

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125289**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

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**MEMORANDUM**

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DATE: April 2, 2009

TO: File, BLA 125289 Simponi (golimumab)

SPONSOR: Centocor Ortho Biotech, Inc.

FROM: Curtis J. Rosebraugh, M.D., M.P.H.,  
Director, Office of Drug Evaluation II *CR* 4/24/09

RE: Risk Evaluation and Mitigation Strategy (REMS)

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Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- (F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Simponi (golimumab) outweigh the risks of serious infections, including invasive fungal infections and other opportunistic infections, as well as malignancies, congestive heart failure and peripheral demyelinating disorders.

In reaching this determination, we considered the following:

- A. Simponi (golimumab) is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. It has been estimated that over two million patients carry a diagnosis of rheumatoid arthritis. Over one million patients carry the diagnosis of psoriatic arthritis, and a similar number of patients have the diagnosis of ankylosing spondylitis.

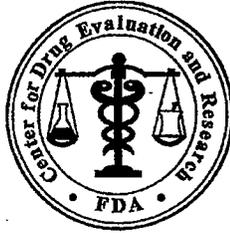
- B. Rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis are chronic inflammatory and destructive arthritides that can result in disability and premature mortality. Elevated levels of Tumor Necrosis Factor (TNF) are essential in the pathogenic processes of these disorders; TNF inhibitors such as Simponi (golimumab) have been demonstrated to control inflammation and inhibit destruction of affected joints.
- C. In five clinical trials lasting six months or longer, compared with placebo, Simponi (golimumab) has been shown to be effective for the above indications.
- D. Simponi (golimumab) will be approved as a treatment to reduce the signs and symptoms of moderate to severe rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis which are chronic auto-immune disorders. The expected duration of therapy with Simponi (golimumab) is life-long.
- E. During the review of the Simponi (golimumab) application we have identified signals of serious risks observed with the use of Simponi (golimumab), namely serious infections, including invasive fungal infections and other opportunistic infections, as well as malignancies, and congestive heart failure (CHF). An occurrence of demyelinating disorders has been observed with Simponi (golimumab) treatment, but association with Simponi (golimumab) exposure remains unclear. Serious infections, malignancies, and congestive heart failure are events that lead to hospitalizations and, in severe cases, may lead to fatal outcomes. Background rates of serious infections in rheumatoid arthritis (RA) patients taking non-biologic DMARDS is approximately 2 to 4 events per 100 patient-years and rates have been estimated to be as high as 5 to 6 events per 100 patient-years in RA patients receiving TNF inhibitors. Background rates of malignancies are approximately 1.3 to 1.4 events per 100 patient-years. Data are variable regarding the effect of TNF inhibition on the risk of malignancy. RA patients have an almost two-fold increased risk of developing CHF as non-RA patients, with a cumulative incidence over 30 years of 34% compared to 25% in non-RA patients in some large published cohorts. Exploratory controlled trials of TNF inhibitors for CHF have demonstrated worse outcomes for patients with CHF who are treated with TNF inhibitors. There are no data available on the background incidence of demyelinating disorders in RA patients. Information on the background incidence of these serious risks in PsA and AS is not available.
- F. Simponi (golimumab) is a new molecular entity.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Simponi (golimumab) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Simponi (golimumab). FDA has determined that Simponi (golimumab) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning these risks could affect patients' decisions to use Simponi (golimumab). FDA has also determined that patient labeling could help prevent serious adverse events related to use of the product.

The elements of the REMS will be a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

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Curtis Rosebraugh, M.D., M.P.H.,  
Director, Office of Drug Evaluation II



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

Date: **April 14, 2009**

To: **Bob Rappaport, MD, Director  
Division of Anesthesia, Analgesia, and Rheumatology  
Products (DAARP)**

Through: **Claudia Karwoski, Pharm.D., Director (Acting) *Claudia Karwoski*  
Division of Risk Management (DRISK) 4/14/09**

From: **OSE Simponi REMS Review Team**

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Christopher Wheeler, Pharm.D., Safety Regulatory Project  
Manager, Office of Surveillance and Epidemiology (OSE)

Subject: **Review of Risk Evaluation and Mitigation Strategy (REMS)  
submitted March 20, 2009**

Drug Names: **Simponi® (golimumab)**

Application Type/Number: **BLA 125289**

Applicant/sponsor: **Centocor Ortho Biotech, Inc.**

OSE RCM #: **2008-1050**

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# **1 Introduction**

This review follows a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Simponi (golimumab) requested by DAARP through email correspondence on October 8, 2008 to address the occurrence of unrecognized histoplasmosis and other invasive fungal infections in patients treated with tumor necrosis factor (TNF) blockers.

