

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s000

**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**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 7, 2014
Reviewer(s):	Felicia Duffy, RN, BSN, MSED Division of Risk Management
Acting Team Leader:	Jamie Wilkins Parker, Pharm.D. Division of Risk Management
Acting Deputy Director:	Reema Mehta, Pharm.D., MPH Division of Risk Management
Drug Name(s):	Cosentyx (secukinumab)
Therapeutic Class:	Recombinant human monoclonal anti-human antibody
Dosage and Route:	150 mg/mL Solution for Injection and 150 mg Powder for Injection
Application Type/Number:	BLA 125504
Applicant/sponsor:	Novartis
OSE RCM #:	2014-937

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for BLA 125504 for Cosentyx (secukinumab) injection and powder for injection.

The proposed REMS was voluntarily submitted by Novartis, received October 22, 2013, as part of the original submission and has the goal of communicating to healthcare professionals and pharmacists the risk of infections associated with secukinumab treatment. The proposed REMS consists of a communication plan (CP) (Dear Healthcare Professional and Dear Pharmacist letters, and Letters to Professional Societies for prescribers and pharmacists), and a timetable for submission of assessments.

1.1 BACKGROUND

1.2 DRUG BACKGROUND

Secukinumab is a recombinant human monoclonal anti-human antibody that selectively targets interleukin 17A (IL-17A). The proposed indication is the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dose is 300 mg by subcutaneous injection with initial dosing at week 0, 1, 2, and 3 followed by monthly maintenance dosing starting at Week 4. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. The proposed methods of dose delivery are prefilled SensoReady[®] pen (autoinjector), prefilled syringe, and lyophilized powder in a vial.

1.3 DISEASE BACKGROUND

The treatment of patients with psoriasis consists of either non-biologic or biologic systemic agents or phototherapy (Table 1).

Table 1: Drugs FDA Approved for the Treatment of Plaque Psoriasis

Drug	Topical	Oral	Injectable
Adalimumab			✓
Aprelimast		✓	
Alefacept			✓
Calcipotriene	✓		
Calcipotriene/betamethasone dipropionate	✓		
Calcitriol	✓		
Desoximethasone		✓	
Dexamethasone sodium phosphate			✓
Etanercept			✓
Infliximab			✓
Methylprednisolone		✓	✓
Tazarotene	✓		
Triamcinolone hexacetonide			✓
Ustekinumab			✓

Currently, three biologic tumor-necrosis factor-alpha (TNF- α) inhibitors (infliximab, etanercept, and adalimumab) and one anti-IL 12/23 agent (ustekinumab) have been approved to treat psoriasis¹. The aforementioned products were all approved with a REMS, which consisted of a Medication Guide (MG) and CP to address the risk of infection. The CP REMS for infliximab, etanercept, and adalimumab were released from their REMS requirement in 2011 because the CP was completed and the REMS assessment demonstrated that the REMS for each drug product met its goal. The MG remains a part of labeling (outside of the REMS).

The REMS is currently ongoing for ustekinumab. The CP REMS was originally approved in 2009. The 3-year REMS assessment (November 2012) concluded that the REMS is meeting its goals of evaluating and mitigating potential risks of serious infections, malignancy, and reversible posterior leukoencephalopathy syndrome by alerting and warning healthcare providers². Although the REMS was meeting its goals, DRISK concluded that the REMS should remain as a requirement through 2014, since the original REMS CP activities included the requirement that the journal information piece in the *Journal of Clinical Oncology and Blood* for quarterly publication through 5 years from the date of approval of the ustekinumab (September 25, 2009)³. A new indication was approved for the treatment of adults with active psoriatic arthritis (PsA); thus, the REMS was modified in September 2013 to include communication efforts for the treatment of adults with active PsA⁴. The CP for ustekinumab will be complete in September 2014. The next REMS assessment is due September 2016.

1.4 REGULATORY HISTORY

- October 22, 2013: BLA 125504 submitted
- June 19, 2014: Mid-cycle Communication Meeting held with the Applicant. DRISK communicated to the Applicant that, at this time, no safety concerns have been identified that require a REMS to ensure safe use.
- October 20, 2014: Advisory Committee Meeting for secukinumab

¹ Lee S, Coleman CI, Limone B, Kaur R, White CM, Kluger J, Sobieraj DM. Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis. Comparative Effectiveness Review No. 85. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007- 10067-I.) AHRQ Publication No.12(13)-EHC144-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm

² Cvetkovich, T. Review of 3-year REMS Assessment Report, dated November 30, 2012.

³ Yancey, C. Review of Requirement for a REMS for Stelara, dated July 12, 2013; revised July 26, 2013.

