

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125261

OFFICE DIRECTOR MEMO



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: September 17, 2009

TO: File, BLA 125261 STELARA (ustekinumab)
Centocor, Inc

FROM: Julie Beitz, M.D.
Director, Office of Drug Evaluation III

RE: Approval Action

Ustekinumab is a fully human IgG1 κ monoclonal antibody that binds with high affinity and specificity to the shared p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23). It is thought to act by inhibiting immune pathways important to the pathogenesis of psoriasis. This memo documents my concurrence with the Division of Dermatology and Dental Product's (DDDP's) recommendation for approval of Stelara (ustekinumab) for use in adult patients with chronic moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

BLA 125261, dated November 28, 2007, was received on November 29, 2007 and granted a standard review. The application was discussed before the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) on June 17, 2008. Several issues were addressed including, efficacy considerations related to weight-based dosing, safety considerations (e.g., risks associated with prolonged immunosuppression), and the utility of various strategies to monitor short- and long-term safety in exposed patients (e.g., prescriber administration vs. self-administration, enrollment in a mandatory patient registry vs. a post-approval observational study).

In a Complete Response letter dated December 18, 2008, the applicant was informed that before this application may be approved, they must 1) address deficiencies involving chemistry, manufacturing, and controls (CMC), and 2) submit a proposed Risk Evaluation and Mitigation Strategy (REMS) as described below.

On January 9, 2009, Centocor submitted a complete response to the Agency's December 2008 letter. A subsequent response dated May 1, 2009 to clinical and clinical pharmacology information requests was considered a major amendment extending the review clock by three months. At this time, all CMC deficiencies have been resolved, an

acceptable REMS has been submitted, and discussions regarding product labeling and postmarketing studies and clinical trials have been completed successfully.

DOSING

Stelara is administered by subcutaneous injection. For patients weighing ≤ 100 kg, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients weighing > 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

CHEMISTRY, MANUFACTURING AND CONTROLS

In the first review cycle, the Division of Monoclonal Antibodies (DMA) identified Out of Trend (OOT) and Out of Specification (OOS) results related to an unexpected increase in visible particulates in drug product lots on stability at 2-8°C. The Agency's Complete Response letter requested that the applicant identify the root cause of the increase in visible particulates, outline corrective actions taken, and develop and validate a sampling and testing method for assessment of the level of visible particulates in the drug product.

The root cause for the OOS results has been determined to be the _____
_____ The
syringes are _____ in the _____
_____. As a result, the
applicant began using glass syringes. DMA has concluded that the applicant has
provided adequate data to demonstrate that 1) the _____ 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 applicant agrees to perform an extensive
qualification study for multiple use of glass syringes.

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The root cause for the OOT results has not yet been fully determined. Data indicate that the root cause differs from the root cause for the OOS results. Even with use of glass syringes there are increased particulates visible in stability samples from the validation batches, compared to earlier clinical batches. These particulates may represent _____ degradation of the product. As a result of the OOT results, the shelf life of the drug product has been shortened to 12 months. The applicant agrees to continue its root cause investigation to identify causative factor(s) that led to the OOT results.

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The applicant has agreed to several additional product-related post-marketing commitments, including 1) improve assay methods for anti-drug antibodies, 2) establish quantitative drug product release and stability specifications for the non-reduced cSDS assay, 3) collect drug product release and stability data to reassess and lower the allowable number of sub-visible particles, 4) reassess release and shelf-life specifications for the drug substance and drug product, 5) conduct end-of-life concurrent validation of _____ at the manufacturing scale, 6) _____, 7) perform reduced scale end-of-life viral removal studies for the _____, 7) revise the _____ SDS-PAGE and IEF stability specifications upon review of available stability data, 8) develop and validate the Microflow Digital Imaging assay and incorporate this assay into the annual stability testing program, 9) perform both IEF and cIEF in parallel for future batches as part of the commercial stability program,

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and 10) develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest and harvest samples.

