CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125261

SUMMARY REVIEW

DIVISION DIRECTOR SUMMARY REVIEW

Date	August 20, 2009
From	Susan J. Walker, M.D., F.A.A.D 8/26/09
Subject	Summary Review
BLA #	125061/0
Applicant Name	Centocor
Date of Submission	Original BLA Submission: November 29th, 2007 Agency Complete Response action: December 18th, 2008 Applicant Complete Response Submission: Jan 9th, 2009 Applicant Major Amendment: May 1st, 2009
PDUFA Goal Date	October 9th, 2009
Proprietary Name / Established (USAN) Name	Stelara/Ustekinumab
Dosage Forms/Strength	Liquid in Vial solution for parenteral injection: Concentration is 90mg/ml Filled into 2mL glass vials containing 90mg (1mL) or 45mg (0.5ml)
Proposed Indication(s)	Treatment of patients 18 years and older with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Carr, M.D.
Statistical Review	Kathleen Fritsch, Ph.D.
Pharmacology Toxicology Review	Jiaqin Yao, Ph.D.
CMC Review/OBP Review	Laurie Graham, M.S. and Vivian Wang M.S.
Microbiology Review	Bo Chi, Ph.D.
Clinical Pharmacology Review Pharmacogenomics Review Pharmacometrics Review	Abimbola Adebowale, Ph.D./Jang-Ik Lee, Pharm.D., Ph.D. Shashi Amur, Ph.D., and Padmaja Mummaneni, Ph.D. Pravin Jadhav, Ph.D.
DDMAC	Andrew Haffer, Pharm.D. and Shefali Doshi, M.D.
DSI	Sherbet Samuels, R.N., M.P.H.
CDTL Review	Jill Lindstrom, M.D.
OSE/DMEPPA	Loretta Holmes, BSN, Pharm. D.
OSE/DRISK	Kathryn O'Connell, M.D., Ph.D.; Kate Heinrich, M.A.
CBER/DVRPA	Rosemary Tiernan, M.D., M.P.H.
MHT SEALD	Leyla Sahin, M.D. Elektra J. Papadopoulos, M.D.

1. Introduction

This review revises and extends my Division Director summary review dated December 16th, 2008 and provides my basis for recommendation of "approval" in this cycle.

BLA 125261/00 was originally received on November 29, 2007 and the first cycle action was a Complete Response on December 18, 2008 based upon outstanding needs for product quality information and clinical information. Product quality deficiencies included lack of established control procedures to validate the performance of manufacturing processes and lack of an accurate testing and sampling method for measurement of visible particulate matter. Clinical informational needs included provision of a Risk Evaluation and Mitigation Strategy (REMS) as provided under FDAAA (section 505 (o)(3)(A) to ensure that the benefits of the drug outweigh the risks.

This review will describe the resolution of the manufacturing issues and the evaluation of the REMS. Additionally, new safety information submitted in the Safety Update in January 2009 describes a case of reversible posterior leukoencephalopathy syndrome (RPLS) and this will be discussed.

2. Background

Ustekinumab is a first-in-class new molecular entity proposed for the treatment of plaque psoriasis. Ustekinumab is a fully humanized IgG1κ monoclonal antibody that binds to the p40 subunit of interleukin (IL)-12 and IL-23. These cytokines share the IL-12 p40 subunit, and have been implicated in the pathogenesis of psoriasis. Ustekinumab binds with high affinity to human IL-12 and IL-23 and neutralizes their bioactivity preventing these cytokines from binding to their IL-12RB1 (IL-12 receptor beta-1) receptor protein expressed on the surface of immune cells. This selective immunosuppressant is classified according to the proposed Anatomical Therapeutic Chemical Classification system as an Interleukin Inhibitor. [1] The immunosuppression is of prolonged duration because of the product's long half-life of three weeks.

