CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 29, 2016
Reviewer:	Jacqueline Sheppard, Pharm.D. Division of Risk Management
Team Leader:	Jamie Wilkins Parker, Pharm.D. Division of Risk Management
Director:	Cynthia LaCivita, Pharm.D., Division of Risk Management
Subject:	Evaluation to determine if a REMS modification is necessary to ensure the benefit outweigh the risks for the proposed indication for Crohn's disease (CD)
Drug Name:	Stelara (ustekinumab) injection
Therapeutic Class:	Human interleukin-12 and -23 antagonist
Indications:	Moderately to Severely Active Crohn's disease
Dosage and Route:	Loading (Intravenous Infusion):

Body Weight	Dose
Less than or equal to 55 kg	260 mg
Greater than 55 kg to less than or equal to 85 kg	390 mg
Greater than 85 kg	520 mg

Maintenance:
90 mg subcutaneous injection every 8 (b) (4) weeks

Application Type/Number:	BLA 761044
Applicant:	Janssen Biotech, Inc.
OSE RCM #:	2015-2787

1. INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates if a risk evaluation and mitigation strategy (REMS) is needed for BLA 761044, Stelara (ustekinumab), for the proposed indication of moderate to severe Crohn's disease. Ustekinumab is approved with a communication plan (CP) only REMS for the plaque psoriasis and psoriatic arthritis indication under BLA 125261; the approved labeling includes a Medication Guide.

Janssen Biotech, Inc. (Janssen) submitted an application for BLA 761044 on November 25, 2015 without a proposed REMS or proposed modifications to the existing REMS. The Sponsor states that a positive risk-benefit has been established for the psoriatic indications and there are no new risks to communicate to healthcare providers via a REMS.

1.1 Disease Background

Crohn's disease is a chronic inflammatory bowel disease. The inflammatory process may affect any part of the gastrointestinal tract from the mouth to the anus. The pattern of inflammation is often cyclical and individuals experience periods of symptomatic relapse and remission. The clinical presentation is abdominal pain and diarrhea which may be complicated by intestinal fistulization or obstruction. The prevalence in the general population is estimated at 201 per 100,000 persons among adults and 43 per 100,000 persons among children. Patients with mild disease are typically treated with 5-aminosalicylic acid (5-ASA), antibiotics, and nutritional therapies. Corticosteroids and immunomodulators such as methotrexate or 6-mercaptopurine (6-MP) may be given if the patient does not respond or presents with more extensive disease.

Patients with risk factors for complicated disease and rapid progression are candidates for treatment with biological tumor necrosis factor (TNF) or integrin inhibitors, of which adalimumab, infliximab, certolizumab pegol, natalizumab and vedolizumab are approved for the treatment of Crohn's disease. While surgery is used frequently in the treatment of Crohn's disease, the goal of surgery is the preservation of intestinal length and function as there is a high rate of disease reoccurrence after bowel resection. Ustekinumab represents an additional therapeutic option to be approved for Crohn's disease; this biologic therapy interferes with the interleukin (IL) inflammatory cytokines IL-12 and IL-23.

1.2 Product Background

Ustekinumab is a human Interleukin IL-12 and IL-23 antagonist with the proposed indication, for the treatment of adult patients with moderate to severe Crohn's disease who have either failed or were intolerant to immunomodulators or corticocosteroids but never failed (b) (4) or who failed or were intolerant to (b) (4) Ustekinumab was approved in January 2009 for the treatment of plaque psoriasis and in September 2013 for the treatment of psoriatic arthritis. The recommended dose for Crohn's Disease is as follows:

Initial Dosing

Body Weight	**Dose**
Less than or equal to 55 kg	260 mg
Greater than 55 kg to less than or equal to 85 kg	390 mg
Greater than 85 kg	520 mg

Maintenance dosing: 90 mg every 8 (b) (4) weeks by subcutaneous injection.

The current prescribing information includes warnings related to the risks of infections; use in patients with tuberculosis; increased risk of malignancies; hypersensitivity; and reversible posterior leukoencophalopathy syndrome (RPLS).

