

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

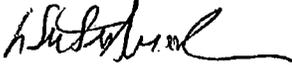
APPLICATION NUMBER:
125261

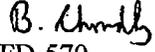
OTHER REVIEW(S)

DIVISION OF PULMONARY AND ALLERGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: September 2nd, 2009

To: Sue Kang, Project Manager (CDER/OND/Division of Dermatology and Dental Products)

From: Lydia I. Gilbert-McClain M.D. FCCP, Deputy Director 
Division of Pulmonary and Allergy Products, HFD-570

Through: Badrul A. Chowdhury, M.D., Ph.D., Director 
Division of Pulmonary and Allergy Products, HFD-570

Subject: BLA 125261

General Information

Date of Request: August 8th 2009

Materials Reviewed: Consult request, sponsor's proposed labeling, Division draft proposed labeling, approved labeling for TNF blockers (Cimzia[certolizumab]; Enbrel[etanercept]; Remicade[infliximab]; and Humira[adlimumab])

Recommendation

Consider combining the information in the proposed language in the Warnings and Precautions section regarding the risk of mycobacterial infection/tuberculosis from section 5.2 and 5.3 into one Warning and Precaution for mycobacterial infections/tuberculosis. Refer to the mycobacterial/ tuberculosis language in the Warnings/precautions section of the currently approved TNF-blocker labels (*see above list under "Materials Reviewed." Cimzia and Humira labels are in PLR format*) and consider some of this language as appropriate. Of note, the risk of reactivation tuberculosis is no longer "theoretical" given the recent report of a case of reactivation TB in a patient on Stelara. Furthermore, the use of the word "theoretical" in the heading may not be necessary to reflect the risk. Note that with the new Physician Labeling Rule (PLR), the Warnings/Precaution listed in the labeling may include adverse reactions that could possibly occur even though the reactions have not yet been observed, as long as these reactions are considered clinically significant enough to warrant a Warning/precaution. In these cases the labeling language would acknowledge that the adverse reaction has not been observed, but may be expected to occur. To this end, it may be more fitting to have the separate heading under section 5.2 read "*Risk for particular Infections*" that would describe the risk of infections other than mycobacterial infections.

The TNF-blockers (Cimzia[certolizumab]; Enbrel[etanercept]; Remicade[infliximab]; and Humira[adlimumab]) all have a boxed warning for mycobacterial infections/reactivation TB. If you have not already done so, please discuss with the division of Anesthetics, analgesics, and

rheumatologic products (DAARP) about the threshold that they used for the boxed warning for the mycobacterial infections/reactivation TB risk.

Background

The Division of Dermatology and Dental Products is seeking our comment on the applicant's proposed wording pertaining to TB and recommendations in the labeling of Stelara a new molecular entity proposed for treatment of plaque psoriasis in adults.

Stelara (ustekinumab) is a first-in-class, monoclonal antibody that blocks IL-12 and IL-23 (by binding a shared subunit). In the pivotal trials, inclusion criteria specified that subjects be considered eligible for enrollment according to the following TB screening criteria:

- Have no history of latent or active TB prior to screening.
- Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
- Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB prior to or simultaneously with the first administration of study agent.
- Within 1 month prior to the first administration of study agent, either have a negative tuberculin skin test, or have a newly identified positive tuberculin skin test during screening in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first administration of study agent.
- Have a chest radiograph (both posterior-anterior and lateral views), taken within 3 months prior to the first administration of study agent and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.

TB skin testing was done with the Mantoux Tuberculin Skin Test, the standard method of identifying persons infected with *M. tuberculosis*. For the purposes of the clinical trials, the most conservative definition of positivity usually reserved for immunocompromised patients was used to define patients as positive even if those patients entering the study were not immunocompromised at baseline. The purpose of using the conservative definition was to increase the sensitivity of the test to detect the likelihood of latent TB.

A total of 68 subjects with latent tuberculosis diagnosed during screening were enrolled in the trials (with appropriate treatment initiated either prior to or simultaneous with first administration of study agent), and all were at some point exposed to ustekinumab because of the crossover design of the Phase 3 studies. None of these patients developed active TB. However, more recently, there was one report of reactivation in a patient on Stelara that was submitted to the Division of Dermatology and Dental products. So it would appear that the risk is not theoretical but real.

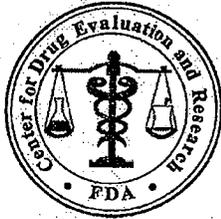
DPAP comment

The Division of Dermatology and Dental products (DDDP) has provided draft labeling to the sponsor that includes a warning about potential infection risks, and a separate warning with the

Division Dermatology and Dental Products
BLA 125261
Stelara (ustekinumab)

3

heading "Pre-treatment evaluation for tuberculosis." The DDDP may consider discussing the mycobacterial/tuberculosis risk and language pertaining to that risk under one heading, and having a separate heading describing the other possible infections risk. Also, all the TNF-blockers carry a boxed warning for mycobacterial infections/reactivation TB and it would be reasonable to discuss this aspect of the labeling with the DAARP division to get their perspective if this has not already been done.



**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: August 12, 2009

To: Susan Walker, MD, Director
Division of Dermatology and Dental Products

Through: Kristina C. Arnwine, PharmD, Team Leader *KCA 8/12/09*
Denise P. Toyer, PharmD, Deputy Director *D.P. Toyer 8/12/09*
Carol A. Holquist, RPh, Director *CHolquist 8/12/09*
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA) *LH 8/12/09*

Subject: Label and Labeling Review

Drug Name: Stelara (Ustekinumab) Injection
45 mg/0.5 mL and 90 mg/mL vials

Application Type/Number: BLA 125261

Applicant: Centocor Ortho Biotech, Inc.

OSE RCM #: 2009-1308

1 INTRODUCTION

This review is written in response to a request from the Division of Dermatology and Dental Products (DDDP) for assessment of the revised container labels and carton labeling for Stelara (Ustekinumab) Injection 45 mg/0.5 mL and 90 mg/mL (BLA 125261).

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the following revised container labels and carton labeling (revised to reflect the company name change) submitted as part of the June 25, 2009 submission (see Appendix A and B).

- Container Labels (45 mg/0.5 mL and 90 mg/mL)
- Carton Labeling (45 mg/0.5 mL and 90 mg/mL)

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved to minimize the potential for medication errors.

We provide comments on the dosage form designation in Section 3.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Janet Anderson, at 301-796-0675.

3.1 COMMENTS TO THE DIVISION

DMEPA notes that as currently presented on the container labels and carton labeling, the Applicant uses the term "solution" as the dosage form for this product. According to the U.S. Pharmacopeia (USP), "solutions intended for parenteral administration are officially entitled 'injections'."¹ We believe the appropriate dosage form designation for this product is "injection", however, we defer to and recommend you consult the CDER Labeling and Nomenclature Committee and Richard Lostritto concerning the appropriate dosage form designation for this product.

3.2 COMMENTS TO THE APPLICANT

A. Container Labels

1. The two product strengths are not effectively differentiated from one another and when the two labels are compared side-by-side, they look identical. Both strengths are presented in an identical color scheme which does not afford adequate differentiation. Additionally, the colors used in the trade dress are identical. These similarities increase

¹ Information obtained from the USP-NF online at:
<http://www.uspnf.com/uspnf/pub/index?usp=32&nf=27&s=1>. Accessed on August 7, 2009.

the potential for product selection errors. Ensure the product strengths are effectively differentiated by the use of contrasting colors, boxing, or some other means.

2. The statement of strength (90 mg/1.0 mL) is not expressed in accordance with USP recommendations for labeling of injectable drug products which states: "*Strength per single mL should be expressed as mg/mL, not mg/1 mL.*" Additionally, we would not recommend the use of a trailing zero because the "1.0 mL" volume could look like "10 mL" rather than "1 mL". Revise accordingly to express the strength as 90 mg/mL or 90 mg per vial.
3. We recognize the net quantity is contained in the statement of strength. However, since this is a small vial size, a net quantity statement should also be included. This statement (e.g., "Each vial contains 0.5 mL", "Contains 0.5 mL per vial", "Each vial contains 1 mL", or "Contains 1 mL per vial", as appropriate) is necessary to inform patients and healthcare providers of how much product is contained in the respective vials.
4. Revise the route of administration statement to read: "For subcutaneous use only" rather than "For subcutaneous injection" in order to prevent confusion with the dosage form statement. Additionally, separate this statement from the dosage form statement.
5. As currently presented, the statement, "single use vial", follows the route of administration. In this position, the statement decreases the prominence of the route of administration. Consider relocating the "single use vial" statement to the upper left corner of the principal display panel. Follow the "single use vial" statement with "Discard unused portion" (i.e., "Single use vial—Discard unused portion").

B. Carton Labeling

1. See A-1 through A-5, above, which are also applicable to the carton labeling.
2. The statement of strength is not consistently presented on the carton labeling (i.e., on the back panel the strength is to the immediate right side of the established name whereas on the other panels the strength is immediately below the established name). Ensure the presentation of the statement of strength on the back panel is consistent with the other panels by relocating it to a position immediately below the established name.
3. Although the carton labeling has a Medication Guide statement, we recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton:
 - a. "Dispense the enclosed Medication Guide to each patient." or
 - b. "Dispense the accompanying Medication Guide to each patient."