The applicant has conducted two adequate and well controlled studies in which efficacy was assessed adequately using the investigator's global assessment score and the Psoriasis Area and Severity score (PASI). The product safety assessment was primarily based upon an integrated analysis of data encompassing studies through 18 months. The safety database revealed no signals suggesting that patients treated with ustekinumab might manifest vulnerability to the spectrum of infections seen in individuals genetically deficient in IL-12 and IL-23. However, the 18 month safety database is likely insufficient to fully characterize the risk of infection and malignancy for chronic use of this product. The use of a Risk Evaluation and Mitigation Strategy (REMS) is necessary.

[1] DVRPA review 07.14.08

3. CMC/Device

First Cycle Deficiencies

Ustekinumab has a concentration of 90mg/mL, and is filled into 2mL glass vials containing either 1mL (90m) or .5 mL (45mg) of product. Potency is defined as percent activity relative to a reference standard, using a cell based assay measuring the inhibition of IL-12 induced IFNγ production by an NK cell line. The dating period for vialed drug was proposed as [redacted] when stored at 2-8°C and protected from light, but this has been shortened to 12 months due to manufacturing issues more fully explored below. b(4)

In the first cycle, the Product Reviewers identified Out of Trend (OOT) and Out of Specifications (OOS) concerns related to unexpected visible particulates in the product when examined for stability at approximately 18 months. It appears that the root cause for the presence of these particulates in these analyses may be different.

The root cause for the presence of particulates in the OOS results is determined to be the [redacted] evaluation. The syringes are [redacted] in the [redacted], which appears to have resulted in [redacted] samples. The applicant subsequently changed the visible particle analytical procedure to using a glass syringe. The Division of Monoclonal Antibodies summary review has concluded that the applicant has provided adequate data to 1) demonstrate that the [redacted] are the root cause of the OOS results and 2) the use of the glass syringes in the visible particle assay can provide a reliable sample method.

The root cause for the appearance of particles in the OOT results are not yet conclusive and it appears that there is likely a from a different root cause. Although the [redacted] may have contributed, even with use of glass syringes there are increased particles visible in stability samples from the validation batches, compared to earlier clinical batches. The sponsor posits that these particles are [redacted] degradation within the product. Particles in the OOT investigation were shown to contain [redacted] No root cause has been identified, although investigations are ongoing. As a result of the OOT samples, the shelf life of the drug product has been shortened [redacted] to 12 months. b(4)

The Division of Monoclonal Antibodies (DMA) has determined the applicant has provided adequate data to resolve these concerns. The applicant agreed to a number of product-related post-marketing commitments, and these should be included in the approval letter.

Inspections:

The Office of Biotechnology Products (Division of Monoclonal Antibodies) and Office of Compliance (Division of Manufacturing and Product Quality) concurred in waiving a pre-approval inspection at the drug product manufacturing facility (Cilag AG, Switzerland). The waiver was recommended, as there are no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed parenteral products at Cilag AG.

The drug substance manufacturing facility (Centocor Biologics in St. Louis, MO) was inspected on April 14- yet18, 2008 (FEI Number 3003418999) and Inspectional Observations (SF483) were noted. These have been resolved.

4. Nonclinical Pharmacology/Toxicology

There are no additional pharmacology/toxicology issues addressed in this supplement.

The mechanism of action of ustekinumab, inhibition of IL-12/IL-23 expression, provides biologic plausibility for enhanced carcinogenic risk. Formal two-year systemic carcinogenicity studies have not been conducted with ustekinumab. However, adequate literature data is available to indicate that inhibition of IL-12/IL-23 expression leads to an increased carcinogenic risk. Systemic administration of IL-12 exhibits an anti-tumor effect in mice, inhibition of IL-12/IL-23 expression with a murine monoclonal antibody enhances tumor formation in mice challenged with squamous cell carcinoma cells and removal of the IL-12/IL-23 gene in knockout mice enhanced tumor formation in mice. There is sufficient nonclinical data in the literature indicating an increased carcinogenic risk with inhibition of IL-12/IL-23 expression to justify inclusion in labeling of this animal data to inform prescribers about the potential carcinogenic risk from ustekinumab use.

