CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761105Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type: BLA
Application Number: 761105
PDUFA Goal Date: April 23, 2019
OSE RCM #: 2018-913

Reviewer Name(s): Bob Pratt, Pharm.D.
Team Leader: Donella Fitzgerald, Pharm.D.
Deputy Division Director: Jamie Wilkins, Pharm.D.
Review Completion Date: April 17, 2019
Subject: Evaluation of need for a REMS

Established Name: Risankizumab
Trade Name: Skyrizi™
Name of Applicant: AbbVie, Inc.
Therapeutic Class: Interleukin (IL)-23 blocker: humanized IgG1 monoclonal antibody
Formulation: 75 mg/0.83 mL per single-dose prefilled syringe (PFS)
Dosing Regimen: 150 mg (two 75-mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Skyrizi™ (risankizumab) is necessary to ensure the benefits of the product outweigh its risks. AbbVie, Inc. (AbbVie) submitted a Biologics License Application (BLA 761105) on April 23, 2018 for risankizumab, a humanized monoclonal antibody that binds to the p19 subunit of human interleukin (IL)-23. The proposed indication is the treatment of moderate to severe plaque psoriasis in adults. The most important safety concern associated with risankizumab is the risk of infections. Other potential safety concerns include malignancies and major adverse cardiovascular events. A REMS was not included in the application.

DRISK and the Division of Dermatology and Dental Products agree that a REMS is not necessary to ensure the benefits of risankizumab outweigh the risks. The efficacy of risankizumab has been established based on significant improvements compared with placebo in the co-primary endpoints, defined as the proportion of patients with a 90% reduction in the psoriasis area and severity index (PASI 90) and the proportion of patients who achieved clear or almost clear on the static physician’s global assessment (sPGA). Additionally, risankizumab demonstrated statistical superiority to placebo, ustekinumab, and adalimumab in key secondary efficacy endpoints. The risks of risankizumab are similar to other products in the class, which prescribers who treat psoriasis should be familiar with. Based on the safety profile and efficacy demonstrated in the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Skyrizi™ (risankizumab) is necessary to ensure the benefits of the product outweigh its risks. AbbVie, Inc. (AbbVie) submitted a Biologics License Application (BLA 761105) on April 23, 2018 for risankizumab, a humanized monoclonal antibody that binds to the p19 subunit of human interleukin (IL)-23. The proposed indication is the treatment of moderate to severe plaque psoriasis in adults. This application is under review in the Division of Dermatology and Dental Products (DDDP). AbbVie did not submit a REMS with the application.

2 Background

2.1 PRODUCT INFORMATION

Skyrizi™ (risankizumab), a new molecular entity, is a humanized monoclonal antibody that binds to the p19 subunit of human IL-23. The binding of risankizumab to IL-23 is thought to inhibit the actions of IL-23 on the proliferation, differentiation and maintenance of T-helper 17 type cells and innate immune cells that are sources of pro-inflammatory cytokines considered responsible for the tissue inflammation and destruction in psoriasis.1

Footnote:
1 FDAAA factor (F): Whether the drug is a new molecular entity.
Risankizumab is to be supplied as a 75 mg/0.83 mL single-dose prefilled syringe (PFS). The proposed dose is 150 mg (two 75-mg injections) administered by subcutaneous (SC) injection at Week 0, Week 4, and every 12 weeks thereafter as chronic therapy. Risankizumab is not currently approved in any other jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761105 relevant to this review:

- 10/10/2018: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major safety concerns or issues that would result in a REMS requirement have been identified at this time.
- 1/22/2019: A late-cycle meeting was held between the Agency and the Applicant. There was no discussion related to the need for a REMS.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Psoriasis is a common, chronic, inflammatory skin disease that can have a significant effect on the patient’s quality of life. The estimated prevalence rate of psoriasis in adults in the U.S. ranges from 2.2% to 3.15%. The disease is characterized by symmetrically distributed cutaneous plaques that typically affect the scalp, extensor elbows, knees, and gluteal cleft. The palms, soles, nails, and other areas may also be involved. Clinical findings include indurated, erythematous plaques with silver scale ranging in size from less than 1 cm to more than 10 cm in diameter. Moderate to severe psoriasis is typically defined as involvement of more than 5 to 10 percent of the Body Surface Area (BSA), or involvement of the face, palm or sole, or disease that is otherwise disabling. The disease is associated with comorbid conditions that include psoriatic arthritis, eye disorders, and other systemic disorders. Psoriasis is also associated with increased overall mortality; although some deaths may be due to adverse effects from systemic therapies, the disease may contribute to an increase in deaths through an increase in the risk of comorbid cardiovascular disease. The pathophysiology of psoriasis is complex and likely involves multiple cellular components and cytokines of the immune system, including IL-23, which is thought to have regulatory effects on T-helper 17 cells that produce the inflammatory cytokine IL-17.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Multiple products are approved for the treatment of adults with moderate-to-severe plaque psoriasis. None of these treatments provide a permanent cure and all are associated with one or more serious risks. Development of additional therapeutic options continues to be an important goal due to variability in effectiveness and tolerability, as well as uncertainty regarding long-term effects.