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: July 16, 2009

To: Sue Kang, DDDP
Brenda Carr, MD, DDDP
Jill Lindstrom, MD, DDDP

From: Andrew Haffer, PharmD, DDMAC *AH* 7/16/09
Shefali Doshi, MD, DDMAC *SD* 7/16/09

Re: BLA# 125261
Comments on draft labeling for Ustekinumab

DDMAC has reviewed the draft PI and Medication Guide for Ustekinumab. DDMAC's comments on the PI and PPI are based on the proposed draft labeling titled "SEALD_Iris 10 APR09 edits to Current FDA Revised Draft Labeling for Ustekinumab_RESUBMISSION (version2_06.05.09)" located in the DDDP eRoom. Many of our comments are the same as those provided in our previous review dated October 22, 2008.

DDMAC's comments are provided directly in the attached document.

If you have any questions about DDMAC's comments please call.

21 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

MEMORANDUM

To: Sue Kang
Division of Dermatology and Dental Products

From: Iris Masucci, PharmD, BCPS *Im*
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: April 10, 2009

Re: Comments on draft labeling for Stelara (ustekinumab) injection
BLA 125261

We have reviewed the proposed label for Stelara (FDA version received by SEALD 2/18/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

Please see attached label for recommended changes.

16 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 22, 2008

To: Sue Kang, DDDP
Brenda Carr, MD, DDDP
Jill Lindstrom, MD, DDDP

From: Andrew Haffer, PharmD, DDMAC *AH* 10/22/08
Shefali Doshi, MD, DDMAC *SD* 10/22/08

Re: BLA# 125261/0
Comments on draft labeling for Ustekinumab

DDMAC has reviewed the draft PI and PPI for Ustekinumab. DDMAC's comments on the PI and PPI are based on the proposed draft labeling titled "Most current labeling for Ustekinumab (10.15.08)-No Trackchanges.doc" located in the DDDP eRoom.

DDMAC's comments are provided directly in the attached document.

If you have any questions about DDMAC's comments please call.

20 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2008.002.A.00016
APPLICATION NUMBER	BLA 125261/0
LETTER DATE/SUBMISSION NUMBER	11/29/2007
REQUESTED DUE DATE	April 21, 2008
DATE COMPLETED	May 7, 2008
DATE OF CONSULT REQUEST	02/01/2008
MEETINGS	Mid-cycle meeting on 4/28/08
REVIEW DIVISION	DDDP
MEDICAL REVIEWER	Brenda Carr, M.D.
REVIEW DIVISION PM	Kalyani Bhatt
SEALD REVIEWER(S)	Elektra J. Papadopoulos
REVIEW COMPLETION DATE	4/23/2008
ESTABLISHED NAME	CNTO 1275 (ustekinumab)
TRADE NAME	
APPLICANT	Centocor, Inc.
ENDPOINT(S) CONCEPT(S)	Health-related QoL
INSTRUMENT(S)	Dermatology Life Quality Index (DLQI); SF-36; Hospital Anxiety Depression Scale (HADS); Work Limitations Questionnaire (WLQ); and Health Economic Assessments
INDICATION	Treatment of moderate to severe plaque psoriasis
INTENDED POPULATION(S)	Adults, men and women

STUDY ENDPOINT REVIEW

Development to Support Labeling Claims, published in the *Federal Register* in February 2006.

B. STUDY ENDPOINT REVIEW

CNTO 1275 is a fully human IgG1 κ monoclonal antibody that binds to the p40 protein subunit of IL-12 and IL-23. The proposed mechanism of action in psoriasis is through the interruption of signaling and cytokine cascades involved in psoriasis pathology. Psoriatic lesions can cause pain, itching, and bleeding, and these physical discomforts combined with the potential psychological effects of the disease may interfere with everyday activities. As such, patient symptoms including pain and itching are important concepts for study in trials of psoriasis products.

Previously, Centocor submitted in serial number 91 to BBIND 9950 for CNTO 1275 (December 21, 2005) background for the DLQI in the form of literature reprints to seek FDA advice regarding the adequacy of the DLQI ~~_____~~ of treatment benefit in moderate to severe psoriasis. The FDA reviewed the submission and responded with a letter to sponsor with the Agency's concerns regarding the validity of the DLQI in this target population. b(4)

In the current original BLA submission, the company has not included an evidence dossier for the DLQI for Agency review, but has referred the Agency to the previous submission made to BBIND 9590 (email communication from Centocor, April 24, 2008).

1 INSTRUMENTS

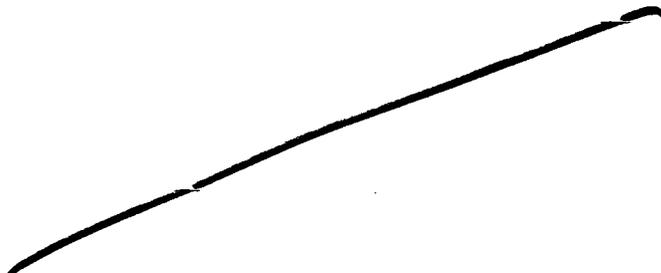
The DLQI is shown in the appendix. According to the clinical protocol for study T08, an eCRF was to be used to collect subject data and assessments that will be used for evaluation of the subjects' response to treatment. It appears as though the DLQI data were captured through electronic means. The sponsor did not submit a user manual for the DLQI and it is not clear whether the instrument was self administered by the subject or administered and reported by the investigator.

Reviewer's comment: The information on the data collection method is necessary for FDA review of the data.

The instrument was administered at baseline, weeks 0, 2, 12, 28, 40, 52, and 76. The itch VAS appeared to be a static assessment and was administered at Weeks 0 and 12. The SF36 was administered at weeks 0, 12, 28, 40, and 52.

Reviewer's comment: The actual instrument used for the itch VAS was not found in the clinical protocols or the BLA submission.

2 SPONSOR'S PROPOSED LABELING



b(4)

3 ENDPOINT MODEL

For the hierarchy of endpoints, please see Section 10 of this review.

4 CONCEPTUAL FRAMEWORK

The six headings and 10 items of the DLQI are as follows:

Symptoms/feelings:

- (1) Itchy, sore, painful, stinging
- (2) Embarrassed, self conscious

Daily activities:

- (3) Shopping, looking after home and garden
- (4) Influence on clothes you wear

Leisure:

- (5) Skin affected social or leisure activities
- (6) Difficulty to do any sport

Work/school:

- (7) Skin prevented you from working, or studying
- If no, how much has it been a problem at work or studying

Personal relationships:

- (8) Skin created problems with your partner or any of your close friends or relatives
- (9) Skin caused any sexual difficulties

Treatment:

- (10) Problem has treatment of your skin been (making home messy or taking up time)

STUDY ENDPOINT REVIEW

Reviewer's comment: When looking at the six headings of the DLQI (i.e., symptoms/feelings, daily activities, leisure, work/school, personal relationships, and treatment), it does not appear that these are measuring what they purport to measure. For example, the concepts of symptoms and feelings are grouped together under the same heading. The single item measuring symptoms includes multiple concepts (itchy, sore, painful stinging) such that it is difficult to confidently state which of these concepts the item is measuring. Further, the one-week recall period used in the clinical trial may introduce recall bias when measuring certain symptoms such as itch and pain, for which shorter recall periods/daily diaries are desirable. (Of note, the DLQI in the published literature uses a two-week recall period.)

5 CONTENT VALIDITY

DLQI:

The DLQI was intended to assess the impact of the disease on a subject's QOL. It is a 10-item questionnaire that includes different aspects that may affect HR QOL: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI score is calculated by summing the score of each question, with an overall score ranging from 0 to 30; a lower DLQI score represents better QOL. The DLQI was to be completed by each subject on a worksheet prior to any efficacy evaluations.

Reviewer's comment: Although the DLQI covers a wide range of impairments, it is not a multiple scale questionnaire. The DLQI spans a wide range but may not have adequate depth into the important concepts that must be measured for HR-QOL claim in the target patient population _____ appropriate psychological, physical and social domains as well as treatment related impact on HR-QOL. Using only 10 items, the DLQI mainly focuses on limitations due to psoriasis. This presents a problem since its title (DLQI) implies "quality of life" and is therefore misleading.

b(4)

The development of the DLQI was first published by Finlay and Khan in 1994. The DLQI was developed to assess the impact of skin disease on the patient's life. The item-generation study involved 120 consecutive patients aged 15-70 years attending the Dermatology Out-patient Department at the University Hospital of Wales. These 120 patients included 15 patients with acne, 14 with psoriasis, 10 with eczema, 9 with moles, 9 with atopic eczema, 8 with viral warts, 7 with basal cell carcinoma and the remaining patients had a variety of other dermatologic conditions.