I concur with the conclusions reached by the pharmacology/toxicology reviewer and supervisors that there are no outstanding pharm/tox issues that preclude approval. The labeling of Ustekinumab should provide the information from the nonclinical studies conducted by the sponsor and from the literature as outlined by the reviewer. A potential increased carcinogenicity risk may be associated with the chronic use of ustekinumab in psoriasis patients. This potential risk is also addressed in the Risk Evaluation and Mitigation Strategy (REMS).

5. Clinical Pharmacology/Biopharmaceutics

This supplement provides additional clinical pharmacology information, specifically, to provide a comparison of the immunogenicity incidence/data collected from all study subjects receiving drug product with levels of particulate matter. Immunogenicity rates were relatively low; however, the presence of ustekinumab interfered with antibody assessment in a large proportion of subjects. The presence of increased amounts of particulates did not appear to result in increased immunogenicity. An improved immunogenicity assay method that can measure anti-drug antibodies (ADA) without interference from levels of ustekinumab that are expected to be present in patients' serum at the time of ADA sampling has been agreed upon as a Post Marketing Commitment.

Original Submission:

Biopharmaceutics: Clinical data suggest "decreased efficacy in antibody-positive subjects, however the data are inadequate for conclusions. The biopharmaceutics reviewer is recommending an in-vitro study (or studies) to determine whether IL-12 and/or IL-23 modulate CP enzyme expression and whether ustekinumab is able to reverse the effects of IL-12/IL-23 on CYP expression (e.g., in vitro hepatocyte study). An alternative in vivo approach would be to determine the potential of ustekinumab for the alteration of CYP substrate metabolism in psoriasis patients (e.g., a cocktail study with CYP probe drugs). The applicant will provide this information as a post-marketing commitment.

Pharmacogenomics: I concur with the recommendation of the pharmacogenomics reviewer that early identification of non-responders through the use of biomarkers would benefit clinicians and patients, and that the sponsor should continue to search for efficacy biomarkers.

Pharmacometrics: The applicant has proposed weight based dosing in two increments, with patients weighing < 100kg receiving 45mg initially and 4 weeks later, followed by dosing every 12 weeks. Patients >100kg would receive 90mg initially and 4 weeks later, followed by dosing every 12 weeks. The Pharmacometrics reviewer has recommended an alternative 3 step dosing, with patients weighing <70kg (154 lbs) receiving 45mg initially and 4 weeks later, followed by dosing every 12 weeks. For patients ≥70kg and < 100kg (220 lbs) the recommended dose is 67.5mg initially and 4 weeks later, followed by dosing every 12 weeks. For patients weighing ≥100kg, the recommended dosing would remain unchanged from the applicant proposal (90 mg initially and 4 weeks later, followed by dosing every 12 weeks). The Advisory Committee voted 7 vs. 3 to recommend the two step dosing as originally proposed by the applicant. The main concerns from the committee were (1) lack of data at 67.5 mg (2) possible delays in generating stability data for 67.5 mg and (3) lack of availability of information on the lowest effective dose. However, there was some interest in this alternative dosing regimen and this should be explored more fully by the sponsor. The sponsor did not pursue substantive dose ranging studies for this product. I concur with the clinical reviewer and the majority of the Advisory Committee that weight based dosing in two increments is appropriate for initial approval. Additional dosing regimens could be explored post marketing.

6. Clinical Microbiology

No clinical microbiology review was provided.

7. Clinical/Statistical-Efficacy

I concur with the conclusions of the primary medical officer that the applicant has provided sufficient evidence of efficacy. The applicant conducted two adequate and well-controlled Phase 3 studies, in which efficacy was assessed at Week 12 by the proportion of subjects who achieved a 75% reduction in the Psoriasis Area Severity Index (PASI 75and by success on the Physician's Global Assessment (PGA). The Phase 3 studies provided substantial evidence of efficacy of ustekinumab in the target population of patients with moderate to severe plaque psoriasis. In both studies, efficacy was demonstrated for both doses as measured by the PASI

scare and the PGA score. Efficacy outcomes were generally similar between dosing groups and across studies. Both doses were proven efficacious in both weight categories; however, higher efficacy outcomes were observed in heavier subjects (> 100 kg) who received 90 mg of ustekinumab compared to those who received 45 mg.