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b FDAAA factor (D): The expected or actual duration of treatment with the drug.

c FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
Currently approved drugs (other than topical agents and corticosteroids) for the treatment of moderate-to-severe psoriasis include methotrexate; tumor necrosis factor inhibitors (etanercept, adalimumab, certolizumab pegol, and infliximab); IL-12 and/or IL-23 inhibitors (ustekinumab, guselkumab and tildrakizumab); IL-17A inhibitors (secukinumab and ixekizumab); IL-17A receptor antagonists (brodalumab); cyclosporine; acitretin; and the phosphodiesterase-4 inhibitor apremilast. Phototherapy with PUVA (UVA light combined with the psoralen methoxsalen) is also used for the treatment of severe and recalcitrant psoriasis.4

Etanercept, adalimumab, certolizumab pegol, infliximab, and ustekinumab were all approved with a REMS that consisted of a Medication Guide (MG) and communication plan (CP) to address the risks of infections and malignancies, as well as reversible posterior leukoencephalopathy syndrome for ustekinumab. Etanercept, adalimumab, certolizumab pegol, and infliximab were released from the REMS requirements in 2011 and ustekinumab was released in 2017 because the CP activities were completed, and the REMS assessments demonstrated that the REMS goals were being met. The MG remains a part of the labeling for each of these drugs. Brodalumab, an IL-17A receptor antagonist, was approved in February 2017 with a REMS consisting of elements to assure safe use that include: 1) healthcare providers who prescribe brodalumab are specially certified, 2) pharmacies that dispense brodalumab are specially certified, and 3) brodalumab can only be dispensed to patients with evidence or other documentation of safe-use conditions; an MG is also included as part of the approved labeling. The goal of the brodalumab REMS is to mitigate the observed risk of suicidal ideation and behavior (SIB) including completed suicides, by ensuring that prescribers are educated about the risk of SIB observed with brodalumab therapy and the need to counsel patients about this risk, and ensuring that patients are informed about the risk of SIB observed with therapy and the need to seek medical attention for manifestations of SIB, new onset or worsening depression, or other mood changes. A comparison of biologic therapies approved for the treatment of moderate-to-severe psoriasis and their pertinent REMS history and safety labeling can be found in Supplementary Table 1 in the Appendix.

4 Benefit Assessment

The risankizumab clinical development program included four randomized, double-blind, placebo- and active-controlled Phase 3 studies to evaluate the efficacy and safety of risankizumab for the treatment of adult patients with moderate to severe plaque psoriasis who had the following: involvement of at least 10 percent of the BSA, a Psoriasis Area and Severity Index (PASI)4 score ≥ 12, and a static Physician Global Assessment (sPGA)e score ≥ 3.

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4 The Psoriasis Area and Severity Index (PASI) is a measure of the average redness, thickness, and scaling (each graded on a 0-4 scale) of psoriatic lesions on four areas of the body (head, upper limbs, trunk, and lower limbs) weighted by the area of involvement using a 72-point scale, with the score of 72 representing maximal disease severity. PASI 90 stands for the status of achieving ≥90% reduction from baseline in the PASI score.

e The static Physician Global Assessment (sPGA) is an average assessment of all psoriatic lesions at a single point in time based on erythema, scale, and induration, without taking the baseline disease condition into account. The sPGA used in the risankizumab studies was scored on a 5-point scale. Scores of 0 or 1 correspond to assessments of clear or almost clear.
Risankizumab was evaluated in two randomized, double-blind, placebo- and ustekinumab-controlled, Phase 3 studies of 52 weeks duration: Study M15-995 [NCT 02684357] and Study M16-008 [NCT 02684270]. Study M15-995 randomized 491 patients 3:1:1 to risankizumab 150 mg SC at Weeks 0 and 4, then every 12 weeks; or to ustekinumab 45-90 mg (based on body weight per the label) SC at Weeks 0 and 4, then every 12 weeks; or to placebo at Weeks 0 and 4 followed by the switching of patients at Week 16 to risankizumab 150 mg SC every 12 weeks. Study M16-008 was of the same design except that 506 patients were randomized.