The Sponsor submitted a proposed REMS for Simponi on December 19, 2008 and DRISK provided comments in an interim review on March 9, 2009. FDA issued comments on the proposed REMS on March 9, 2008. The Sponsor submitted a revised REMS proposal on March 20, 2009 which is the subject of this review.

## **2 Material Reviewed**

- September 4, 2008 FDA Request for TNF Class Safety Labeling Changes and REMS to address the risk of histoplasmosis.
- October 8, 2008 e-mail of Golimumab REMS notification from DAARP to Centocor Ortho Biotech.
- Centocor Ortho Biotech's Proposed REMS submission submitted December 19, 2008.
- DRISK Review of Cimzia REMS dated December 24, 2008.
- Cimzia (certolizumab pegol) (modified) REMS Approval Letter, signed December 31, 2008 by Joyce Korvick, DGP.
- Worthy K, DRISK Interim Review of Simponi REMS dated March 3, 2009.
- Centocor Ortho Biotech's revised Proposed REMS for Simponi (BLA 125289) dated March 19, 2009.
- Mills S. Review of Patient Labeling (Medication Guide), BLA 125289, dated March 20, 2009.
- Mena-Grillasca, Carlos, DMEPA Carton and container labeling review, dated March 20, 2009

## **3 Proposed REMS**

### **3.1 Goals**

The sponsor proposed the following goal:

To communicate and mitigate the risks associated with Simponi therapy by:

- Alerting and warning healthcare professionals about cases of unrecognized histoplasmosis and other invasive fungal infections associated with tumor necrosis factor (TNF) blocker use.
- Educating patients about the risks associated with Simponi therapy including tuberculosis (TB) and infections caused by viruses, fungi, and bacteria spreading throughout the body.

## **3.2 REMS Elements**

The proposed REMS includes a Medication Guide, communication plan, and a timetable for submission of assessments with the information needed for assessment of the REMS. Each element is described below and the final formatted REMS is presented in Appendix A.

### **3.2.1 Medication Guide**

DRISK's review of the proposed Medication Guide (MG) was completed on March 20, 2009.

- Medication Guides will be dispensed with each SIMPONI<sup>®</sup> pre-filled syringe or autoinjector in accordance with 21 CFR 208.24. The Medication Guide will be included in each carton that contains one 50 mg pre-filled syringe or auto injector. The conspicuous statement: "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide" will be added to each carton.
- Medication Guides will also be provided to physician offices for distribution by prescribing physicians.

### **3.2.2 Communication Plan**

The Sponsor will implement a communication plan for healthcare providers (HCPs), specifically rheumatologists, pulmonologists, infectious disease specialists, and primary care physicians (e.g. Family Practice, General Internists, Obstetrician/Gynecologists, and Emergency Medicine) who may potentially prescribe TNF blockers or treat patients who may present with symptoms, by conveying the following information:

- The risk of developing invasive fungal infections, including histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections during treatment with TNF blockers
- Provide descriptive information on the signs and symptoms of fungal infections, including histoplasmosis.
- Provide references and background information regarding the treatment of these infections.

These physicians will be identified through the American Medical Association “All physician” database. The total number of prescribers, sub-specialists and primary care physicians (as defined above) from this data set is approximately 400,000.

This element of the REMS is not intended to continue over the lifetime of the product; it will function only to disseminate the new safety information about histoplasmosis and other invasive fungal infections associated with TNF blocker use.