⁴ Yancey, C. Amendment to the Proposed REMS Modification for Stelara for Psoriatic Arthritis, dated September 17, 2013; revised September 19, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Novartis. Proposed Risk Evaluation and Mitigation Strategy for Cosentyx (secukinumab), received October 24, 2013 (S-000/Seq 000)
- Novartis. REMS Supporting Document for Cosentyx (secukinumab), received October 24, 2013 (S-000/Seq 000)
- Novartis. Draft Prescribing Information for Cosentyx (secukinumab), received October 24, 2013 (S-000/Seq 000)
- Novartis. Draft Prescribing Information for Cosentyx (secukinumab), received December 23, 2013 (S-000/Seq 0003)

2.2 MATERIALS INFORMING THE REVIEW

- Novartis. Clinical Overview in Moderate to Severe Plaque Psoriasis for Cosentyx (secukinumab), dated October 16, 2013 (S-000/Seq 0000).
- Woitach, Amy. Division of Dermatology and Dental Products Clinical Review Mid-Cycle Summary for Cosentyx (secukinumab), dated June 2014.

3 RESULTS OF REVIEW OF PROPOSED SECUKINUMAB RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM FOR COSENTYX⁵

The efficacy and safety of secukinumab were evaluated in four randomized, double-blind, placebo-controlled Phase 3 trials (A2302, A2303, A2308, and A2309). The primary objective of these four studies was to demonstrate the efficacy of secukinumab (150 mg and 300 mg) in subjects with moderate to severe chronic plaque psoriasis. The co-primary efficacy endpoints were assessed at Week 12 for Psoriasis Area and Severity Index (PASI) 75 ($\geq 75\%$ improvement from Baseline PASI score) and Investigator's Global Assessment (IGA) mod 2011 score 0 (clear) or 1 (almost clear) [IGA 0/1: achievement of 0/1 AND improved by at least 2 points on the IGA mod 2011 score which ranges from 0 (clear) to 4 (severe)], compared to placebo.

Although the study design was the same in the four pivotal trials, the formulation or mode of delivery was different: 2 used lyophilized powder (A2302 and A2303) and 2 used the liquid formulation, either in a prefilled syringe (A2308) or in an autoinjector (A2309). Study A2303 also had an additional active comparator (etanercept).

A total of 2343 randomized patients were included in the placebo-controlled efficacy studies: A2302 N=738, A2303 N=1306, A2308 N=177, A2309 N=182. Within each study, the patients were randomized in a 1:1 ratio across all treatment groups for the induction periods. A total of 2003 patients continued into the maintenance periods of studies A2302 (N=722) and A2303 (N=1281).

⁵ Novartis. Clinical Overview in moderate to severe plaque psoriasis. October 16, 2013.

According to the Applicant, superiority of secukinumab 150 mg and 300 mg to placebo was demonstrated for the co-primary efficacy criteria of PASI 75 and IGA mod 2011 0 or 1 at 12 weeks in all 4 pivotal controlled trials (>62% for PASI 75 and >48% for IGA mod 2011 0 or 1), with the greatest benefit shown for the 300 mg dose during this period (>72% for PASI 75 and >59% for IGA mod 2011 0 or 1). Both secukinumab doses (300 mg and 150 mg) were statistically significantly ($p < 0.0001$) superior to etanercept at Week 12 in achieving IGA mod 2011 0 or 1 and PASI 75 response, and in achieving PASI 90 based on descriptive analysis, in the active-controlled trial A2303.

Superiority of secukinumab to placebo was demonstrated for the co-primary efficacy at 12 weeks in both doses in the pivotal controlled trials by the following: IGA efficacy response: 65.3% and 61.8% for 300 mg; and 50.6% and 51.1% for 150mg, PASI 75 efficacy response: 81.2% and 75.8% for 300 mg; 70.6% and 67.0% for 150 mg, and maintenance of response was also demonstrated. The Phase 3 studies provide substantial evidence that secukinumab demonstrates efficacy in the target population of patients with moderate to severe plaque psoriasis.⁶

3.2 SAFETY CONCERNS⁷

Safety data from 34 trials was combined into 3 data pools. Pool A consisted of 4 placebo-controlled Phase 3 trials in psoriasis patients with placebo and active comparator for comparisons of short-term safety (12 weeks) among secukinumab, placebo, and etanercept. Pool B consisted of 10 psoriasis trials with Phase 2/Phase 3 trials to assess longer-term safety data (52 weeks). Pool C included all patients treated with secukinumab (all trials, various indications) in 34 studies to maximize the chances detecting rare events with secukinumab. Adverse events were summarized for patients in the psoriasis studies (Pools A and B) and not for patients exposed to secukinumab in any indication (Pool C) due to the different medical conditions studied.

