones, cartilage and tissue.

While taking REMICADE can block the TNF that causes inflammation, it can also lower your body's ability to fight infections. So, taking REMICADE can make you more prone to getting infections or it can make an infection that you already have worse. You should call your doctor right away if you think you have an infection.

What important information should I know about treatment with REMICADE?

REMICADE, like other medicines that affect your immune system, is a strong medicine that can cause serious side effects. Possible serious side effects include:

<u>Serious Infections:</u>

- Some patients have had serious infections while receiving REMICADE. Some of the patients have died from these infections. Serious infections include TB (tuberculosis), and infections

caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you may be getting an infection. If you have any of these symptoms while you are taking or after you have taken REMICADE, you should tell your doctor right away.

Heart Failure:

- If you have been told that you have a heart problem called congestive heart failure and you are currently being treated with REMICADE, you will need to be closely monitored by your doctor. If you develop new or worse symptoms that are related to your heart condition, such as shortness of breath or swelling of your ankles or feet, you must contact your doctor immediately.

Allergic Reactions:

- Some patients have had severe allergic reactions to REMICADE. These reactions can happen while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE treatment and give you medicines to treat the allergic reaction.
- Some patients who have been taking REMICADE for Crohn's disease have had allergic reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call your doctor right away if you develop any of these symptoms or any other unusual symptoms such as difficulty swallowing.

Nervous System Disorders:

- There have been rare cases where people taking REMICADE or other TNF blockers have developed disorders that affected their nervous system. Signs that you could be having a problem include: changes in your vision, weakness in your arms and/or legs, and numbness or tingling in any part of your body.

Other Important Information:

People who have been treated for rheumatoid arthritis or Crohn's disease for a long time tend to be more prone to a type of blood cancer called lymphoma. There have been some patients that while taking REMICADE developed other types of cancer, but, the number of people taking REMICADE that developed cancer does not seem to be much different from what you would expect to see in people who are not taking REMICADE.

Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these symptoms your doctor may decide to stop your treatment with REMICADE.

What are the more common side effects of REMICADE?

The more common side effects with REMICADE are respiratory infections (that may include sinus infections and sore throat), coughing and stomach pain.

Who should not take REMICADE?
YOU SHOULD NOT take REMICADE if you have:

- Heart failure, unless your doctor has talked to you and decided that you are able to take REMICADE.
- Had an allergic reaction to REMICADE or any other product that was made with murine (mouse) proteins.

What health concerns should I talk to my doctor about?
Before receiving your first treatment with REMICADE you should tell your doctor if you:

- Have or think you may have any kind of infection. The infection could be in only one place in your body (such as an open cut or sore), or an infection that affects your whole body (such as the flu). Having an infection could put you at risk for serious side effects from REMICADE.
- Have an infection that won't go away or a history of infection that keeps coming back.
- Have had TB (tuberculosis), or if you have recently been with anyone who might have TB. Your doctor will examine you for TB and perform a skin test. If your doctor feels that you are at risk for TB, he or she may start treating you for TB before you begin REMICADE therapy.
- Have lived in or visited an area of the country where an infection called histoplasmosis or coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If you don't know if the area you live in is one where histoplasmosis or coccidioidomycosis is common, ask your doctor.
- Have or have previously had heart failure or other heart conditions.
- Have or have had a condition that affects your nervous system, like multiple sclerosis, or Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a seizure.
- Are pregnant or nursing.
- Have recently received or are scheduled to receive a vaccine.

Can I take REMICADE while I am on other medicines?
Tell your doctor if you are taking any other medicines including over the counter medicines, supplements or herbal products before you are treated with REMICADE. If you start taking or plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

How will REMICADE be given to me?
REMICADE will be given to you by a healthcare professional. REMICADE will be given to you by an IV. This means that the medicine will be given to you through a needle placed in a vein in your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for a period after you receive REMICADE, you will be monitored by a healthcare professional. Your doctor may ask you to take other medicines along with REMICADE.

Only a health care professional should prepare the medicine and administer it to you.

How often will I receive REMICADE?