The patients were asked to write down all the ways in which their skin disease affected their life. After the analysis of the responses from the first 70 patients, no additional problems were recorded from the subsequent 50 patients, suggesting that almost all the important aspects of life affected by a skin disease were identified. The items identified were utilized to develop a questionnaire, which underwent pilot testing. Further information on the final questionnaire was gathered by surveying 200 patients, 52 of whom had psoriasis.

STUDY ENDPOINT REVIEW

The sponsor has provided a tabular summary of these studies in their submission to BBIND 9590.

Reviewer's comment: Although the DLQI has been used in research settings, to this

The DLQI was developed in a clinic with input from patients with a broad variety of skin conditions both inflammatory and non-inflammatory including acne, psoriasis, and atopic dermatitis, moles, viral warts, and basal cell carcinoma among others. Therefore, we do not have documentation that the item generation was performed with input from the target population of interest in this application, moderate to severe plaque psoriasis patients.

b(4)

Further, source documentation of the item generation process is not provided in this publication.

b(4)

Concepts in the DLQI include the following: symptoms, feelings, daily activities, leisure activities, work or school, personal relationships, and treatment. Patients are requested base their report based on a 2-week recall period. The following scoring is used: 'not at all' = '0', 'a little' = '1', 'a lot' = '2' and 'very much' = '3'. The answer 'not relevant' is scored as '0'. These scores are summed, resulting in a maximum score of 30 and a minimum of 0. The higher the score, the greater the impairment.

Reviewer's comment: Justification for the recall period for the DLQI was not included in the submission. It appears that a one-week recall period was used in the clinical studies. However, a two-week recall period is in the published literature. If there is variability in symptom severity from day to day, it is unclear whether patients can adequately recall their experiences over a one-week or a two-week period in an unbiased way. As such, we do not have confidence in what patients are using to base their reports (i.e., what is actually being reported vs. what is being asked in the individual items).

Kimball et al (2004) reported on anchor-based and distribution-based methods to determine the minimal important difference (MID), the "smallest difference in score in the domain of interest which patients perceive as beneficial". The anchor utilized in this study, was the patient assessment of psoriasis measured by a single item, where patients assessed their psoriasis on a scale from 0 (none) to 5 (severe). The report concluded that a "A clinically meaningful change in the patient global assessment of 1 point corresponds to a mean improvement of 5 points in the DLQI. Regression of the improvement in the DLQI on the improvement in the patient global assessment indicate that for each one-unit increment in global score, the DLQI increases by 4.6 points."

Data has been submitted in which DLQI has been compared with other measures including the SF-36, the Psoriasis Disability Index and others. Nichol et al (1996) reported that the DLQI and the Psoriasis Disability Index were strongly and positively correlated with each other ($r = 0.82$, $p < 0.001$). The DLQI was also correlated with a health-related QoL measure, the PSORIQoL ($r = 0.81$) (Mckenna et al, 2005).

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Reviewer's comment: These data of the measurement properties of the DLQI, do not compensate for the lack of data on the DLQI's development.

Itch:

The change from baseline in the Itch VAS at Week 12 was compared between the 45 mg group and the placebo group and between the 90 mg group and the placebo group using an ANOVA on the van der Waerden normal scores with weight as a binary covariate (≤ 90 kg, > 90 kg). The Itch VAS was used to assess itch using a horizontal line. The line represented the range of itch severity, from 0 (no itch at all) at one end to 10 (severe itch) at the other. The subject was asked to put a single vertical line across the horizontal line at the spot that he/she felt best reflected the severity of itch at the time of the assessment.

SF-36:

The 36-item short form health survey (SF-36) is a PRO instrument that provides a profile of scores to measure overall health status. The SF-36 consists of multi-item scales measuring the following 8 health domains: 1) physical functioning; 2) role limitations due to physical health problems; 3) bodily pain; 4) general health; 5) vitality (energy/fatigue); 6) social functioning; 7) role; limitations due to emotional problems; and 8) mental health (psychological distress and psychological well-being). The questionnaire can also be used to compute physical and mental component summary scores. The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments (Ware and Sherbourne, 1992). Higher SF-36 scores indicate better QOL. The SF-36 was to be completed by each subject on a worksheet prior to any efficacy evaluations.

Reviewer's comment: As stated above, the SF-36 provides a profile of composite scores (the MCS and PCS) to measure overall health status and does not capture disease-specific concerns in psoriasis. Therefore, the SF-36 cannot be used as a basis for disease-specific claims in psoriasis. The content validity of the SF-36 has not been demonstrated for the purpose of measuring health-related quality of life in moderate to severe psoriasis patients in a clinical study setting. At face value, the items included in the SF-36 do not appear to be representative of psoriasis symptoms that are described in the published literature (e.g., itch, pain, stinging).

b(4)

Hospital Anxiety Depression Scale (HADS):

The HADS was specifically developed by Zigmond and Snaith to provide a screening device for anxiety and depression in physically ill patients in a general hospital setting. Despite the term Hospital in the title, subsequently the scale has been widely used in primary care and outpatient community settings. In Study T09, the standard scoring algorithm and guidelines for interpretation of HADS scores according to Zigmond and Snaith was to be used.

Reviewer's comment: It is not clear to this reviewer how the HADS is scored. The sponsor should submit the scoring algorithm, if they seek labeling claims with respect to

STUDY ENDPOINT REVIEW

the HADS. However, the HADS does not appear in the sponsor's proposed labeling and it is not a major secondary endpoint.

The HADS provides separate measures of the two constructs, anxiety (A-scale) and depression (D-scale), which are to be scored separately according to Zigmund and Snaith. For each construct a score below 8 is in the normal range, 8-10 is "borderline" and above 10 indicates a probable disorder of the relevant mood (Snaith, 1993). The HADS covers symptoms and functioning in anxiety and depression and includes a total of 14 items and a one-week recall period. The response options include a 4-point Likert scale and lower scores indicated better patient status. The HADS is a widely used screening device of depression, however, its validity in the target population

b(4)

Work Limitations Questionnaire (measured in T09):

The WLQ is a 25-item, self-administered questionnaire intended to measure the impact of chronic health conditions on job performance and work productivity among employed populations. According to the BLA submission, studies have supported its reliability and validity in various patient populations (Lerner et al, 2001 is cited). We do not have adequate development and validation history to establish the content validity of the WLQ in the target patient population

b(4)

Health Economics (measured in T09):

Health economics assessments including subjects' employment status, days missed from work, and daily productivity were also collected.

Reviewer's comment: It appears that these endpoints are included for economic evaluation and are not intended for labeling claims. These endpoints should be regarded as exploratory.

b(4)

6 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

It is premature to evaluate the reliability as well as other measurement properties without first establishing the content validity of the instrument for the intended population. In general, the patient population in which the PRO instrument was developed and the instrument's measurement properties determined should reflect the target patient population that will be enrolled in the phase 3 clinical studies.

7 INTERPRETATION OF SCORES

According to the submission, a DLQI score of 0 indicates no detectable impairment in the subjects' quality of life and a reduction of 5 or more points is considered clinically meaningful.

Reviewer's comment: An abstract (Kimball et al, 2004) was submitted to the IND, which concluded that a minimum change in DLQI score defining an improvement was a reduction of 5 or more points. It is not known to this reviewer whether this work was subsequently published in the peer review literature, as a search in pubmed (DLQI AND minimally important difference) did not produce a subsequent publication.

8 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

Describe all language/culture groups to be included in the clinical trial(s) and evidence to support use of PRO instrument in each.

Study T08 took place in 29 sites in the US, 16 sites in Canada, and 3 sites in Belgium.

Study T09 took place in 70 investigative sites: 3 sites in Austria, 19 sites in Canada, 1 site in France, 10 sites in Germany, 2 sites in Switzerland, 3 sites in the United Kingdom, and 32 sites in the United States.

We do not have the following information:

- Process used to translate and culturally adapt for populations that will be enrolled in trial
- Qualifications of those who completed the translation/adaptations
- Evidence of comparability in measurement properties between versions

STUDY ENDPOINT REVIEW

9 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

It is unclear how who entered the data into the electronic CRF. This should be clarified, and whether the instrument was reformatted to electronic format. If the data were captured electronically, the sponsor should establish source documents for the patient reported outcome data.

10 PROTOCOL AND ANALYSIS PLAN

Protocol C0743T08 (STUDY T08):

Study T08 was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque-type psoriasis in 29 sites in the US, 16 sites in Canada, and 3 sites in Belgium.

Objectives: The primary objective of this study was to evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque psoriasis. The secondary objectives were to: (1) Evaluate the maintenance of response with CNTO 1275 and (2) Evaluate the impact of CNTO 1275 on quality of life (QOL).

Number of Subjects: 750 planned (250 subjects per group); 766 subjects were randomized to treatment and analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who have a Psoriasis Area and Severity Index (PASI) ≥ 12 , and at least 10% of their total body surface area (BSA) involved.

Duration of Treatment: The first to the last study agent administration was 48 weeks or more.

Primary Endpoints:

The primary endpoint for the study was the proportion of subjects who were PASI 75 responders at Week 12.