In Pool A, the incidence of treatment-related adverse events (AEs) in the two secukinumab dose groups was higher compared to placebo (17.4% and 20.2% for 300 mg and 150 mg, respectively, vs. 13.0% for placebo), but lower than etanercept (22.9%). The most common AEs in the trials were infections (which is well documented for products in this drug class). The majority of infections in all treatment groups consisted of mild to moderate upper respiratory infection, such as nasopharyngitis and upper respiratory tract infection, which were not serious and did not necessitate treatment discontinuation. There were no serious opportunistic infections reported or deaths reported as a result of infection.

The Applicant also addressed the potential of increased risk of an exacerbation of Crohn's disease. Over the entire treatment period for Pool B, 3 cases of Crohn's disease were reported for secukinumab (2 on 150 mg and 1 on an alternative 150 mg dose regimen), two cases exacerbations of existing Crohn's disease, and 1 case was a new event. All 3 events were severe AEs (SAEs). Of the 2 exacerbation cases, one resolved with treatment and the other was ongoing at the time of reporting, and both led to

⁶ Woitach, Amy. Cosentyx Clinical Review Mid-Cycle Summary. June 2014

⁷ Novartis. Summary of Clinical Safety in moderate to severe plaque psoriasis. October 14, 2013.

discontinuation of study treatment. The new event resolved with treatment and did not cause study treatment discontinuation. No cases of Crohn's disease were reported for 300 mg, placebo or etanercept.

A total of 6 deaths occurred in patients participating in psoriasis clinical studies. No on-treatment deaths were reported in the 12-week induction periods of Pool A and Pool B. Five deaths were reported in the post-induction period, including 1 on-treatment death in a patient on an alternate secukinumab dose regimen (150 mg maintenance treatment at start of relapse), 2 off-treatment deaths for 150 mg secukinumab, 1 patient who switched from placebo to secukinumab 300 mg maintenance treatment died 3 weeks post-study, and 1 off-treatment death for a placebo patient. In addition, one patient died during the screening phase (complete suicide). The incidence of on-treatment death in the Pool B entire treatment period was 0.03% (1/3430) for secukinumab vs. 0% (0/793) for placebo and 0% (0/323) for etanercept.

3.3 RISK MANAGEMENT PLAN PROPOSED BY THE APPLICANT

The Applicant proposed a REMS to communicate to healthcare providers and pharmacists about the risk of infections associated with secukinumab. The REMS includes a CP (Dear Healthcare Provider and Dear Pharmacist letters, and Letters to Professional Societies). The MG will be maintained as part of labeling and was not included as an element of the REMS. The Applicant also proposed a Warning and Precaution in the labeling to communicate the increased risk of infections associated with secukinumab.

4 DISCUSSION

The benefits of treatment with secukinumab were demonstrated by meeting the co-primary endpoints of the proportion of subjects who achieved a 75% reduction in the PASI 75 and the proportion of subjects who achieved clear or almost clear skin on the IGA.

To mitigate the above risk of infection, the Applicant voluntarily proposed a REMS with a CP and labeling which includes a MG. The increased risk of infection associated with secukinumab is a risk associated with IL medications. In comparing placebo-controlled trials for secukinumab vs. ustekinumab, the risk of infection was 16.5%⁸ vs. 27%, respectively⁹. It is expected that the prescriber population that is currently responsible for prescribing ustekinumab will be the same for secukinumab; therefore, there will be a baseline familiarity with the management of the risks associated with this medication. Furthermore, the medications infliximab, adalimumab, and etanercept, which had REMS programs that were most similar to that proposed for secukinumab (risk of infection), had their REMS released after the REMS CP requirements were complete and the REMS assessment showed that healthcare professionals understood the key messages regarding ILs and risk of infection. Since the same prescriber population is expected for secukinumab, DRISK believes that the prescriber population will use the knowledge

⁸ Ibid.

⁹ Centocor Ortho Biotech, Inc. Stelara (ustekinumab) Injection. Package Insert, approved March 4, 2014.

gained through the aforementioned REMS regarding the risk of infection and apply it to managing patients prescribed secukinumab.

After discussion with the review team, it was agreed that the risk of infection can be effectively communicated via the proposed labeling. Therefore, DRISK's recommendation is for this product not to have a REMS at this time.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, risk mitigation measures beyond professional labeling are not warranted for secukinumab at this time. Secukinumab has proven to reduce the severity of symptoms in patients with moderate to severe plaque psoriasis. Based on the known safety profile for the drug class and the risks associated with secukinumab from the clinical trials, the benefit-risk profile is acceptable and can be mitigated through the professional labeling.

Should the Division have any concerns or questions, or feel that a REMS may be warranted for this product after further review, please contact DRISK.

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/s/

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10/07/2014

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