Risankizumab was evaluated in a randomized, double-blind, adalimumab-controlled, Phase 3 study of 44 weeks duration, Study M16-010 [NCT 02694523]. The study randomized 605 patients 1:1 to risankizumab 150 mg SC at Weeks 0 and 4, then every 12 weeks; or to adalimumab 80 mg SC at Week 0, followed by 40 mg SC at Week 1 and then every 2 weeks. Patients who were initially randomized to adalimumab continued treatment with adalimumab or switched to risankizumab for Weeks 16 through 44 based on their PASI response at Week 16.

Risankizumab was evaluated in a randomized, double-blind, placebo-controlled, Phase 3 study of 104 weeks duration, Study M15-992 [NCT 02672852]. The study randomized 507 patients 4:1 to risankizumab 150 mg SC at Weeks 0 and 4, then every 12 weeks; or to placebo at Weeks 0 and 4, followed by a switch to risankizumab for Weeks 16 to 88. At the Week 28 visit, all patients were assessed for response; non-responders continued open label risankizumab, but responders were re-randomized 1:2 to continue risankizumab or to treatment withdrawal (placebo) to assess maintenance of response.

The co-primary efficacy endpoints in all studies were the proportion of patients who simultaneously achieved ≥90% reduction from baseline in in PASI score (PASI 90) at Week 16 and a static physician global assessment (sPGA) of clear or almost clear (0 or 1) at Week 16. The primary analysis in Studies M15-995, M16-008, and M15-992 compared risankizumab to placebo, whereas the primary analysis in Study M16-010 compared risankizumab to adalimumab. Secondary endpoints included various PASI and sPGA responses at several time points as well as other measures. Patients who completed the studies were eligible to enroll in a long-term open label extension.

Table 1 shows the efficacy results for the co-primary endpoints at Week 16 for the studies controlled with placebo and ustekinumab.

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1 Ustekinumab study drug was sourced from the European Union.
2 Patients with a ≥90% reduction in PASI score at Week 16 continued to received adalimumab, whereas patients who had <50% reduction in PASI score at Week 16 were switched to risankizumab. Patients who had a reduction in PASI score between 50% and 90% were re-randomized 1:1 to either continue adalimumab or switch to risankizumab.
Table 1. Proportion of patients with PASI 90 and sPGA score of 0 or 1 at Week 16 in placebo- and ustekinumab-controlled studies

<table>
<thead>
<tr>
<th></th>
<th>Study M15-995</th>
<th>Study M16-008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risankizumab</td>
<td>Placebo</td>
</tr>
<tr>
<td>Randomized</td>
<td>294</td>
<td>98</td>
</tr>
<tr>
<td>PASI 90</td>
<td>220 (75%)</td>
<td>2 (2%)*</td>
</tr>
<tr>
<td>sPGA 0 or 1</td>
<td>246 (84%)</td>
<td>5 (5%)*</td>
</tr>
</tbody>
</table>

* Risankizumab vs. placebo p < 0.001; † Ranked secondary endpoint: risankizumab vs. ustekinumab p < 0.001

Risankizumab was statistically superior to placebo or ustekinumab for the co-primary endpoints and additionally for all key secondary endpoints in M15-995 and M16-008.

Table 2 shows the efficacy results for the co-primary endpoints at Week 16 for the adalimumab-controlled and placebo-controlled studies. Risankizumab was statistically superior to adalimumab or placebo for the co-primary endpoints in each study.

Table 2. Proportion of patients with PASI 90 and sPGA score of 0 or 1 at Week 16 in adalimumab-controlled and placebo-controlled studies

<table>
<thead>
<tr>
<th></th>
<th>Study M16-010</th>
<th>Study M15-992</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risankizumab</td>
<td>Adalimumab</td>
</tr>
<tr>
<td>Randomized</td>
<td>301</td>
<td>304</td>
</tr>
<tr>
<td>PASI 90</td>
<td>218 (72%)</td>
<td>144 (47%)*</td>
</tr>
<tr>
<td>sPGA 0 or 1</td>
<td>252 (84%)</td>
<td>183 (60%)*</td>
</tr>
</tbody>
</table>

* Risankizumab vs. adalimumab p < 0.001; † Risankizumab vs. placebo p < 0.001

For the re-randomized patients in Study M15-992, 87% of patients who received continuous risankizumab had an sPGA (the primary endpoint after re-randomization) of clear or almost clear at Week 52 compared with 61% of patients re-randomized to withdrawal of therapy. In addition, statistically significant differences in favor of risankizumab were observed for all ranked secondary endpoints. In Study M16-010, risankizumab was statistically superior to adalimumab for the ranked secondary endpoints at Week 16.