Major Secondary Endpoints:

Major secondary comparisons are as follows:

1. The proportion of subjects with a PGA score of cleared (0) or minimal (1) at Week 12 will be compared between the 45 mg group and the placebo group and between the 90 mg group and the placebo group.
2. In subjects randomized to placebo or continued q12 week dosing at Week 40, the time to loss of PASI 75 response based on the data collected through the last subject out for the Week 52 visit will be compared between subjects who continue on q12 week dosing (45 mg q12 weeks and 90 mg q12 weeks combined) and subjects who receive placebo.

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3. The change in DLQI from baseline at Week 12 will be compared between the 45 mg group and the placebo group and between the 90 mg group and the placebo group.

Other Planned Comparisons:

In addition to the primary and major secondary analyses, the following were listed under "other planned analyses".

- Change from baseline in the physical (PCS) and mental component (MCS) summary scores of SF-36 will be summarized over time. The change from baseline in the PCS and MCS at week 12 will be compared between the 45 mg group and the placebo group and between the 90 mg group and the placebo group.
- Percent improvement from baseline in NAPSI will be summarized over time.
- Change from baseline in the itch VAS will be summarized at Week 12.

Statistical Considerations (in both T08 and T09):

A Cochran-Mantel-Haenszel (CMH) chi-square test was used to compare the proportion of subjects responding to treatment.

The change in DLQI from baseline at Week 12 was to be compared between the 45 mg group and the placebo group and between the 90 mg group and the placebo group using an ANOVA on the van der Waerden normal scores with weight as a binary covariate (≤ 90 kg, > 90 kg). To maintain an overall Type I error rate of 0.05, Holm's procedure was to be used.

Protocol C0743T09 (STUDY T09):

The change from baseline in HADS and change from baseline in WLQ at Week 12 were compared between the CNTO 1275 treatment group (45 mg and 90 mg combined) and the placebo group, between the 45 mg group and the placebo group, and between the 90 mg group and the placebo group using an ANOVA on the van der Waerden normal scores with weight as a binary covariate (≤ 90 kg, > 90 kg).

The following rules for handling missing data were used. For a partially answered questionnaire (e.g., not all 10 questions in the DLQI questionnaire were answered):

- If 1 question was left unanswered, this question was scored 0. The total score and each of the 6 component scores were then calculated.
 - If 2 or more questions were left unanswered, the questionnaire was not scored; the total score and each of the 6 component scores were set to missing.
-

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RESULTS:

Table 1 Summary of DLQI Endpoints in Phase 3 Psoriasis studies (Source: Table 6 mod 2.5)

	PHOENIX 1			PHOENIX 2		
	Placebo	CNTO 1275		Placebo	CNTO 1275	
		45 mg	90 mg		45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
Change from baseline in DLQI						
Week 12 (median) ^a	0.0	-6.0	-7.0	-0.5	-8.0	-9.0
mean ± SD	-0.6 ± 5.97	-8.0 ± 6.87	-8.7 ± 6.47	-0.5 ± 5.66	-9.3 ± 7.12	-10.0 ± 6.67
Week 24/28 (median) ^b	NA	-7.0	-8.0	NA	-8.0	-9.0
mean ± SD	NA	-8.1 ± 7.23	-9.6 ± 7.17	NA	-9.5 ± 7.26	-10.3 ± 6.96
Week 40 (median) ^b	NA	-7.0	-9.0	NA	NA	NA
mean ± SD	NA	-8.2 ± 7.23	-9.5 ± 6.96	NA	NA	NA
DLQI score of 0 at Week 12 ^a	1%	33%	34%	1%	37%	39%
Reduction of 5 or more points from baseline in DLQI score at Week 12 ^a	18%	65%	71%	21%	72%	77%

^a p < 0.001 for each CNTO 1275 group vs placebo comparison.

^b PHOENIX 1 assessed DLQI at Week 28 and PHOENIX 2 assessed DLQI at Week 24.

NA = Not applicable.

Table 2 Subjects with DLQI Score of 0 at Week 12 (Source: Table 12 Study T09 CSR)

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0	410	409	411
Subjects evaluated	402	403	404
Subjects with DLQI of 0	4 (1.0%)	148 (36.7%)	158 (39.1%)
p-value		< 0.001	< 0.001

Table 3 Subjects with Reduction of ≥ 5 points from Baseline in DLQI (Source: Table 13 Study T09 CSR)

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0	410	409	411
Subjects evaluated	401	401	402
Subjects with a reduction of 5 or more in DLQI	86 (21.4%)	288 (71.8%)	309 (76.9%)
p-value		< 0.001	< 0.001

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Table 4 Summary of Change from Baseline in DLQI Component Scores at Week 12 (Source: Attachment 3.67 Study T08 CSR)

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0	255	255	256
Component scores			
Symptoms and feelings			
n	252	254	249
Mean ± SD	-0.4 ± 1.54	-2.6 ± 1.78	-2.9 ± 1.69
Median	0.0	-3.0	-3.0
IQ range	(-1.0, 1.0)	(-4.0, -1.0)	(-4.0, -2.0)
Range	(-6, 3)	(-6, 2)	(-6, 1)
p-value		< 0.001	< 0.001
Daily activities			
n	252	254	249
Mean ± SD	0.1 ± 1.61	-1.6 ± 1.66	-1.7 ± 1.62
Median	0.0	-1.0	-2.0
IQ range	(-1.0, 1.0)	(-3.0, 0.0)	(-3.0, 0.0)
Range	(-6, 5)	(-6, 4)	(-6, 2)
p-value		< 0.001	< 0.001
Leisure			
n	252	254	249
Mean ± SD	-0.1 ± 1.68	-1.2 ± 1.81	-1.4 ± 1.81
Median	0.0	-1.0	-1.0
IQ range	(-1.0, 1.0)	(-2.0, 0.0)	(-2.0, 0.0)
Range	(-6, 6)	(-6, 3)	(-6, 1)
p-value		< 0.001	< 0.001
Work and school			
n	252	254	249
Mean ± SD	-0.1 ± 0.92	-0.6 ± 0.94	-0.7 ± 0.89
Median	0.0	0.0	-1.0
IQ range	(0.0, 0.0)	(-1.0, 0.0)	(-1.0, 0.0)
Range	(-3, 3)	(-3, 3)	(-3, 3)
p-value		< 0.001	< 0.001

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	Placebo	CNTO 1275	
		45 mg	90 mg
Personal relationships			
n	252	254	249
Mean ± SD	-0.2 ± 1.45	-1.0 ± 1.62	-1.1 ± 1.58
Median	0.0	0.0	-1.0
IQ range	(-1.0, 0.0)	(-2.0, 0.0)	(-2.0, 0.0)
Range	(-6, 4)	(-6, 3)	(-6, 3)
p-value		< 0.001	< 0.001
Treatment			
n	252	254	249
Mean ± SD	0.0 ± 1.03	-0.9 ± 1.15	-0.9 ± 1.07
Median	0.0	-1.0	-1.0
IQ range	(0.0, 0.5)	(-2.0, 0.0)	(-2.0, 0.0)
Range	(-3, 3)	(-3, 3)	(-3, 2)
p-value		< 0.001	< 0.001

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Reviewer's comment: The change results in the components of the DLQI from the Study T09 were found to be very similar. In both studies, the symptoms and feelings component showed the most change. On average, patients in the active treatment arms improved by about 3 points compared with approximately half of a point improvement on average in placebo. The work and school component of the DLQI showed the least amount of change.

Reviewer's comment: It might be helpful to have the results of a cumulative distribution function of the DLQI total scores as well as the baseline and change information related to the individual items. In sum, summaries of patient responses to the individual items are useful to see which components might be driving the overall score.

In study T08, of the 764 subjects in the DLQI dataset, 66 patients endorsed the item "Over the last week, has your skin prevented you from working or studying?". A total of 651 subjects responded "no" and 47 responded "not relevant". The fact that 66 subjects (almost 9% of the total study population) endorsed this question is striking and suggests that a subset of the study population had significant impairment as a result of their skin. It is unclear whether this is directly related to the skin itself or whether this is related to time off from work to seek treatment for the skin problem. It would be helpful to have cognitive debriefings verifying that patients understand the questions consistently and in the way the question is intended.

The applicant also used the SF-36 in Study T08 and the Hospital Anxiety and Depression Scale and Work Limitations Questionnaire in Study T09 with the stated intention of measuring improvements in health-related quality of life.

According to the study report for Study T09, at Week 12, subjects treated with CNTO 1275 had a significantly greater improvement in HADS as compared with the placebo

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group for each CNTO 1275 group compared with placebo). Improvements in HADS achieved at Week 12 were sustained through Week 24 in both CNTO 1275 groups.

Similarly, in Study T09, at Week 12, both CNTO 1275 treatment groups achieved significant improvement in productivity compared with placebo ($p < 0.001$ each CNTO 1275 group versus placebo). Subjects in the placebo group did not show any improvement in productivity. The change from baseline in productivity was maintained through Week 24.