The communication plan includes a Dear Healthcare Professional Letter and the Simponi Serious Infection Education Guide. These materials will also be available in printable form on a separate REMS website that can be accessed via a link (e.g. “Important Safety Information Regarding Serious Infections including TB and Fungal Infections”) from the company website.

A mass mailing of educational materials will include the professional labeling, the Dear Healthcare Professional Letter, the Simponi Serious Infection Education Guide, and the Medication Guide will be directed at all as defined above. The timeframe for dissemination of this “mass mailing” was not specified and should be (see Comments below).

These materials will also be distributed via the Health Care Notification Network that includes physicians who opt in for e-mail delivery of Dear Healthcare Professional letters.

### **3.2.2.1 Dear Healthcare Professional Letter**

The sponsor will disseminate a Dear Healthcare Professional Letter within 60 days of the REMS approval. The purpose of this letter is to inform HCPs of the risk for developing invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections during treatment with TNF blockers, the signs and symptoms of possible systemic fungal infections, the need to suspect fungal infection in symptomatic patients who live or travel to endemic regions, and the need to reevaluate the benefit/risk prior to restarting TNF blocker therapy after recovery of an antifungal infection. Comments on the Dear HCP Letter are provided in Appendix B.

### **3.2.2.2 Simponi Serious Infection Education Guide**

Centocor Ortho Biotech has developed an educational piece for health care professionals that will serve as an additional mechanism to inform healthcare professionals of the risks associated with Simponi and other TNF blockers. Comments on the guide are provided in Appendix C.

### **3.2.3 Elements to Assure Safe Use**

The REMS does not include any Elements to Assure Safe Use.

### **3.2.4 Implementation System**

An implementation system is not a required component of the proposed REMS if there are no elements to assure safe use.

### **3.2.5 Timetable for submission of Assessments**

The sponsor proposes the following timetable for submission of assessments of the Simponi REMS:

- 1<sup>st</sup> FDAAA Assessment: 18 months from product launch
- 2<sup>nd</sup> FDAAA Assessment: 3 years from product launch
- 3<sup>rd</sup> FDAAA Assessment: 7 years from product launch

We recommend that assessments be submitted within 60 days of the close of the interval.

### **3.3 REMS Assessment Plan**

Information needed for assessment is not a required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS Supporting Document.

1. An evaluation of patients' and prescribers' understanding of the serious risks of Simponi, including the risk of histoplasmosis and other invasive fungal infections.
2. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to dispensing requirements, and corrective actions taken to address noncompliance
4. Specification of measures that would be taken to increase awareness if surveys of HCPs indicate that prescriber awareness is not adequate.
5. Periodic summaries of adverse event reports of histoplasmosis and other invasive fungal infections including an analysis of deaths and whether appropriate antifungal therapy was instituted promptly.
6. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS are needed.

## **4 CONCLUSIONS AND RECOMMENDATIONS**

The Division of Risk Management and the OSE Simponi REMS Review Team find the proposed REMS for Simponi (golimumab) acceptable with acceptance of the recommendations below and acceptance of the track changes to the REMS (Appendix A), DHCP Letter (Appendix B) and Simponi Serious Infection Education Guide (Appendix C).

DMEPA provided recommendations on the carton and container labeling in a separate review dated March 20.

We have the following recommendations and comments:

#### **4.1 Comments to DAARP**

We recommend incorporating the information needed for assessment of the REMS into the approval letter.

Information needed for assessment will include but is not be limited to:

- A. An evaluation of patients' and prescribers' understanding of the serious risks of Simponi, including the risk of histoplasmosis and other invasive fungal infections.
  - i. The survey instruments and methodologies will be provided to FDA for review and comment at least 2 months before it is administered to patients and prescribers.
- B. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- C. A report on failures to adhere to dispensing requirements, and corrective actions taken to address noncompliance
- D. Specification of measures that would be taken to increase awareness if surveys of healthcare prescribers indicate that prescriber awareness is not adequate.
- E. Periodic summaries of adverse event reports of histoplasmosis and other invasive fungal infections including an analysis of deaths and whether appropriate antifungal therapy was instituted promptly.
- F. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS are needed.