1.3 Regulatory History

The following is a summary of the regulatory history relevant to determine if a REMS modification is needed for the proposed indication for moderate to severe Crohn's disease.

September 25, 2009: The Agency approved ustekinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for phototherapy or systemic therapy. The application was approved with a REMS that included a Medication Guide and a communication plan (CP).

May 4, 2012: The Stelara REMS was modified to remove the Medication Guide from the REMS (it is retained as part of labeling) and to remove informing prescribers of a patient registry from the CP.

September 20, 2013: The Agency approved for the use in PsA, which included a REMS Modification to add a new prescriber population to the REMS and update REMS materials with the new indication as appropriate.

November 25, 2015: Janssen submitted BLA 761044 for the indication of Crohn's disease. The Applicant did not submit a proposed REMS modification. The Sponsor states that a positive risk-benefit has been established for the psoriatic indications and there are no new risks to communicate to healthcare providers via a REMS.

2. MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Janssen Biotech, Inc. Ustekinumab BLA 761044 submission, <eCTD Sequence 0000>, Original 1, dated November 25, 2015.
  - Section 2.5, Clinical Overview
  - Section 2.7.4, Summary of Clinical Safety
- DGIEP, Draft Prescribing Information, BLA 761044, July 13, 2016
- FDA, REMS for Stelara (ustekinumab), BLA 125261, modified September 2013

3. RESULTS OF REVIEW

3.1. OVERVIEW OF CLINICAL PROGRAM

The efficacy of ustekinumab for the treatment of Crohn's disease was evaluated in a clinical program that included two phase 2 and three phase 3 studies. The two phase 2 studies were small multi-center randomized trials examining two regimens of ustekinumab induction therapy. The Phase 3 studies were randomized, double-blind, placebo controlled studies (CRD3001, CRD3002, and CRD3003) conducted in adults with moderately to severely active Crohn's disease.

CRD3001 evaluated 769 patients with a history of inadequate response or intolerance to TNF antagonists. CRD3002 evaluated 640 patients with a history of inadequate response or intolerance to corticosteroids or immunomodulators. In each clinical trial, study patients were treated with a single intravenous dose of ustekinumab (fixed 130 mg dose or weight based 6 mg/kg) or placebo at Week 0. At week 6, all subjects were evaluated for the primary endpoint of clinical response.

Study CRD3003 was a maintenance study in which 388 patients were treated with ustekinumab 90 mg every 12 weeks or 90 mg every 8 weeks or placebo. All subjects in CRD3003 were responders to ustekinumab induction. The primary efficacy endpoint was clinical remission at week 44.

The Agency's analysis of the Applicant's submissions is described in Section 3.2 below.

3.2. SUMMARY OF EFFICACY

Induction

The induction studies (CRD 3001 and 3002) had identical primary and secondary endpoints. The primary endpoint was a clinical response at week 6, defined as a reduction from baseline Crohn's Disease Activity Index (CDAI) score. Study CRD 3001,which examined 741 patients who failed or were intolerant to TNF treatment, showed an increase in the mean change from the baseline between the treatment groups (130 mg or weight based dosing) and placebo (18.1, 22.1, and 11.9) respectively. The clinical reviewer confirmed that ustekinumab induced clinical response and clinical remission in the study of patients with primary failure or intolerance to TNF treatment. Clinically meaningful differences were seen as change from baseline CDAI score especially at week 8.

In Study CRD 3002, which examined 627 patients who failed or were intolerant to conventional therapy, the mean change was (29.1, 35.3, and 14.7), respectively. Subjects in CRD3001 had more severe and long-standing disease than patients in CRD 3002. The clinical reviewer confirmed that ustekinumab induced clinical response and clinical remission in the study of patients who had failed conventional therapy (immunomodulators and/or corticosteroids). For clinical remission at week 8, there was a near doubling of the treatment effect versus placebo for weight based dosing.

In both studies, this change from mean represents a statistically significant difference within each treatment arm ($p < 0.050$). The pattern of efficacy was generally similar across the two

groups, but higher rates were observed in study group CRD 3002 who had not previously failed or were intolerant to TNF α antagonist treatment as opposed to subjects in CRD3001.