Reviewer's comment: These data are encouraging.

b(4)

Table 5 Summary of Itch VAS at Baseline (Study T08)

	Placebo	45mg CNTO	90mg CNTO
Itch VAS (0-10 cm)			
n	254	254	255
Mean ± SD	7.04 ± 2.736	6.74 ± 2.662	6.68 ± 2.724
Median	7.90	7.50	7.40
IQ range	(5.40, 9.20)	(5.10, 8.80)	(5.00, 8.90)
Range	(0.0, 10.0)	(0.0, 10.0)	(0.0, 10.0)

Half of the patients had substantial itching at baseline, with IQ range between 5 and 9, overall and one quarter having itch rated as ≥ 9 out of 10.

The change from baseline in itch is shown in the following table.

Table 6 Itch VAS: Change from Baseline at Week 12 (Study T08)

	Placebo	CNTO 1275	
		45 mg	90 mg
Subjects randomized at Week 0	255	255	256
Week 12			
n	252	253	249
Mean ± SD	-0.78 ± 2.538	-4.91 ± 3.142	-5.14 ± 3.020
Median	-0.30	-5.50	-5.50
IQ range	(-1.90, 0.40)	(-7.50, -2.30)	(-7.60, -2.70)
Range	(-9.1, 8.0)	(-9.9, 5.4)	(-10.0, 4.9)
p-value		< 0.001	< 0.001

The median change from baseline in itch was -5.5 in both active groups compared with -0.3 in the placebo group. These differences from placebo were statistically significant. Of note, some of the patients in all three treatment groups experienced worsening of itch with the upper value in the range 8 (placebo), 5.4 (CNTO 45 mg) and 4.9 (CNTO 4.9). However, over 75% of patients in the active arms experienced a decrease in itch. While,

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from these summary data, there did not appear to be a substantial change in itch in the placebo arm.

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7 Page(s) Withheld

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M E M O R A N D U M

Date: 4-25-2008 **Date Consulted:** 2-2-2008

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team

Through: Karen B. Feibus, M.D.
Medical Team Leader, Maternal Health Team

Through: Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Dermatology and Dental Products

Drug: BLA 125261 Ustekinumab

Subject: New molecular entity for the treatment of chronic moderate to severe plaque psoriasis

Materials Reviewed: Relevant data submitted in BLA 125261, _____
correspondences between FDA and Centocor, and FDA and Abbott, meeting minutes;
Pubmed literature review of psoriasis in pregnancy, and psoriasis.

b(4)

Consult Questions:

1. Please comment on the sponsor's proposed labeling, given the stringent contraceptive measures required in Phase 3. We would also be most appreciative of any additional comments/advice that you might have.

2. Please comment on the sponsor's plans for monitoring post-marketing pregnancy exposures to their product.

EXECUTIVE SUMMARY

Strict contraception requirements were part of the study design in phase 3 clinical trials. These requirements were based on a suspected reproductive toxicity that was seen in animal studies of a similar product. This reproductive toxicity was subsequently not confirmed, and therefore these requirements do not need to be incorporated into the label. However, women of reproductive age may potentially be exposed to this product, and in order to obtain information regarding the effects of this drug in pregnant women, a pregnancy registry needs to be established. Data obtained from the proposed Scandinavian pregnancy registry, which is based on the Remicade registry, is limited, and may not be representative of the U.S. population. The proposed North American Adverse Event Registry has several limitations. Therefore, the Maternal Health Team recommends that the sponsor submit a protocol for a prospectively enrolled pregnancy registry based in the United States. In order to obtain information about the drug's presence in breast milk, and its effects in the infant, a lactation study should also be conducted.

INTRODUCTION

On November 29, 2007, Centocor, Inc., a wholly owned subsidiary of Johnson and Johnson, submitted a biologic license application (BLA 125261) to the Division of Dermatology and Dental Products, for Ustekinumab, a first in class new molecular entity. The sponsor's product is a fully human IgG1 κ monoclonal antibody that binds to the p40 protein subunit of the human cytokines IL-12 and IL-23. The proposed indication is treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Based on data submitted in BLA 125261, and data from a competitor's IND, ——— this review responds to DDDP's questions regarding the strict contraception requirements in phase 3 clinical trials, labeling, and pregnancy registries.

b(4)

BACKGROUND

Overview of psoriasis in pregnancy

Chronic plaque psoriasis is a common skin condition that can cause considerable morbidity, occupational disability, and deterioration in one's quality of life¹. Psoriasis has an estimated lifetime prevalence of 0.6 - 4.8% in the U.S. adult population², with three quarters of patients presenting before the age of 40 years. Psoriasis has a multifactorial mode of inheritance, and about 30% of patients with psoriasis have a first degree relative with the disease. The incidence is similar for the two sexes, although

¹ Gelfand J, et al. Epidemiology of psoriatic arthritis in the population of the United States. J American A Derm 2005;53:573.e1-573.e13.

² Naldi L. Epidemiology of psoriasis. Curr Drug Targets Inflamm Allergy 2004;3:12-8.

women generally develop the disease earlier than men. The prevalence in pregnant women is unknown, but probably reflects that of non-pregnant women of childbearing age. Chronic plaque psoriasis is thought to improve in 40-60% of patients during pregnancy, with most improvement during the late first and second trimesters³. This improvement has been associated with elevated levels of progesterone⁴, which down-regulates the T cell proliferative response that is altered in psoriasis. Psoriasis worsens in 20-30 % of women during pregnancy, and may require more intense treatment⁵.

Psoriasis does not affect fertility or pregnancy outcomes⁶; however, the comorbidities associated with severe chronic plaque psoriasis, such as depression and anxiety⁷, may potentially adversely affect the pregnant woman and her ability to care for herself.

Management of chronic moderate to severe plaque psoriasis in pregnancy is fraught with difficulty due to drug associated teratogenic risks, increased incidence of adverse pregnancy outcomes, and toxic side effects. Ultraviolet B therapy is considered safe in pregnancy, but randomized controlled trials in the general psoriasis population have shown effectiveness in only up to 65% of patients⁸. A controlled trial of psoriasis treatment with an average dosing regimen of cyclosporine⁹ showed similar efficacy. Cyclosporine therapy has been associated with fetal growth restriction and prematurity and can have serious side effects such as myelosuppression, hepatotoxicity, and renal impairment. Psoralen plus Ultraviolet A light (PUVA) is mutagenic and is contraindicated in pregnancy. Retinoids and methotrexate are contraindicated in pregnancy due to associated teratogenicity. The biologics infliximab, etanercept, alefacept, and efalizumab appear to be effective in psoriasis patients who have failed other treatments. At this time, there is limited human data available on the safety of biologics in pregnancy; however, more information will become available through pregnancy registries for these products.

Overview of the sponsor's product, Ustekinumab (BLA 125261)

Ustekinumab is a fully human IgG1 κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit of the human cytokines interleukin IL-12 and IL-23. It inhibits the bioactivity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12R β 1 receptor protein expressed on the surface of immune cells. IL-12 and IL-23 are heterodimeric cytokines secreted by activated antigen presenting cells, such as macrophages and dendritic cells. IL-12 and IL-23 participate in immune function by contributing to NK cell activation and CD4+ T cell differentiation and activation. However, abnormal regulation of IL-12 and IL-23 has been associated

³ Tauscher AE, Fleischer AB et al. Psoriasis and pregnancy. *Cutan Med Surg* 2002;6:561-70.

⁴ Weatherhead S et al. Management of psoriasis in pregnancy. *BMJ* 2007;334:1218-20.

⁵ Raychaudhuri SP, et al. Clinical course of psoriasis during pregnancy. *Int J Dermatol*. 2003;42(7):518-20.

⁶ Seeger JD, et al. Pregnancy and outcome among women with inflammatory skin diseases. *Dermatology* 2007;214(1):32-9.

⁷ Luba K, Stulberg D. Chronic plaque psoriasis. *American Family Physician* 2006;73:636-44.

⁸ Gordon PM, Diffey BL, Matthews IN, Farr PM. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 1999;41:728-32.

⁹ Ellis CN, Fradin MS, Messana JM, Brown MD, Siegel MT, Hartley AH, et al. Cyclosporine for plaque-type psoriasis. Results of a multidose, double-blind trial. *N Eng J Med* 1991;324:277-84.

with immune-mediated diseases, such as psoriasis. Ustekinumab prevents IL-12 and IL-23 contributions to immune cell activation, such as intracellular signaling and cytokine secretion. Thus, it is believed to interrupt signaling and cytokine cascades that are central to psoriasis pathology. The molecule is an immunoglobulin G1 (IgG1), with a molecular weight in the range of 148,079 to 149,690 Daltons. The median half-life is 3 weeks.

Centocor submitted two multicenter, randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic (>6 months) plaque psoriasis who had a minimum body surface area (BSA) involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥ 12 , and who were candidates for phototherapy or systemic therapy. No concomitant anti-psoriatic therapies were allowed during the study with the exception of low-potency topical corticosteroids on the face and groin after week 12. A total of 1996 patients were enrolled in the two studies.