Rheumatoid Arthritis

If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE and may change your dose or dose you more frequently (as often as every 4 weeks).

Crohn's Disease or Fistulizing Crohn's Disease

If you are receiving REMICADE for active Crohn's disease or fistulizing Crohn's disease, you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE and may change your dose.

What if I still have questions?

If you have any questions, or problems, always talk first with your doctor. You can also visit the REMICADE internet site at www.remicade.com.

Product developed and manufactured by:
CENTOCOR, INC.
200 Great Valley Parkway
Malvern, PA 19355

Revised draft xxx, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BL 103772 / 5056

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

TELECON

Date: September 3, 2003; 6:00 PM

To: BLA STN 103772/5020, 103772/5056

From: Beverly Conner, Pharm.D., OTRR/DARP, HFM-588

Sponsor: Centocor Inc.

Product and Subject: Infliximab approvals, 103772/5020 to include a contraindication for patients with [redacted] update the Warnings and Adverse Reactions sections; and update the patient information sheet and 103772/5056 to revise the Patient Information Sheet.

Sponsor Representative (s): Stella Jones, Ph.D.

FDA Representative(s): Beverly Conner, Pharm.D.

Conversation: I spoke to Dr. Stella Jones and confirmed that facsimile of the approval letters for 103772/5020 and 103772/5056 were received by Centocor.

M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

REVIEW MEMO

Review Date: August 15, 2003

To: BLA STN 103772/5056

From: Beverly Conner, Pharm.D., DARP, OTRR, HFM-588

Through: Karen Jones, OCTGT Branch Chief, DARP, OTRR

Sponsor: Centocor Inc.

Product and Subject: Infliximab, Remicade®; Prior approval labeling supplement to revise the Infliximab Patient Information Sheet.

Supplement Submission Date: April 3, 2003

Supplement STN 103772/5056 was submitted to make corrections to the Patient Information Sheet as a result of the April 1, 2003, STN 103772/5032 efficacy supplement approval "to expand indication to include reducing the number of draining rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease." In the April 1, 2003, approval letter for 103772/5032 FDA requested that Centocor submit the revisions to the Patient Information Sheet to FDA by April 15, 2003. The company easily met this deadline with their submission of April 3, 2003.

Toni Stifano, CBER Office of Compliance and Nancy Chamberlin of Advertising and Promotional Labeling Branch were assigned to the supplement and requested to provide revisions to the package insert. Nancy Chamberlin recommended changes and these are included in her review memo of June 10, 2003. I forwarded these recommendations to Toni Stifano. On July 18, 2003 the review committee held a labeling meeting to discuss labeling revisions to Patient Information Sheet for 103772/5056 and 103772/5020 (the PI for this supplement was also reviewed). Dr. Karen Weiss, Dr. Marc Walton, Dr. Ellis Unger, Toni Stifano, myself and Marci Kiester and Eva Barron of OMP, DDMAC attended this meeting. On July 23, 2003, I sent a revised patient information sheet that incorporated the corrections discussed during the July 18th meeting and sent it to all of the attendees of the July 18th meeting for comment. These draft comments also went out for comment to Dr. Li Liang and

Dr. Jeffrey Siegel since they were the key reviewer for STN 103772/5032. I received electronic corrections back from Toni Stifano, Drs. Seigel, and Walton; these are attached with the each of the reviewer's e-mails.

FDA's revisions were incorporated in the draft Patient Information Sheets and faxed back to the company on July 25, 2003. On July 28, 2003, Dr. Stella Jones, of Centocor called with several concerns regarding the changes. The issues included: a question of why the Crohn's disease maintenance dosing information had been deleted from the document; why certain important information was moved from the first page of the document to less visible areas; and last, why was the word REMICADE bolded throughout the document. I told Dr. Jones I would arrange a teleconference that included Toni Stifano.