Maintenance

All patients randomized in the maintenance phase (CRD3003) were responders to ustekinumab induction. The primary endpoint was clinical remission at Week 44. Study CRD3003 examined 388 patients, divided into 3 groups, with each group receiving either placebo, 90 mg every 12 weeks or 90 mg every 8 weeks for 44 weeks. At the end of the 44 week study, there was a statistically greater response ($p< 0.050$) of patients in clinical remission in both treatment groups (49%, 53%) compared to placebo (36%). The clinical reviewer confirmed that greater than 50% of patients who received ustekinumab achieved clinical remission in the maintenance phase portion of this study.

3.3. SUMMARY OF SAFETY

For the purpose of this review, serious adverse events (SAEs) are defined by the regulatory definition of a serious outcome, such as death, a life-threatening reaction, or hospitalization, among other outcomes. The safety information for ustekinumab in Crohn's disease included data from the five phase 2 and phase 3 clinical studies during which 1,749 patients received at least one dose of ustekinumab by either subcutaneous injection or intravenous infusion.

3.3.1. Deaths

There were no reported deaths during the placebo controlled periods or through the end of the study period.

There were 5 deaths that occurred during the long-term extension of study CRD3003. There were three cardiovascular related deaths (a cardiorespiratory arrest in a 56 year old male with a known history of coronary heart disease who died after bowel surgery; acute MI in a 46 year old male with unstable angina; and a sudden death in a 61 year old male with a history of tobacco use, from a presumed ventricular arrhythmia), one death from chronic renal failure in a 72 year old female with chronic renal failure who refused dialysis, and one suicide by asphyxia by a 24 year old male after incarceration. The clinical reviewer concurs that these deaths are unrelated to the study drug.

3.3.2. Nonfatal serious adverse events

Nonfatal SAEs were reported in low numbers and were comparable across treatment groups within Crohn's disease, the approved indications, and placebo. The exposure adjusted incidence of SAEs per 100 patient-years over the entire treatment period was 250.92 for patients who received ustekinumab across all indications compared with 250.12 in the placebo group.

3.3.3. Other adverse events

The safety data from the Crohn's disease studies were consistent with the other approved indications with the exceptions of the new adverse drug reactions of acne (1.1%), asthenia (1.2%), vomiting (4.3%) and vulvovaginal mycotic infections (3.1%). The clinical team did not express serious concerns about these adverse reactions.

4. Currently Approved REMS

Ustekinumab's REMS currently includes a CP and a timetable for submission of assessments. The goal of the REMS is to evaluate and mitigate the potential risks of serious infections and malignancy, and RPLS associated with Stelara by alerting and warning healthcare providers about the risks. The professional labeling for Stelara includes these risks in Warnings and Precautions section of the label; Stelara does not have a boxed warning. In order to implement the CP, the Sponsor was required to disseminate risk information to dermatologists, rheumatologists who are likely to prescribe or inject Stelara, oncologists who may treat malignancies, infectious disease specialists and gastroenterologists who may be consulted about infections, and neurologists who may treat RPLS.

In the currently approved REMS, outreach to gastroenterologists was done through twice yearly printed information pieces in the *American Journal of Gastroenterology* and *Gastroenterology* for three years from the date of the initial approval of the Stelara REMS. Additionally, specific information for gastroenterologists was required to remain available on the Stelara website for a period of 5 years from the initial approval.

5. DISCUSSION

Based on the results of the clinical studies in support of the new application (BLA 761044), ustekinumab was found to be efficacious for the treatment of Crohn's disease. The safety profile of ustekinumab for Crohn's disease was found to be consistent with the approved indications of psoriasis and psoriatic arthritis with the exception of the new non-serious adverse drug reactions of acne, asthenia, vomiting, and vulvovaginal mycotic infections.

Ustekinumab was initially approved for the treatment of moderate to severe plaque psoriasis in September 2009 and for the treatment of psoriatic arthritis in September 2013 with a communication plan only REMS. The goal of the approved REMS is to mitigate the potential risks of serious infections, malignancy, and RPLS by informing prescribers of these risks.