Week 12 Efficacy Results

	Stelara 45 mg	Stelara 90 mg	Placebo
Study 08	N=255	N=256	N=255
PASI 75 response	171 (67%) p<0.001	170 (66%) p<0.001	8 (3%)
PGA Cleared/Minimal	154 (60%) p<0.001	158 (62%) p<0.001	10 (4%)
Study 09	N=409	N=411	N=410
PASI 75 response	273 (67%) p<0.001	311 (76%) p<0.001	15 (4%)
PGA Cleared/Minimal	278 (68%) p<0.001	302 (73%) p<0.001	20 (5%)

Source: Biostatistical Review (28 July 2008), BLA 125261, Dr. Kathleen Fritsch, pp.31.

The applicant has committed to providing information to inform maintenance of response with dosing intervals longer than every 12 weeks, based upon information in the trials which indicates that some patients may maintain a reasonable treatment response with less frequent dosing than 12 weeks. This additional information may be useful in minimizing long-term exposure while continuing to maximize therapeutic effect.

8. Safety

First Cycle Summary:

The first cycle assessment of safety was based primarily on the integrated analyses of data from three studies: PHOENIX1, PHOENIX2 and ACCEPT. The medical reviewer concludes the applicant provided substantial evidence of the safety of ustekinumab in the target population through 18 months of exposure. Overall rates and patterns of serious adverse events in these trials suggested no increased risk when ustekinumab-treated subjects were compared to placebo-treated subjects or to each other (i.e., 45 mg compared to 90 mg). This conclusion held when specific categories of events were considered, including serious cardiac events, serious infections, serious malignancies, and serious nervous system disorders. Overall rates for treatment-emergent adverse events were generally similar between all treatment groups, and generally suggested no dose response when ustekinumab groups were compared. The most common adverse events were nasopharyngitis and upper respiratory tract infection. Adverse drug reactions were not generally worrisome in pattern or frequency of occurrence.

Safety Update

The Safety Update provided in the applicant's Complete Response includes a case report of a 65-year-old female who received 11 doses of ustekinumab through Sept 11, 2008 and was admitted to the hospital with a seizure and altered state of consciousness, requiring intubation, on [redacted] Computer tomography (CT) revealed a left hypothalamic hypodensity and white matter changes in the cerebellar region. The patient's condition progressively improved and she was discharged on [redacted] with a diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS) secondary to ustekinumab. The investigator assessed the case as severe in intensity and possibly related to treatment with the study agent. This syndrome was first described by Hinchey[2] et al in 1996, and is considered to be associated with renal insufficiency or hypertension, and with immunosuppression. More recent evidence indicates that in some cases the syndrome is not reversible. While RPLS has been observed in patients treated with immunosuppressive agents, including cyclosporine, tacrolimus and interferon alpha, a specific etiology is unknown. Delay in diagnosis may lead to permanent damage. This condition should be described in the package insert, the medication guide, and be included in the REMS.

b(6)

Summary of Safety Database

The safety database revealed no signals suggesting that patients with pharmacologic blockade of IL-12/IL-23 demonstrate vulnerabilities to the narrow spectrum of infections seen in individuals genetically deficient in these cytokines. Specifically, there were no reports of infections by nontuberculous mycobacteria or of salmonella. There was one report of a serious gastroenteritis, and the subject's presentation and clinical course did not suggest salmonellosis. Of note, 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. Two additional subjects were diagnosed with latent tuberculosis post-screening. Through the end of the reporting, there were no reports of complications from tuberculosis.

Ustekinumab is an immunosuppressant intended for chronic use in psoriasis patients. Potential adverse events that may be related to the use of ustekinumab include serious infections and malignancy. Based on data from rodent models, there is a theoretical concern that blockade of IL-12/IL-23 may heighten patients' risk for malignancy. Humans genetically deficient in IL-12/IL-23 appear to have particular susceptibilities to infections from BCG, environmental mycobacteria and non-typhoidal salmonella but no apparent excess risk for malignancy, although most of these patients have yet to reach middle age. There are no apparent signals for particular infection susceptibilities or malignancy in the safety database for ustekinumab submitted in support of the BLA; however, follow-up is only through 18 months.