On July 29, 2003, Toni Stifano explained to Dr. Stella Jones that her answer for moving moved certain information around was two-fold. First she is following a format so that the document will be consistent with the patient information for other products from other companies and the second reason being that the patient will not be alone in making the decision on whether he/she should be treated with Infliximab since it is administered IV in a clinic, hospital, or doctor's office. The prescribing MD should have enough history to evaluate whether the patient is a good candidate and he should act as the intermediary in making sure the patient is informed of the risks of the product. Toni noted that she accidentally deleted the Crohn's prescribing information. Centocor agreed to revise the Patient Information Sheet per FDA suggested changes and I recommended that the company submit the final draft patient information sheet for this supplement when the review of the CHF patient information sheet for STN 103772/5020 is completed.

On September 3, 2003, Centocor submitted the final draft patient package sheet by e-mail and noted that the formal submission would be submitted as an electronic amendment.

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Case Management
Advertising and Promotional Labeling Branch
REVIEW MEMORANDUM

DATE 6/10/2003

FROM: Nancy Chamberlin, PharmD., CSO, NChamberlin
APLB/DCM/OCBQ, HFM-602

TO: Beverly Conner, CSO, DARP/OTRR, (HFM-588)

THROUGH: Glenn N. Byrd, M.B.A., Branch Chief, APLB GB
APLB/DCM/OCBQ, HFM-602

RE: Infliximab (Remicade®) 5056
Labeling submission (STN# 103772/~~16921~~)
Manufacturer: Centocor
Label Review No(s): P 030603002
Description: Patient Information Sheet

I have reviewed the labeling submission dated April 2, 2003, which was forwarded via email on April 17, 2003, and have the following comments:

- On page 3, the sponsor proposes to add [redacted] o the list of serious infections. They should also ad[redacted] o match the package insert.
- Please add [redacted] statements in lay language to the important information the patient should know about the treatment section.
- On page 4, the sponsor had modified the adverse events listing; however, it was incomplete. Please revise the adverse events listing to include other items that occurred such as [redacted]

Please advise the sponsor to make appropriate revisions.

Firm name: Centocor (P030603002)

Letter type: Memorandum

History:
Prepared by N. Chamberlin 6/3/03
Comments by G Byrd: 6/4/03
Finalized by N. Chamberlin: 6/10/03

File: Remicade.patientpi.review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Stella S. Jones, Ph.D.
Centocor, Incorporated
200 Great Valley Parkway
Malvern, PA 19355-1307

APR 10 2003

Dear Dr. Jones:

SUBMISSION TRACKING NUMBER (STN) BL 103772/5056 has been assigned to your recent supplement to your biologics license application for Infliximab, received on April 3, 2003, to revise the Patient Information Sheet.

Unless we notify you within 60 days of the receipt date that the supplement is not sufficiently complete to permit substantive review, this supplement will be considered filed.

All future correspondence or supportive data relating to this supplemental application should bear the above STN and be addressed to the Director, Division of Application Review and Policy, Office of Therapeutics Research and Review, HFM-585, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD, 20852-1448.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need to discuss the technical aspects of this supplement, you may obtain the name of the chairperson of the review committee by contacting this division at 301-827-5101. Any questions concerning administrative or procedural matters should also be directed to this division.

Sincerely yours,

Carl Dyc

for Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: DARP BLA File, HFM-585
Beverly Conner, HFM-588

OTRR/DARP: K.Townsend:4.9.2003
S:\STN 2003\103772.5056.PAS.doc

COMMUNICATION TYPE:

LETTER: Acknowledgment Letter (ACK)
Summary Text: STN Assignment – Pre Approval (PAS)

SS & RIS Data Check:

- **If "Unacceptable for Filing (UN)" add under LETTER.**
- **Communication**
- **Verify inclusion of Option 1 paragraph for manufacturing supplmts *(if Alt. 6 is not used).***

RIS Data Check:

- **Submission Screen: In Arrears Box Is Checked**
- **Milestone: Confirm "UN" Entry & User Fees Not Paid -- The Clock Has Stopped. First Action Due Close Date And The New "UN" Entry Date Should Match**
- **No Action Due Date**
- **STN Status – Unacceptable for Filing**

Division	Name/Signature	Date
DARP	B Conner	4/9/03
DARP	Dep for Joyce	4-10-03
DARP	Kelly Townsend	4/15/03