DRISK and DGIEP concur that a REMS modification to the approved Stelara REMS is not necessary to ensure the benefits outweigh the risks for Stelara for the proposed treatment of moderate to severe Crohn's disease for the reasons listed below.

The most likely prescribers of ustekinumab for Crohn's disease will be gastroenterologists. Gastroenterologists are familiar with the immunosuppressive and neurologic risks associated with other immunomodulators and TNf-α blockers used to treat Crohn's disease. See Table 1 for the current treatment scheme for Crohn's Disease.

Table 1. Treatment Scheme for Crohn's Disease

Drug Name	Warning and Precaution	Box Warning	REMS
Corticosteroids			
Entocort EC (Budesonide)	Hypercorticism and adrenal suppression immunosuppression	No	No
Uceris (Budesonide)	Hypercorticism and adrenal suppression immunosuppression	No	No
Immunomodulators			
Tysabri (natalizumab)	Progressive Multifocal Leukoencephalopathy (PML) Herpes Encephalitis and Meningitis Hepatotoxicity Hypersensitivity Immunosuppression Laboratory Test Abnormalities	PML	PML (ETASU)
Entyvio (vedolizumab)	Hypersensitivity Infections PML	No	No
TNF-Alpha Blockers			
Humira (adalimumab)	Serious Infections Malignancies Hypersensitivity and Autoimmunity Immunizations and Hepatitis B Reactivation Neurologic and Hematologic Reactions Use with Anakinra and Abatacept Heart Failure	Serious Infections Malignancies	No
Cimzia (certolizumab pegol)	Serious Infections Malignancies Heart Failure Hypersensitivity Immunizations Hepatitis B Reactivation Neurologic and Hematologic Reactions Use with Biological DMARDs Autoimmunity Immunosuppression	Serious Infections Malignancies	No
Remicade (infliximab)	Serious Infections Malignancies Immunizations and Hepatitis B Reactivation Hepatotoxicity Heart Failure Neurologic and Hematologic Reactions Hypersensitivity Use with Anakinra, Abatacept, and Biological DMARDs Autoimmunity	Serious Infections Malignancies	No

The newly identified risks of acne, asthenia, vomiting, and vulvovaginal mycotic infections, associated with the treatment of Crohn's disease with ustekinumab do not rise to the level of a warning and precaution and will be communicated through professional labeling.

The professional labeling for Stelara includes the following risks in Warnings and Precautions section of the label: 5.1 Infections, 5.2 Theoretical risk for vulnerability to particular infections, 5.3 Pre-treatment evaluation for tuberculosis, 5.4 Malignancies, 5.5 Hypersensitivity reactions, 5.6 Reversible posterior leukoencephalopathy syndrome, 5.7 Immunizations and 5.8 Concomitant therapies.

Stelara professional labeling does not include boxed warning. DRISK's recommends that product labeling be maximized before requiring risk mitigation strategies beyond labeling. There were no observed cases of RPLS observed in the clinical trials for ustekinumab in the Crohn's disease trials and the warning for immunosuppression and RPLS will continue to be communicated through professional labeling.

In addition, gastroenterologists were part of the targeted outreach during the communication plan REMS for the psoriasis and psoriatic arthritis indication of ustekinumab. Usetekinumab was approved in 2009, and while the risks inherent to the drug have not changed, the strategies required to mitigate the risks are different due to the differences stated above. A REMS modification is not necessary to ensure the benefits outweigh the risks for the proposed indication for moderate to severe Crohn's disease

Therefore, at this time, DRISK is not recommending a modification to the Stelara REMS.

6. CONCLUSION AND RECOMMENDATIONS

Based on the available data, therefore a REMS modification is not necessary to ensure the benefits outweigh the risks for the proposed indication, treatment of moderate to severe Crohn's disease.

Should DGIEP have any concerns or questions, or feel that a modification to the existing REMS is warranted for this product to accompany this BLA approval, or if new safety information becomes available, please send a consult to DRISK.

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/s/

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07/29/2016

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