EFFICACY

Two randomized, double-blind, controlled trials (PHOENIX 1 and PHOENIX 2) evaluated the efficacy of injections of ustekinumab 45 mg and 90 mg relative to placebo. A total of 766 and 1230 patients were enrolled in these trials, respectively. Patients were randomized 1:1:1 to 45 mg, 90 mg or placebo, dosed at Weeks 0 and 4, and assessed at Week 12. Patients randomized to placebo were crossed over after the Week 12 assessment to active treatment. Ustekinumab treatment was continued in both groups every 12 weeks thereafter. High proportions of patients in both ustekinumab groups (66% to 76%) achieved a Psoriasis Area and Severity Index 75 (PASI 75) response at Week 12 (the primary endpoint) compared with 3-4% of placebo-treated patients. In addition, the Physician Global Assessment (PGA) of psoriasis of cleared or minimal was noted for 59-73% of ustekinumab-treated patients as compared to 4% for placebo-treated patients. Evidence for maintenance of effect through one year in patients receiving maintenance doses every 12 weeks was also demonstrated.

In patients weighing > 100 kg, efficacy was reduced in those who received 45 mg compared to 90 mg. Product labeling will recommend that patients \leq 100 kg be dosed with 45 mg and patients > 100 kg with 90 mg. The Advisory Committee unanimously recommended approval of ustekinumab with a majority voting in favor of the sponsor's proposed weight-based dosing paradigm.

PHARMACOKINETIC CONSIDERATIONS

Ustekinumab is slowly absorbed and reaches maximum serum concentration in 13.5 days and 7 days after a single SC injection of 45 mg and 90 mg, respectively. The mean elimination half-life ranged from 14.9 to 45.6 days across all psoriasis studies following intravenous and subcutaneous administration. Based on population pharmacokinetic analyses, patient weight is the most clinically relevant factor in determining optimal dosing. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines during chronic inflammation. Thus, ustekinumab could normalize the formation of CYP450 enzymes. Upon initiation of treatment with ustekinumab, in patients taking concomitant CYP450 substrates, particularly those with a narrow therapeutic index, monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the drug dose adjusted as needed.

SAFETY

Ustekinumab is an immunosuppressant to be used chronically in psoriasis patients. Risks of chronic immunosuppression include serious infections and malignancy. Ustekinumab cannot be tested in a traditional 2-year rodent study to evaluate carcinogenic potential;

species-specific binding limits its evaluation to humans and non-human primates. The original BLA submission contained safety data on 2266 ustekinumab-treated patients, 373 of which had at least 18 months exposure.

Infections. Ustekinumab may increase the risk of infections and reactivation of latent infections. In the placebo-controlled period of clinical trials in psoriasis patients, 27.4% of ustekinumab-treated patients reported infections compared with 24% of placebo-treated patients. Serious infections occurred in 0.3% and 0.4% of ustekinumab- and placebo-treated patients, respectively, and included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections. The most frequently reported infections in ustekinumab- and placebo-treated patients were nasopharyngitis and upper respiratory tract infections.

Individuals genetically deficient in IL-12/IL-23 are particularly susceptible to disseminated infections from mycobacteria (including nontuberculous or environmental mycobacteria), salmonella (including nontyphi strains), and BCG vaccinations. It is not known whether patients with pharmacological blockade IL-12/IL-23 from treatment with ustekinumab will be susceptible to these types of infections.

Malignancies. Ustekinumab may increase the risk of malignancy. In the controlled and uncontrolled portions of clinical trials in psoriasis patients, 0.4% of ustekinumab-treated patients reported malignancies, including non-melanoma skin cancers (0.36 per 100 subject-years of follow-up). This incidence is similar to that in the general US population. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS). One case of RPLS was observed in a patient who experienced headache, seizures and confusion after receiving 12 doses of ustekinumab over approximately two years. The patient fully recovered after treatment discontinuation.

Immunogenicity. The incidence of antibodies to ustekinumab in phase 3 trials was 3-5%; the presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results.

PEDIATRIC CONSIDERATIONS

Pediatric Use. The safety and effectiveness of ustekinumab have not been evaluated in pediatric patients.

Required Pediatric Studies. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of a pediatric plan proposal until December 1, 2022 because pediatric studies should be delayed until additional adult safety and efficacy data have

been collected. Pediatric studies are deferred pending analyses of a) safety data from adults in PHOENIX 1, PHOENIX 2, the PSOLAR Registry, and the Nordic Database Initiative, and b) safety data in pediatric patients exposed to ustekinumab *in utero* or postnatally (see below).