#### **4.2 Comments to Centocor Ortho Biotech**

1. The REMS is acceptable if you incorporate the proposed changes. Please see attached REMS document for track changes (Appendix A).
2. The Medication Guide content and distribution procedure<sup>1</sup> as well as the revised carton and container labeling are acceptable<sup>2</sup>.
3. The proposed Communication Plan is acceptable if the DHCP Letter and Simponi Serious Infection Education Guide are revised based on the track changes provided. Please see attached track changes comments on the letter and the guide (Appendices B and C).

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<sup>1</sup> Mills S. Review of Patient Labeling (Medication Guide), BLA 125289, dated March 20, 2009.

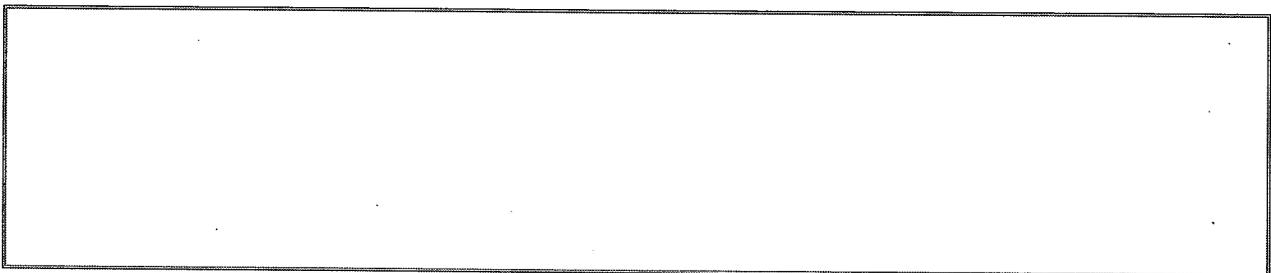
<sup>2</sup> Mena-Grillasca, Carlos, DMEPA carton and container labeling review, dated March 20, 2009.

4. Submit and note any changes in healthcare professional and patient survey protocols and sample questions to FDA at least 60 days prior to conducting the surveys.
5. The REMS Supporting Document should include a description of the Information Needed for Assessment (REMS Assessment Plan) that will be included in your REMS Assessment Submissions.

Information needed for assessment will include but is not be limited to:

1. An evaluation of patients' and prescribers' understanding of the serious risks of Simponi, including the risk of histoplasmosis and other invasive fungal infections.
  - a. Provide the survey instruments and methodologies to FDA for review and comment at least 2 months before it is administered to patients and prescribers.
2. A report on periodic assessments of the dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to dispensing requirements, and corrective actions taken to address noncompliance
4. Specification of measures that would be taken to increase awareness if surveys of healthcare prescribers indicate that prescriber awareness is not adequate.
5. Periodic summaries of adverse event reports of histoplasmosis and other invasive fungal infections including an analysis of deaths and whether appropriate antifungal therapy was instituted promptly.
6. Based on the information reported, an assessment of and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS are needed.

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## **APPENDIX A: SIMPONI REMS**

### **BLA 125289 SIMPONI™ (golimumab)**

Tumor necrosis factor alpha (TNF- $\alpha$ ) blocker

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

#### **I. GOALS:**

To communicate and mitigate the risks associated with SIMPONI™ therapy by:

1. Alerting and warning healthcare professionals about cases of unrecognized histoplasmosis and other invasive fungal infections associated with Tumor Necrosis Factor (TNF) blocker use.
2. Educating patients on the risks associated with SIMPONI therapy, specifically serious infections including tuberculosis (TB) and infections caused by viruses, fungi, and bacteria spreading throughout the body.

#### **II. REMS Elements**

##### **A. Medication Guide**

1. Medication Guides will be dispensed with each SIMPONI pre-filled syringe or autoinjector in accordance with 21 CFR 208.24. The Medication Guide will be included in each carton that contains one 50 mg pre-filled syringe or auto injector. The conspicuous statement: "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide" will be added to each carton.
2. Medication Guides will be provided to Physician offices for distribution by prescribing physicians.

Please see the appended Medication Guide.