Both studies evaluated the safety and efficacy of Ustekinumab versus placebo in 766 patients with plaque psoriasis. In both studies, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 12 by the PASI (PASI 75). Patients achieving at least 90% improvement in PASI from baseline (PASI 90) were considered PASI 90 responders and patients with at least 50% improvement in PASI from baseline (PASI 50) were considered PASI 50 responders. Patients were randomized in equal proportion to placebo, 45 mg or 90 mg of Ustekinumab. Patients randomized to Ustekinumab received 45 mg or 90 mg doses at weeks 0 and 4 followed by the same dose every 12 weeks. Patients randomized to receive placebo at Weeks 0 and 4 crossed over to receive Ustekinumab (either 45 mg or 90 mg) at weeks 12 and 16, followed by the same dose every 12 weeks. To evaluate the efficacy of every 12-week dosing, patients who were PASI 75 responders at both weeks 28 and 40 were re-randomized to either continue dosing of Ustekinumab every 12 weeks or to placebo (i.e., withdrawal of therapy).

In both studies, improvement was seen within 2 weeks of the first dose. Maximum PASI 75 response was generally achieved by Week 24 (76% of the patients in the 45 mg group, and 85% of the patients in the 90 mg group). In both studies, the efficacy of Ustekinumab was significantly superior ($p < 0.001$) to placebo across all subgroups. All three components of the PASI (plaque thickness/induration, erythema, and scaling) contributed comparably to the improvement in PASI. The safety data showed that Ustekinumab was well tolerated. As a selective immunosuppressant, Ustekinumab has the theoretical risks of infection and malignancy. Rates of infections and malignancies were consistent with rates expected in the general psoriasis population (follow up was one year or less). Please see the medical officer review by Dr. Brenda Carr for a detailed analysis of the safety and efficacy data submitted by the sponsor.

REVIEW OF DATA AND RESPONSE TO CONSULT QUESTIONS

Question 1.

For their Phase 3 trials, the sponsor required the following: "Women of childbearing potential and all men must be using adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) and must agree to continue to use such measures and not become pregnant or plan a pregnancy until 12 months after receiving the last injection of study agent." Animal studies conducted with a similar product (different sponsor) showed a potential effect of masculinization in female monkey fetuses; however, there is no apparent nonclinical signal with the sponsor's product.

The sponsor proposes pregnancy category B and the following language for the label:

[REDACTED]

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The label does not discuss the contraceptive measures required in Phase 3.

Please comment on the sponsor's proposed labeling, given the stringent contraceptive measures required in Phase 3. We would also be most appreciative of any additional comments/advice that you might have.

Response

During the development of Ustekinumab, the FDA became aware of preclinical reproductive and developmental toxicity studies for a similar product that showed masculinization of female monkeys in utero. [REDACTED]

[REDACTED] Mechanistically, the two monoclonal antibodies are similar, but Ustekinumab is a fully human IgG1, κ antibody generated in human immunoglobulin transgenic mice, and ABT-874 is a fully human IgG1, λ antibody isolated from a human antibody phage display library¹⁰. A small protrusion at the anterior end of the vaginal cleft was observed at gestation day 100 in 0/8, 1/8, 3/8, and

¹⁰ Kimball AB, et al. Safety and Efficacy of ABT 874, a fully Human Interleukin-12/23 Monoclonal Antibody, in the Treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. Archives of Dermatology 2008;144 (2); 200-207.

1/7 female monkey fetuses in all dosage groups, that is, 0, 5, 25, and 100 mg/kg/week respectively.

Based on FDA's recommendations, these findings were incorporated into the phase 3 clinical trial consent form, and the protocol included strict contraception requirements for women. Contraception requirements for men were not based on a suspected reproductive risk, but as a precaution, due to lack of data regarding potential pregnancy exposure. Ustekinumab's reproductive toxicology studies in monkeys and mice were negative. An expert panel reviewed the _____ data and recommended repeat reproductive toxicology studies to evaluate if this was a true finding, and if so, determine if this was reversible. Repeat studies done in 132 female cynomolgus monkeys showed that the clitoral protrusion represented an insignificant developmental delay, rather than a frank malformation. Please see the pharmacology/toxicology review by Dr. Jiaqin Yao for a detailed analysis of the reproductive and developmental toxicity studies submitted in support of this application. b(4)

The contraception requirements in men and women for a year after the last treatment were due to phase 2 trials which showed detectable serum drug levels for more than six months in some patients who received the highest exposure (90 mg weekly x 4 weeks). Until drug levels could be studied using the maintenance regimens employed in phase 3, the sponsor considered it prudent to require that subjects avoid pregnancy for 12 months after their last administration of drug¹¹. Please see the clinical pharmacology review by Dr. Pravin Jadhur for a detailed analysis of the pharmacokinetics submitted in support of this application.

_____ b(4)

Question 2.

Please comment on the sponsor's plans for monitoring post-marketing pregnancy exposures to their product.

Response

During Ustekinumab's clinical trials, there were 13 pregnancies with maternal exposure to drug, and 17 with paternal exposure. Of the 13 maternal exposure pregnancies, one was a first trimester exposure that resulted in a live birth with no adverse outcome or congenital abnormality in the neonate. Another case was a first and second trimester

¹¹ Centocor-FDA correspondence 4-18-2008

exposure that resulted in a live birth with no adverse outcome or congenital abnormality in the neonate. Five elective terminations occurred, but no information on the presence or absence of fetal anomalies was provided. One spontaneous abortion occurred at 12 weeks gestation in a 42 year old woman. Two cases with the drug exposure in the first trimester had unknown outcomes. The remaining three cases exposed in the first trimester were still pregnant at the time of the submission.

Ustekinumab's reproductive and developmental toxicology studies demonstrated fetal exposure to drug, indicating that it crosses the placenta. In humans, IgG molecules cross the placenta by an active transport mechanism that uses F_c receptors¹²; however, limited data suggest that this mechanism is not functional until sometime during the second trimester, with estimates ranging from the 16th¹³ to the 28th week¹⁴ of gestation.

As part of its risk management plan, the sponsor proposed surveillance of pregnancy exposures to Ustekinumab with a Scandinavian pregnancy registry based on the Remicade pregnancy registry, and a North American adverse event registry, PSOLAR (Psoriasis Longitudinal Assessment and Registry). The Scandinavian pregnancy registry is a prospective 5-year study of pregnancy outcomes in pregnant women with exposure to Ustekinumab in actual clinical practice and of the health of their infants until one year after birth. Pregnant women with the same disease but without Ustekinumab exposure, will serve as controls. The sources of data are the Swedish Medical Birth Register, Prescription Drug Register, Hospital Discharge Register, and the Danish Medical Birth Register, Register of Medicinal Product Statistics, and National Patient Registry.

Use of these databases alone for outcomes data on pregnancies exposed to Ustekinumab has a number of significant limitations. The Swedish Medical Birth Register contains information on pregnancy outcomes on all live births, and only on fetal deaths after 28 weeks gestation. It is not clear what outcomes are available in the Danish Medical Birth Register. While the Scandinavian pregnancy registry is valuable because of its ability to use established databases, it would not capture important information about pregnancy losses up to 28 weeks gestation. The United States has a more heterogeneous and significantly larger population than the Scandinavian countries, and it is not clear that data findings from Sweden and Denmark could be accurately generalized to the U.S. population. The sponsor should establish a pregnancy registry based in the United States. Data from the Scandinavian database study would likely complement information derived from the U.S. pregnancy registry. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>.

¹² Mahadevan U, Kane S, Sandborn WJ, et al. Intentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease. *Aliment Pharmacol Ther* 2005;21:733-738.

¹³ Saji F, et al. Dynamics of immunoglobulins at the feto-maternal interface. *J Reprod Fertil* 1999;4:81-89.

¹⁴ Crowe JE Jr. Influence of maternal antibodies on neonatal immunization against respiratory viruses. *Clin Infect Dis* 2001;33:1720-1727.

The North American Adverse Event Registry, although a prospective study, does not include details regarding surveillance of adverse events in pregnancy, collection of data regarding terminations, and follow-up of neonates after birth. It also doesn't mention a control group of pregnant women. Because of these limitations, it would not be adequate as a surveillance program to evaluate pregnant women who are exposed to Ustekinumab.

Ustekinumab Effects during Lactation

Animal studies of Ustekinumab showed that it is excreted in the milk of lactating monkeys. There are no data on the effects of Ustekinumab during human lactation. Centocor recommends that a woman should decide whether to discontinue nursing or discontinue the drug. Immunoglobulins are excreted in human milk, however published data suggest that they are minimally absorbed from the gastrointestinal tract¹⁵. To assess the presence of Ustekinumab in breastmilk and in breastfed infants, a lactation study should be conducted. The sponsor may choose to do this as a nested study, using patients who are enrolled in their pregnancy registry.