The safety database did not signal that the malignancy risk suggested in animal models might be translating to humans; however, a signal of this sort might not be revealed in a database in which the maximum duration of follow-up was through 18 months, with 373 ustekinumab-exposed subjects followed through this period. Similarly, the database might not be of

[2] Hinchey et al: N Engl J Med. 1996 Feb 22; 334(8): 494-500 A Reversible Posterior Leukoencephalopathy Syndrome

sufficient size to detect low frequency events. Therefore, the available data permit only tentative conclusions regarding these risks, and additional, longer-term data are needed to assess for these theoretical risks in patients treated with ustekinumab. There should be substantial additional safety data obtained from adult studies prior to consideration for approval in the pediatric population.

The theoretical risk of malignancy was extensively discussed before the DODAC on June 17th, 2008 with a focus on the need for complete ascertainment and long-term assessment of cancer events. I am in concurrence with the OSE consultant's conclusions concerning the utility of exposure registry information. The utility of these registries for identification of malignancy risk (or any other risk) while reasonable and prudent is simply unknown to us. While it has been suggested that additional controlled clinical trials of ustekinumab may offer a more robust buttress for malignancy risk assessment than exposure registry observational studies, it is unclear how these studies would be designed and conducted and whether the potential signal in the animal data is sufficient to mandate what could become decades of premarketing trials. A psoriasis disease specific registry may be a more optimal vehicle for obtaining adverse event information.

I concur with the recommendations of the clinical reviewer that the applicant should adhere to their proposed plans for Pharmacovigilance which include: continuation of the Psoriasis Longitudinal Assessment and Registry (PSOLAR); initiation of the Nordic Database Initiative (NDI); submit data analyses from the Pregnancy Research Initiative; establish a U.S. based prospective observational registry; conduct a lactation study in patients who are breast feeding; continue the long-term extensions of Phase 3 trials (Phoenix 1 and 2).

The applicant should evaluate additional dosing regimens and provide information on maintenance of response with dosing intervals longer than every 12 weeks.

RISK EVALUATION AND MITIGATION STRATEGY (REMS):

Ustekinumab will be approved with a risk evaluation and mitigation strategy intended to ensure that the benefits outweigh the risks.

The goal of this REMS is to mitigate the risk of opportunistic infections and the potential risk of malignancy associated with Stelara by:

- Alerting and warning patients and healthcare providers about the risks
- Informing and educating healthcare providers and patients about the PSOLAR voluntary disease specific registry
- Informing and educating healthcare providers about the need to report serious adverse events

The REMS for this product contains a medication guide, a communication plan, and a timetable for assessments of the REMS. There are no "elements to assure safe use" (ETASU). The applicant has been advised that REMS materials are not appropriate for use in a promotional manner. Specifics of the REMS include:

A. A medication guide developed as provided for under 21CFRPart 208. The distribution plan includes appending to the package insert and also providing medication guides (or the means to produce medication guides) to distributors, packers or authorized dispensers with the intent that "authorized dispensers" provide a medication guide to each patient with each use. The medication guide will also be available on the ustekinumab patient and professional websites.

B. A communication plan providing for the dissemination of information about the potential risks of serious infection, malignancy and neurologic events (RPLS), including the scientific basis for these concerns, provide information concerning importance of adverse event reporting and methods available for reporting adverse events, and provide information intending to encourage participation in registries.

The audience for the communication plan will be dermatologists, oncologists, rheumatologists, infectious disease specialists, gastroenterologists, and pharmacists and neurologists. Use of the MedWatch program to report serious adverse events should be encouraged in the communication plan.