##### **B. Communication Plan**

In accordance with FDCA 505-1(e)(3), Centocor will implement a communication plan consisting of a Dear Healthcare Provider Letter and the SIMPONI Serious Infection Education Guide to be disseminated to rheumatologists, pulmonologists, infectious disease specialists, and primary care physicians (eg, Family Practice, General Internists, Obstetrician/Gynecologists, and Emergency Medicine) who may potentially prescribe TNF blockers or treat patients who receive TNF blockers. The communication plan will convey the following information:

- The risk of developing invasive fungal infections, including histoplasmosis, coccidioidomycosis, blastomycosis, and other opportunistic fungal infections while treating with TNF blockers
- Provide descriptive information on the signs and symptoms of fungal infections, including histoplasmosis.
- Provide references and background information regarding the treatment of these infections.

The Dear Healthcare Provider Letter will be disseminated within 60 days of REMS approval.

These materials will also be available in printable form on a separate REMS website that can be accessed via a link (eg, "Important Safety Information Regarding Serious Infections including TB and Fungal Infections") from the company website within 60 days of the REMS approval.

A mass mailing of educational materials including the professional labeling, the Dear Healthcare Letter, the SIMPONI Serious Infection Education Guide, and the Medication Guide will be directed at all prescribers, Pulmonary and Infectious Disease physicians, and Primary Care physicians (as defined above) within 21 days of REMS approval.

Please see the appended Dear Healthcare Professional Letter and SIMPONI Serious Infection Education Guide.

**C. Elements to Assure Safe Use**

The REMS does not include any Elements to Assure Safe Use.

**D. Implementation System**

An implementation system is not a required component of the proposed REMS if there are no elements to assure safe use

**E. Timetable for submission of assessments**

Centocor Ortho Biotech Inc. will submit a REMS Assessment to FDA at the following timetables:

<u>Assessment Submission</u>	<u>Timing Interval Relative to Approval</u>
1st REMS Assessment	18 months after approval
2nd REMS Assessment	3 years after approval of the REMS
3rd REMS Assessment	7 years after approval of the REMS

## APPENDIX B: SIMPONI Dear Healthcare Professional Letter

Dear Healthcare Professional:

Centocor Ortho Biotech Inc., the makers of SIMPONI™ (golimumab), a new Tumor Necrosis Factor-alpha (TNF- $\alpha$ ) blocking human monoclonal antibody, would like to inform you of important safety information regarding the risk of serious fungal infections associated with TNF- $\alpha$  blockers. The Food and Drug Administration (FDA) has reported that histoplasmosis and other invasive fungal infections are not consistently recognized in patients taking the TNF- $\alpha$  blockers: Cimzia® (certolizumab pegol), Enbrel® (etanercept), Humira® (adalimumab), and Remicade® (infliximab).<sup>1</sup> This has resulted in delays in appropriate antifungal treatment, sometimes even resulting in death.

SIMPONI (golimumab) is approved by the FDA for the treatment of adult patients (18 years or older) with: moderate to severe rheumatoid arthritis in combination with methotrexate, psoriatic arthritis (either alone or in combination with methotrexate), and ankylosing spondylitis.

Decisions to use SIMPONI must balance the potential benefits with the potential risks of therapy based upon your patient's individual needs. You should carefully review the enclosed prescribing information for SIMPONI, which includes the following important information about the risk of serious infections including TB and invasive fungal infections, such as histoplasmosis, as described in the *Boxed Warnings* of the SIMPONI prescribing information.

**The following information is important for healthcare professionals and patients treated with TNF- $\alpha$  blockers including SIMPONI:**

- TNF- $\alpha$  blockers are immunosuppressants. Patients taking TNF- $\alpha$  blockers are at risk for developing infections including invasive fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, candidiasis, aspergillosis, pneumocystosis, and other opportunistic fungal infections.
- For patients who reside or travel in regions where mycoses are endemic (eg, Ohio and Mississippi River valleys and southwestern United States), invasive fungal infection should be suspected if they develop a serious systemic illness.