CONCLUSIONS

Because chronic moderate to severe plaque psoriasis occurs in women of childbearing potential and pregnant women, fetal exposure to this product may occur either inadvertently or advertently. Strict contraception requirements based on a perceived potential risk with a similar product were not substantiated in animal reproductive toxicology studies of Ustekinumab. Therefore, it is reasonable to not include contraception requirements in the label. Knowledge of the effects of Ustekinumab on pregnant woman and their fetus is needed. In addition to the sponsor's proposed Scandinavian pregnancy registry, a pregnancy registry based in the United States should be established. The proposed North American Adverse Event Registry has several limitations, and is not adequate to monitor pregnancy and fetal outcomes following exposure of the product during pregnancy. To assess the presence of Ustekinumab in breast milk and the potential effects in nursing infants, a lactation study should be done as part of a post-marketing commitment.

RECOMMENDATIONS

2. The Maternal Health Team recommends that the sponsor develop and maintain, in addition to the proposed Scandinavian pregnancy registry, a U.S. based prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to Ustekinumab during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development,

¹⁵ Van de Pierre P. Transfer of antibody via mother's milk. *Vaccine* 2003;(21):3374-3376.

and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>. The sponsor should submit a draft pregnancy registry protocol for review by DDDP and MHT within four months of product approval. A final protocol should be submitted no later than six months after product approval and should include revised labeling to incorporate pregnancy registry contact information.

3. The Maternal Health Team also recommends that Centocor conduct a lactation study in women who are breastfeeding while being exposed to Ustekinumab. This may be in a subset of women enrolled in the registry, who choose to breastfeed their infants, to assess the presence of Ustekinumab in breast milk and potential effects in nursing infants. For guidance on how to conduct a lactation study, the sponsor should review the Draft Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling <http://www.fda.gov/cder/guidance/5918dft.pdf>. The sponsor should submit a draft protocol for review by DDDP and MHT within six months of product approval.
4. The Maternal Health Team’s recommended revisions to the sponsor’s proposed labeling are provided below. Additions are underlined, and deletions are struck out. Recommended label changes with track changes will be sent separately.

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b(4)

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

Office of Biotechnology Products
Federal Research Center
Tel. 301-796-4242

Memorandum

Label Review

Application Number: STN 125261/0
Name of Drug: Stelera™ (ustekinumab)
Sponsor: Centocor Ortho Biotech, Inc.
Material Reviewed: Stelera™ (ustekinumab) Labels
Submission Date: November 28, 2007
OBP Receipt Date: (Resubmission) July 1, 2009

Background:

STN 125261 for ustekinumab is an original Biologic License Application (BLA) indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. The product is supplied as 45 mg/0.5 and 90 mg/1.0 in a single –use glass vials.

Labels Reviewed: Stelera™ (ustekinumab) carton label
Stelera™ (ustekinumab) container label
Stelera™ (ustekinumab) Prescribing Information

Review

I. Container

A. 21 CFR 610.60 Container Label

1. Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

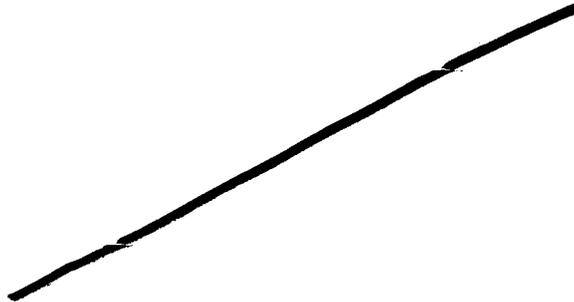
- a. The proper name of the product – ustekinumab – is displayed along with the proprietary name, (trade name). This conforms to the regulation.
 - b. The name, addresses, and license number of the manufacturer – The complete address should be listed, along with the U.S. license number. The manufacturer is listed as Centocor Ortho Biotech, Inc., Horsham, PA 19044, US License no 1821. The statement “Manufactured for” is incorrect. This does not conform to the regulation.
 - c. The lot number or other lot identification – The lot number is not located on the container label. This does not conform to the regulation.
 - d. The expiration date – The expiration date is not displayed on the container label. This does not conform to the regulation.
 - e. The recommended individual dose, for multiple dose containers – This is a single use vial. A statement appears on the label to this effect. This conforms to the regulation.
 - f. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the label. This conforms to the regulation.
 - g. If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – The container label is too small to display the Medication guide statement. The statement is located on the carton. The. This conforms to the regulation.
2. Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. – The container is enclosed in a package (carton). This section does not apply.
 3. Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name

(expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. – This conforms to the regulation.

4. No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. – This container bears a label.
 5. Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation.
- B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
 - C. 21 CFR 201.5 Drugs; adequate directions for use – This is not needed for the vial label as the minimum requirements are listed in 21 CFR 610.60.
 - D. 21 CFR 201.6 Drugs; misleading statements – The only name that appears on the label is the proprietary and proper name. This conforms to the regulation.
 - E. 21 CFR 201.10 Drugs; statement of ingredients – It is recommended that the size difference between trade name and proper name (ustekinumab) can be decreased to avoid prominence of the trade name.
 - F. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”) are prominent and do not overlap. This conforms to the regulation.
 - G. 21 CFR 201.17 Drugs; location of expiration date – The expiration date is not listed on the label. This does not conform to 21 CFR 610.60.
 - H. 21 CFR 201.25 Bar code label requirements – Bar code appears on the label. This does conform to the regulation.
 - I. 21 CFR 201.50 Statement of identity – The established name, (ustekinumab) is stated on the label. The established name and proprietary

name, (trade name), conform to 21 CFR 201.10. This conforms to the regulation.

- J. 21 CFR 201.51 Declaration of net quantity of contents – The net quantity of contents (45mg/0.5ml or 90mg/1.0ml) is declared on the label. This does conform to the regulation.
- K. 21 CFR 201.55 Statement of dosage – The statement “Single Use Vial” is displayed on the label. This conforms to the regulation.
- L. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only”, other pertinent information, but does not list a lot number and expiration date. This does not conform to the regulation.



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II. Carton

A. 21 CFR 610.61 Carton/Package Label –

- a. The proper name of the product – The proper name, (ustekinumab), and the proprietary name, (Stelara), are displayed on the front and back panels of the carton. This conforms to the regulation.
- b. The name addresses, and license number of the manufacturer. The presentation of the manufacturer is incorrect. This does not conform to the regulation.

- c. The lot number or other lot identification – The lot number is on the bottom panel of the carton. This conforms to the regulation.
- d. The expiration date – The expiration date is not listed below the lot number on the side panel of the carton. This does not conform to the regulation.
- e. The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words “no preservative” –The statement “No Preservative” is displayed on the back panel of the carton. This conforms to the regulation.
- f. The number of containers, if more than one – There is only one package container per drug. Each package contains one vial of drug. This conforms to the regulation.
- g. The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable – The amount of product is expressed as a concentration.
- h. The recommended storage temperature – The statement “Store in a refrigerator 36 to 46°F (2-8°C)” is displayed on the back panel of the carton. This conforms to the regulation.
- i. The words “Shake Well”, “Do not Freeze” or the equivalent, as well as other instructions, when indicated by the character of the product – The statement “Protect from light. Do not freeze. Keep out of the reach of children. Do not shake.” is displayed on the back panel of the carton. This conforms to the regulation.
- j. The recommended individual dose if the enclosed container(s) is a multiple-dose container – Only one single-use vial in each carton. Therefore, this does not apply.
- k. The route of administration recommended, or reference to such directions in and enclosed circular – The statement “For Subcutaneous injection” is located on the front panel of the carton.

- l. Known sensitizing substances, or reference to an enclosed circular containing appropriate information – Will ask applicant to supply applicable information
 - m. The type and calculated amount of antibiotics added during manufacture – Will ask applicant to supply applicable information
 - n. The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information – Will ask applicant to provide if applicable
 - o. The adjuvant, if present – Will ask applicant to provide if applicable
 - p. The source of the product when a factor in safe administration – Will ask applicant to provide if applicable
 - q. The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information. – Will ask applicant to provide if applicable
 - r. Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words “No U.S. standard of potency” – “No U.S. Standard of Potency” is not displayed on the label. This does not conform to the regulation.
 - s. The statement “Rx only” for prescription biologicals – The statement “Rx Only” is located on the front and back of the carton. This conforms to the regulation.
 - t. If a Medication Guide is required under part 208 of this chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label – This conforms to the regulation.
- B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2©(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of “specified” biological products listed in 21 CFR*

- 601.2(a)] – This is an exempted (monoclonal antibody products for in vivo use). Therefore the label does not need to conform to this regulation.
- C. 21 CFR 610.63 Divided manufacturing responsibility to be shown – Centocor Ortho Biotech Inc. is the only manufacturer listed on the label. This conforms to the regulation.
- D. 21 CFR 610.64 Name and address of distributor
The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: “Manufactured for _____”, “Distributed by _____”, “Manufactured by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. – The distributor is Centocor Ortho Biotech Inc. and is listed as “Manufactured for: “on the label and the drug product is made in Switzerland.” This does not conform to the regulation.
- E. 21 CFR 610.65 Products for export – This is for US use only. Therefore, this does not need to conform to the regulation.
- F. 21 CFR 610.67 Bar code label requirements
Biological products must comply with the bar code requirements at §201.25 of this chapter. – Bar code appears on the carton label. This does conform to the regulation.
- G. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the right corner on top of the front and back panels of the carton. The NDC number conforms to 21 CFR 207.35 as a 3-2 Product-Package Code configuration. This conforms to the regulation.
- H. 21 CFR 201.5 Drugs; adequate directions for use – The label states “Information for use and dosage-See Package Insert.” This conforms to the regulation.
- I. 21 CFR 201.6 Drugs; misleading statements – The names shown on the carton label are (Stelera) and the (ustekinumab). Therefore, this cannot be confused with other drug, device, food, or cosmetic. This conforms to the regulation.
- J. 21 CFR 201.10 Drugs; statement of ingredients – It is recommended that the size difference between trade name and proper name (ustekinumab) can be decreased to avoid prominence of the trade name. This does not conform to the regulation.