Communication plan elements include:

1. Dear Healthcare Provider Letters
2. A Dear Pharmacist letter to be distributed to all pharmacists
3. An adverse event awareness campaign, "Service Announcements", which include:

- [redacted]Placement of information on adverse event reporting within advertising in professional journals and targeting physicians who prescribe ustekinumab or who may encounter patients with ustekinumab related adverse events.
- An intensive adverse event reporting awareness campaign at major national meetings of appropriate specialties;
- Dissemination of adverse event reporting information thru direct mail with Dear HCP letters
- Displays at dermatology and oncology scientific mtgs
- Possible dissemination with registration materials at annual scientific dermatology and oncology meetings
- Possible posting on AAD website through outreach efforts to AAD

- Collaboration with dermatology, oncology, rheumatology, infectious disease, neurology and gastroenterology professional societies

4. Encouragement for prescriber's to enroll patients into PSOLAR with active education concerning this registry; enhancement of REMS communications via various means.

5. REMS specific materials accessible as a "link" from the applicant's main website. This separate website is considered a component of the REMS communication plan and should only contain language approved as a part of the REMS.

   Consideration of CME programs within the REMS is under discussion at the time of closure of this review.

C. The REMS assessment schedule includes 1st Assessment at 18 months after approval, 2nd assessment at 3 yrs after approval, and 3rd assessment at 7 years after approval.

9. Advisory Committee Meeting

The Dermatologic and Opthalmologic Drugs Advisory Committee met on June 27th, 2008 and was asked to provide specific advice and recommendations concerning a) the dosing regimen b) carcinogenicity c) long-term safety and d) self-administration. Following substantial discussions, the Committee voted unanimously that the applicant had provided sufficient information to demonstrate efficacy, and to support the dosing schedule of every 12 weeks. In addressing the dosing regimen, the majority of the committee (7-3) voted for approval of the dosing he (45mg and 90mg) as studied by the applicant. Members voting for a third dose (67.5mg) felt the population weighing between 70kg and 100kg would have an increased risk of side effects and toxicity if given the 90mg dose. The Committee advised (Yes 1, No 10) that the applicant had not provided sufficient information to inform patients and physicians regarding how/when to stop treatment with ustekinumab. They also advised that the database provided was not fully sufficient in either length of time or number of subjects to fully characterize the critical safety concerns. The Committee voted 11-0 that they were concerned about the potential malignancy risk associated with this class of products, that this was important information to convey to prescribers, but that additional animal studies were not needed.

The Committee voted unanimously for approval without additional premarket studies, and voted unanimously that the applicant's risk assessment proposals (PSOLAR, 5 year extension of pivotal trials) were not sufficient to characterize the long term safety.

10. Pediatrics

The applicant's pediatric assessment requested a deferral for all pediatric studies. Pediatric study requirements were discussed at the PERC. The submission of the pediatric plan is deferred until December 1st, 2022 because pediatric studies should be delayed until additional adult safety and efficacy data have been collected. These pediatric studies should be deferred

pending completion and analyses of safety data from adults in PHOENIX 1, PHOENIX 2, PSOLAR registry, Nordic Database Initiative, and in-utero/breast feeding studies. These studies are further described in post-marketing commitments/requirements. The analyses must establish that there are no safety issues that would preclude studies in pediatric patients.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

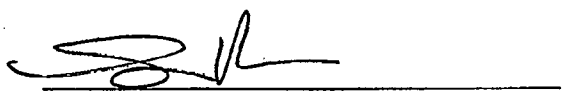
12. Labeling

Proprietary Name: DMEPA recommends approval of the proprietary name Stelara.

Final labeling is currently under review.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action – Approval
- Risk Benefit Assessment - The benefits from treatment with ustekinumab are sufficient to provide a meaningful treatment for selected patients. The approved labeling will provide information for patients and prescribers. The product is available for prescription only and individual assessment of risks and benefits will be determined within the context of the physician/patient relationship.
- Recommendation for Postmarketing Risk Management Activities -This product is approved with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a Medication Guide and a Communication Plan.
- Recommendation for other Postmarketing Study Commitments – These will be conveyed with the approval action.



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