- Patients should be encouraged to report signs of infection and be closely monitored during and after treatment with SIMPONI and other TNF- $\alpha$  blockers for the development of any signs and symptoms of invasive fungal infection including fever, malaise, weight loss, sweats, cough and dyspnea, pulmonary infiltrates on X-ray or serious systemic illness.
- Patients who develop an infection, including any persistent or reoccurring infections should have their SIMPONI or other TNF- $\alpha$  blocker discontinued and undergo a complete diagnostic workup. Empiric antifungal therapy should be considered until the pathogen(s) are identified in consultation with an infectious diseases specialist when feasible.
- SIMPONI may be restarted after recovery from the infection based on a reevaluation of risks and benefits. The decision to restart SIMPONI therapy and the duration of the antifungal therapy should be made in consultation with an infectious diseases specialist when feasible.

For further information please refer to the following FDA link:

[http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF\\_blockersHCP.htm](http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm)

Please Note: This letter does not include a comprehensive description of the serious and significant risks associated with the use of SIMPONI. Please read the accompanying full prescribing information and Medication Guide for a complete description of the serious and significant risks associated with the use of SIMPONI, including the Boxed Warning regarding the risk of serious infections, Contraindications, Warnings, Precautions and Adverse Events.

It is important that all adverse events potentially associated with SIMPONI be reported so that the adverse event profile reported in the prescribing information can be updated appropriately as post-approval experience is gathered. You can assist us with monitoring the safety of SIMPONI by reporting adverse events to Centocor Ortho Biotech Inc. at 1-800-457-6399.

Adverse event information may also be reported to the FDA MedWatch Reporting System by the following methods:

- Online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
- Phone at 1-800-FDA-1088
- Fax at 1-800-FDA-0178, using the MedWatch Form 3500 (available at [www.fda.gov/medwatch/getforms.htm](http://www.fda.gov/medwatch/getforms.htm))
- Mail, using the postage-paid MedWatch Form 3500 (see above), to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787

Please see the enclosed:

- SIMPONI package insert, and
- Medication Guide

Sincerely,

Enclosures

References:

- <sup>1</sup> Information for Healthcare Professionals Cimzia<sup>®</sup> (certolizumab pegol), Enbrel<sup>®</sup> (etanercept), Humira<sup>®</sup> (adalimumab), and Remicade<sup>®</sup> (infliximab).  
[http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF\\_blockersHCP.htm](http://www.fda.gov/cder/drug/InfoSheets/HCP/TNF_blockersHCP.htm)  
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## APPENDIX C: SIMPONI Serious Infection Education Guide

**Treatment with SIMPONI™ or other anti-TNF- $\alpha$  agents puts patients at increased risk for serious infections including TB and invasive fungal infections that can lead to hospitalization and death.**

- Invasive fungal infections including histoplasmosis and coccidioidomycosis are frequently unrecognized.
  - Patients being treated with SIMPONI or other anti-TNF- $\alpha$  agents are more susceptible to invasive fungal infections especially when residing or visiting endemic areas of the world.
- Due to the rarity of these infections, these invasive fungal infections are frequently unrecognized and treatment is frequently delayed.
  - If these conditions are not considered in the differential diagnosis, appropriate therapy may be delayed with potentially life-threatening consequences.
  - Patients being treated with SIMPONI or other anti-TNF- $\alpha$  agents may present with disseminated infection, rather than local disease.
  - Antigen and antibody tests for these invasive fungi may be falsely negative in patients, being treated with SIMPONI or other anti-TNF- $\alpha$  agents. Patients should undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, as well as antigen detection and serum antibody titers.
- Patients have died when the initial physician who came in contact with the patient did not consider or recognize the invasive fungal infection (eg, histoplasmosis, coccidioidomycosis).
  - Invasive fungal infections must always be considered when a patient receiving SIMPONI or other anti-TNF- $\alpha$  agents, presents acutely ill, particularly with a history of residence in or travel to endemic areas. A high index of suspicion is key to appropriate management of this risk.
  - Urgent consultation with an infectious disease specialist and/or empiric antifungal therapy should be considered in patients at risk for invasive fungal infections, including those being treated with SIMPONI or other anti-TNF- $\alpha$  agents who develop severe systemic illness.