POSTMARKETING REQUIREMENTS UNDER 505(o)

In accordance with section 505(o)(3)(A), we have determined that postmarketing studies and clinical trials will be needed to further assess the serious risks associated with use of ustekinumab.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risk of serious infection; or to identify unexpected serious risks of malignancy, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal, or hematologic events, adverse pregnancy and fetal outcomes, adverse effects on immune system development, or altered metabolism of co-administered drugs.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that the applicant will be required to:

- Enroll 4000 ustekinumab-treated subjects into the Psoriasis Longitudinal Assessment Registry (PSOLAR) and follow them for 8 years;
- Provide data analyses from the Nordic Database Initiative regarding the occurrence of these serious events with exposure to ustekinumab;
- Establish a US-based, prospective, observational pregnancy exposure registry; maternal outcomes should be assessed throughout pregnancy and infant outcomes through at least the first year of life;
- Provide data analyses from the Pregnancy Research Initiative;
- Conduct a lactation study in women who are breastfeeding while exposed to ustekinumab to assess the presence of ustekinumab in breast milk and potential adverse effects in nursing infants; and
- Conduct an *in vitro* study to assess whether IL-12 and/or IL-23 modulate expression of major CYP enzymes.

Finally, we have determined that only clinical trials will be sufficient (rather than an observation study) to assess the known risk of serious infection; or to identify unexpected serious risks of malignancy, tuberculosis, opportunistic infections, hypersensitivity

reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal, or hematologic events, or altered metabolism of co-administered drugs. Therefore, based on appropriate scientific data, FDA has determined that the applicant will be required to:

- Complete the treatment and evaluation of patients enrolled in the PHOENIX 1 and PHOENIX 2 trials for a total of 5 years;
- If the results of the *in vitro* study discussed above are positive (i.e., if there is marked modulation of any of the major CYP enzyme(s)), conduct a clinical trial to determine the potential of ustekinumab to alter CYP substrate metabolism in psoriasis patients (e.g., using a cocktail of relevant CYP probe drugs).

POSTMARKETING STUDY COMMITMENTS

In addition to the commitments described above to perform an extensive qualification study for multi-use of the glass syringes which are used for pooling of vials for the visible particle assay, and to continue the root cause investigation to identify the causative factor(s) that led to OOT visible particle counts on stability for the clinical and validation drug product batches, the applicant also commits to the following:

- Provide information on maintenance of response with dosing intervals longer than every 12 weeks among relevant populations (e.g., subjects whose psoriasis is cleared as measured by PGA and PASI or who have minimal psoriasis);
- Evaluate approaches to improve drug tolerance in the assay method for anti-drug antibodies (ADA);
- Establish quantitative drug product release and stability specifications for the non-reduced cSDS assay when sufficient commercial experience with the assay has been gained;
- Collect drug product release and stability data to reassess and lower the allowable number of sub-visible particles;
- Reassess release and shelf-life specifications for the ustekinumab drug substance and drug product within 2 years from the date of this approval;
- Conduct end-of-life concurrent validation of _____ at the manufacturing scale;
- Perform reduced scale end-of-life viral removal studies for the _____
- Revise the _____ SDS-PAGE and IEF stability specifications upon review of available stability data;

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- Develop and validate the Microflow Digital Imaging assay and incorporate this assay into the annual stability testing program with appropriately justified specifications;
- Perform both IEF and cIEF in parallel for future batches as part of the commercial stability program until sufficient data demonstrate that the cIEF is as stability indicating as the IEF; and
- Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest _____) and harvest samples.

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RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

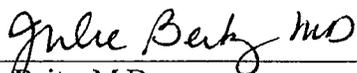
Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Stelara (ustekinumab) to ensure that the benefits of the drug outweigh the risks of serious infections and malignancy.

Centocor's proposed REMS will consist of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

TRADENAME REVIEW

The Division of Medication Error Prevention and Analysis has found the proposed tradename "Stelara" to be acceptable. The likelihood of confusing "Stelara" (available as single-use vials) with "Stalevo" (marketed as tablets) is expected to be minimal.

 MD 9-17-09

Julie Beitz, M.D.
Director
Office of Drug Evaluation III