- K. 21 CFR 201.15 Drugs; prominence of required label statements – All required statement (“Rx Only”) are prominent and do not overlap. This conforms to the regulation.
- L. 21 CFR 201.17 Drugs; location of expiration date – The expiration date does not appear under the lot identification number on the side panel of the carton label. This does not conform to 21 CFR 610.60.
- M. 21 CFR 201.25 Bar code label requirements – Bar code appears on the carton label. This conforms to the regulation.
- N. 21 CFR 201.50 Statement of identity – The established name, (ustekinumab), is stated on the label. The established name (ustekinumab) and proprietary name, (trade name) conform to 21 CFR 201.10. This conforms to the regulation.
- O. 21 CFR 201.51 Declaration of net quantity of contents – Net quantity of contents is declared on the carton label. This conforms to the regulation.
- P. 21 CFR 201.55 Statement of dosage – The label states “Information for use and dosage-See Package Insert”. This conforms to the regulation.
- Q. 21 CFR 201.100 Prescription drugs for human use – The label bears statements of “Rx Only”, an identifying lot number, storage conditions, and reference to the package insert. The statement “Protect from Light. Do not freeze. Keep out of the reach of children. Do not shake.” appears on the back panel of the carton.

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Other- / /

Conclusions and Recommendation:

The following deficiencies were noted in the initial review of the ustekinumab container and carton labels:

1. As defined in 21 CFR 600.3(t), manufacturer is the “applicant.” Please revise the manufacturer information from “Manufactured for: Centocor to “Manufacturer:” to comply with 21 CFR 610.62. In addition, the drug product manufacturing that occurs in Switzerland must be disclosed to comply with 19 USC 1304. Please add the statement, “Product of Switzerland”. Change made and acceptable.
2. Please add the lot number and expiration date to the container label to comply with minimum partial label requirements per 21 CFR 610.60. Change made and acceptable.
3. Please add applicable agents or a reference to applicable agents to carton labels to comply with 21 CFR 610.61(l) (m) (n) (o) (p) (q). If inactive ingredients will be listed, they must be in alphabetical order per USPC Official 5/1/09-8/1/09, USP 32/NF27, <1091> Labeling of Inactive Ingredients. Comment not sent to sponsor.
4. Please add the statement “No U.S. standard of potency” to the carton labels to comply with regulation 21CFR 610.61(r). Change made and acceptable.
5. Please consider changing the font size of the proper name to decrease the difference in prominence between the proper name and the trade name. Sponsor confirmed proper name is one half the size of the tradename.
6. Please remove the trailing zero after the decimal point in the strength designation on the carton and container labeling from 90 mg/1.0 mL to 90 mg/mL to comply with the Institute for Safe Medication Practices “List of Error Prone Abbreviations, Symbols and Dose Designations.” Change made and acceptable.
7. Please consider revising the presentation of the dosage form and route of administration to the following presentation:
STELERA (ustekinumab)
Injection
For subcutaneous use

The agency is working toward standardizing the presentation of the trademark, proper name or established name, dosage form, and route of administration. Change made and acceptable.

The following deficiencies were noted upon the initial review of the ustekinumab Patient Package Insert: Comments not sent to Sponsor.

1. Please revise the title line of the Patient Package Insert to the following presentation to comply with 21 CFR 201.57(a)(2):

**STELERA (ustekinumab)
injection, for subcutaneous use**

2. Please remove the trailing zero after the decimal point in the strength designation from the presentation 90 mg/1.0 mL to 90 mg/mL to comply with the Institute for Safe Medication Practices "List of Error Prone Abbreviations, Symbols and Dose Designations."
3. Per USPC Official 5/1/09-8/1/09, USP 32/NF27, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients in alphabetical order.

Revised Labels with acceptable changes

 <p>Stelara™ (ustekinumab) Injection For subcutaneous use 45 mg/0.5 mL Each vial contains 0.5 mL</p>	<p>Single use vial— Discard unused portion</p> <p>NDC 57894-060-02</p> <p>Information for use and dosage— See package insert</p> <p>Rx only</p> <p>Store at 36-46° F (2-8° C) Protect from light Do not shake Do not freeze</p>	<p>Manufactured for: Centocor Ortho Biotech Inc., Horsham, PA 19044 U.S. License No. 1821</p> 	<p>Lot# TK Exp. TK</p> <p>AW_52952</p>
 <p>Stelara™ (ustekinumab) Injection For subcutaneous use 90 mg/mL Each vial contains 1 mL</p>	<p>Single use vial— Discard unused portion</p> <p>NDC 57894-061-02</p> <p>Information for use and dosage— See package insert</p> <p>Rx only</p> <p>Store at 36-46° F (2-8° C) Protect from light Do not shake Do not freeze</p>	<p>Manufactured for: Centocor Ortho Biotech Inc., Horsham, PA 19044 U.S. License No. 1821</p> 	<p>Lot# TK Exp. TK</p> <p>AW_52954</p>

45 mg Version A-Enlarged 150%

45 mg/0.5 mL
Injection
(ustekinumab)
Stelara™

FRONT SIDE

Single use vial-
Discard unused portion
NDC 57894-060-02

Injection
For subcutaneous use
Store in a refrigerator at 36-46°F (2-8°C)
Protect from light
No preservative
Do not shake. Do not freeze
Keep out of the reach of children

Manufactured by Cellego AG,
Schaffhausen, Switzerland for
Centocor Ortho Biotech Inc.,
Horsham, PA 19044
US License No. 3033
No U.S. standard of potency Product of Switzerland

57894-061-02

AW_54034

Single use vial-
Discard unused portion
NDC 57894-060-02

Injection
(ustekinumab)
Stelara™
Injection
For subcutaneous use
45 mg/0.5 mL

Each vial contains 0.5 mL.
Information for use and dosage-
See package insert
Rx only
ATTENTION: Dispense the enclosed
Medication Guide to each patient.

Lot# TK
Exp. TK

Single use vial-
Discard unused portion
NDC 57894-060-02

Injection
(ustekinumab)
Stelara™
Injection
For subcutaneous use
45 mg/0.5 mL

90 mg Version A-Enlarged 150%

90 mg/mL
Injection
(ustekinumab)
Stelara™

FRONT SIDE

Single use vial-
Discard unused portion
NDC 57894-061-02

Injection
For subcutaneous use
Store in a refrigerator at 36-46°F (2-8°C)
Protect from light
No preservative
Do not shake. Do not freeze
Keep out of the reach of children

Manufactured by Cellego AG,
Schaffhausen, Switzerland for
Centocor Ortho Biotech Inc.,
Horsham, PA 19044
US License No. 1821
No U.S. standard of potency Product of Switzerland

57894-061-02

AW_52953

Single use vial-
Discard unused portion
NDC 57894-061-02

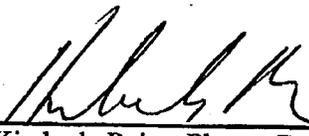
Injection
(ustekinumab)
Stelara™
Injection
For subcutaneous use
90 mg/mL

Each vial contains 1 mL.
Information for use and dosage-
See package insert
Rx only
ATTENTION: Dispense the enclosed
Medication Guide to each patient.

Lot# TK
Exp. TK

Single use vial-
Discard unused portion
NDC 57894-061-02

Injection
(ustekinumab)
Stelara™
Injection
For subcutaneous use
90 mg/mL

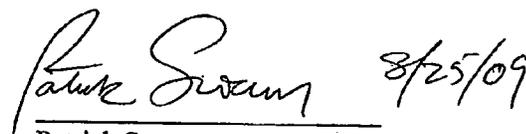

Kimberly Rains, Pharm. D.
Regulatory Project Manager
CDER/OBP/IO

Concurrence/Comments:

1. The following comment was sent to the sponsor :
The name, addresses, and license number of the manufacturer should read:
Manufactured by Cilag AG,
Schaffhausen, Switzerland
for
Centocor Ortho Biotech, Inc.
Horsham, PA 19044 Product of [Country]
License No. 1821
Distributed by [Name, address]

Change made and acceptable.


Laurie Graham
Product Reviewer
CDER/OPS/OBP/DMA


Patrick Swann
Deputy Director
CDER/OPS/OBP/DMA