## **Background: Systemic Fungal Infections**

### **1. Exposure**

- a. Result of airborne exposure to organisms that cause histoplasmosis or coccidiomycosis or other fungal agents
- b. Increased in areas endemic for specific fungal agents
  - 1) Histoplasmosis - Ohio and Mississippi River valley (Prevalence-up to 80%)
- c. Coccidioidomycosis - Southwestern US, particularly Arizona and the San Joaquin Valley in California (Prevalence-up to 50%)

### **2. Other Risk Factors**

- a. Immunosuppression
- b. Chronic lung disease
- c. Elderly and children less than 2 years old
- d. Occupation (farmers, construction workers, spelunkers)
- e. Exposure to a large inoculum (ie, dust storms)

### **3. The role of tumor necrosis factor-alpha (TNF- $\alpha$ ) in severe fungal infections**

- a. TNF- $\alpha$  may play a role in granuloma formation and containment of fungal infection
- b. Cases of severe fungal infections including histoplasmosis and coccidioidomycosis have been reported in patients treated with anti-TNF therapies and have resulted in death.

### **4. Active Fungal Disease**

- a. Patients should be closely monitored during and after treatment with SIMPONI for the development of signs or symptoms of possible systemic fungal infection including fever, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates on X-ray, or serious systemic illness including shock.
- b. Patients who develop an infection should be discontinued from SIMPONI therapy and undergo a complete diagnostic workup, which may include fungal cultures, histopathological or cytological evaluations, antigen detection and serum antibody titers.

### **Before initiating and during treatment with SIMPONI**

Manage the **potential risk of severe fungal infection** with proper evaluation, monitoring and treatment.

1. **Evaluate:** Make a thorough history (including history of residence in or travel to endemic areas), physical, and, if indicated, a directed evaluation (eg, laboratory tests, chest x-ray) part of your regular examination.
2. **Monitor:** Continue to monitor patients for signs and symptoms of systemic fungal infection. (eg, respiratory symptoms, a general ill feeling, fever, chest pains, and a dry or nonproductive cough).
3. **Treat:** While diagnostic workup is being performed, appropriate empiric anti-fungal therapy should be considered and/or urgent consultation with an infectious disease specialist for patients with signs and symptoms of systemic fungal infection. Empiric treatment is not a substitute for thorough work-up to establish definitive diagnosis and therapy.



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

Date: March 20, 2009

To: Bob Rappaport, MD, Director  
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Denise Toyer, PharmD, Deputy Director *DD Toyer*  
Carol Holquist, RPh, Director *Carol Holquist 3-20-09*  
Division of Medication Error Prevention and Analysis

From: Carlos M Mena-Grillasca, RPh, Acting Team Leader *CMena*  
Division of Medication Error Prevention and Analysis *3/20/09*

Subject: Label and Labeling Review

Drug Name(s): Simponi (Golimumab) 50 mg/0.5 mL

Application Type/Number: BLA 125289

Applicant/sponsor: Centocor, Inc.

OSE RCM #: 2008-1069

## **EXECUTIVE SUMMARY**

This memorandum is in response to a June 25, 2008 request from the Division of Anesthesia, Analgesia and Rheumatology Products for a review of labels and labeling Simponi (Golimumab; BLA# 125289) for evaluation to identify areas that could lead to medication errors. Using Failure Mode and Effects Analysis<sup>1</sup>, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, carton labeling and insert labeling to identify vulnerabilities that could lead to medication errors.

Our findings indicate that the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. We provide recommendations below that aim at reducing the risk of medication errors. We would be willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, OSE project manager, at 301-796-0151.

### **1 MATERIALS REVIEWED**

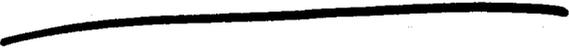
For this product, the Applicant submitted on June 25, 2008 container labels and carton labeling for the prefilled syringe (retail) and the autoinjector (retail and sample) presentations and the insert labeling. However, on December 19, 2008 the Applicant submitted a revised insert labeling. Finally, on January 23, 2009 the Applicant submitted revised container label and carton labeling for the autoinjector retail presentation. See Appendix A and B for images.

- Retail Container Labels (prefilled syringe and autoinjector)
- Retail Carton Labeling (prefilled syringe and autoinjector)
- Sample Container Label and Carton Labeling (autoinjector)
- Insert Labeling (no image) – DMEPA's comments have been incorporated in DRISK's review.

### **2 RECOMMENDATIONS**

#### **2.1 COMMENTS TO THE APPLICANT**

A.



b(4)

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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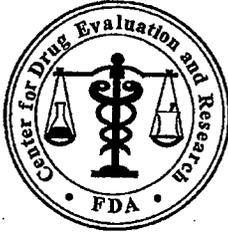
         Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

         Draft Labeling (b5)

         Deliberative Process (b5)

*Withheld Track Number: Labeling Review- 11*



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

Date: March 20, 2009

To: Bob A. Rappaport, M.D., Division Director  
Division of Anesthesia, Analgesia, and Rheumatology  
Products (DAARP)

Through: Jodi Duckhorn, M.A., Team Leader *J. Duckhorn 3/20/2009*  
Division of Risk Management (DRISK)

From: Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 3/20/2009*  
Patient Product Information Reviewer  
Division of Risk Management (DRISK)

Subject: DRISK Review of Patient Labeling (Medication Guide and  
Patient Instructions for Use) and Distribution Plan

Drug Name(s): Simponi (golimumab) Injection

Application Type/Number: BLA #125289/0

Applicant/sponsor: Centocor, Incorporated

OSE RCM #: 2008-1050

## **1 INTRODUCTION**

Centocor, Inc. submitted an original Biologics Licensing Application, BLA# 125289 for Simponi (glimumab) Injection on June 25, 2008.

This review is written in response to a request from DAARP for the Division of Risk Management to review the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes, but is not limited to a draft Medication Guide (MG).

FDA has determined that Simponi (glimumab) Injection poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Simponi (glimumab) Injection. FDA has determined that Simponi (glimumab) Injection is a product with a serious a significant public health concern that meets one of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: Simponi (glimumab) Injection is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use the product.

Centocor, Inc. submitted a Medication Guide and REMS for Simponi on December 19, 2008. This review provides comments and revisions to the Sponsor's proposed Medication Guide and Patient Instructions for Use for Simponi. The REMS is currently under review by DRISK. That review will be provided to DAARP under separate cover.

## **2 MATERIAL REVIEWED**

- Draft Simponi (glimumab) Injection Prescribing Information (PI) as revised by the Review Division on March 12, 2009 and March 19, 2009.
- Draft Simponi (glimumab) Injection Medication Guide (MG) and Patient Instructions for Use (PIFU) submitted on December 19, 2008 and revised by the review division on March 12, 2009 and March 18, 2009.

## **3 DISCUSSION**

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft MG submitted by the sponsor has a Flesch Kinkaid grade level of 8.2, and a Flesch Reading Ease score of 62.5. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading

ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). The reading scores as revised by DAARP are a Flesch Kincaid grade level of 8.7, and a Flesch Reading Ease score of 61.1%. Our revised MG has a Flesch Kincaid grade level of 6.6 and a Flesch Reading Ease score of 71.4%.

The DRISK Patient Labeling Reviewer met with members of DAARP (medical officer, medical team leader, cross-divisional team leader, and project manager) on March 17, 2009 to review some of the differences in content and format between the proposed MG for Simponi and the MGs for the other TNFs products. DAARP updated the labeling (PI and MG) based on a labeling meeting the same day and the DRISK/DAARP MG discussion, and provided this to DRISK on March 18, 2009. The review division changes include some of DRISK's preliminary review suggestions that were shared at the meeting. Because of the substantial work already done by DRISK prior to and while waiting for these additional labeling changes, the base document used in this DRISK review is the review division MG dated March 12, 2009. As a result, all tracked changes between the March 12, 2009 and March 18, 2009 review division MG are not shown. We have added the relevant changes proposed by the review division as appropriate, ensured that the language is patient-friendly. We have provided comments when we made substantial changes to what DAARP has proposed.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- rearranged information due to PLR format
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APFont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APFont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

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       Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)