The review team concluded that clinical studies M15-995 and M16-008 provide substantial evidence that risankizumab is efficacious for the treatment of adult patients with moderate to severe plaque psoriasis.

5 Risk Assessment & Safe-Use Conditions

For this review, the full safety analysis set includes 2234 patients with plaque psoriasis who were exposed to at least one dose of risankizumab (18, 90, 150, or 180 mg) in the Phase 2 and Phase 3 clinical studies. The primary safety analysis includes the 16-week double-blind phase of the Phase 2 and Phase 3 studies in patients randomized to risankizumab 150-180 mg (N=1348), ustekinumab (N=239), adalimumab (N=304), and placebo (N=300).

FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.
5.1 Serious Adverse Events

5.1.1 Deaths

There were five deaths reported in patients treated with risankizumab in the Phase 2 and Phase 3 clinical studies of psoriasis. Five additional deaths were reported in the 120-day safety update. Four of the five deaths in the Phase 2 and Phase 3 studies were treatment-emergent, which was defined as occurring within 105 days after the last dose of risankizumab:

1) 47-year-old male with a prior history of myocardial infarction with stent placement, atrial fibrillation with electrical cardioversion, ischemic heart disease, hypertension, chronic heart failure, dyslipidemia, obesity, atherosclerosis, and cardiac hypertrophy experienced death 9 days after the last dose of risankizumab (Study day 73) due to acute myocardial infarction.

2) 57-year-old male with concurrent coronary artery disease, chronic obstructive pulmonary disease, and other comorbidities experienced congestive heart failure and angina and underwent angioplasty on Study day 48. The patient's death occurred 161 days after the last dose of risankizumab (estimated as 189 days after the start of treatment) from undetermined causes.

3) 60-year-old male with a medical history of morbid obesity, hypertension, diabetes, hypercholesterolemia and possible myocardial infarction died from an undetermined cause, 66 days after the last dose of risankizumab (Study day 263).

4) 70-year-old male died from metastatic colorectal carcinoma 55 days after the last dose of risankizumab (Study day 224).

5) 32-year-old male died due to an overdose of oxycodone and cocaine.

The review team noted the patients in the first three cases above had multiple risk factors more likely to be contributory to the cause of death than study drug; the contribution of study drug to the deaths of the fourth and fifth patients cannot be determined.

The five additional deaths reported in the 120-day safety update occurred in psoriasis patients treated with risankizumab. The causes of death were reported as seizure in a patient with epilepsy; sudden death in a patient with multiple cardiac risk factors; sudden death in a patient with multiple risk factors; pancreatitis; and worsening congestive heart failure (CHF). The review team noted that underlying disease and multiple risk factors were likely contributory to the cases of sudden death and the epilepsy-related death, but the contribution of study drug to the fatal cases of pancreatitis and CHF cannot be determined.

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1 Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

2 FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

3 Study day is defined as the number of days since the start of treatment.
### 5.1.2 Treatment-emergent serious adverse events

In the primary safety analysis, which consisted of the risankizumab 150-180 mg group, the proportion of patients who had a treatment-emergent serious adverse event (SAE) was lower in the risankizumab group (2.3% [31/1348]) compared with either the placebo group (4.0% [12/300]), ustekinumab group (5.0% [12/239]), or adalimumab group (3.0% [9/304]). The MedDRA SOCs with the highest frequency of SAEs in the risankizumab group were infections (n=7), neoplasms (n=6), cardiac (n=4), and respiratory (n=4). The rate of SAEs per 100 patient-years (PY) did not show an appreciable difference when comparing the treatment groups, with perhaps the exception of respiratory events (see Table 3 below); however, the number of respiratory SAEs was zero in the other treatment groups and the duration of exposure to risankizumab was greater in comparison to that for the other groups.

Table 3. Serious adverse event (SAE) frequencies and rates per 100 patient-years in the primary safety analysis by the most commonly reported SOCs in the risankizumab group.

<table>
<thead>
<tr>
<th>SOC</th>
<th>Risankizumab 150-180mg (PY=417.5) N of SAE (Events/100 PY)</th>
<th>Placebo (PY=92.0) N of SAE (Events/100 PY)</th>
<th>Ustekinumab (PY=75.9) N of SAE (Events/100 PY)</th>
<th>Adalimumab (PY=95.0) N of SAE (Events/100 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>7 (1.7)</td>
<td>1 (1.1)</td>
<td>4 (5.3)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>6 (1.4)</td>
<td>1 (1.1)</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4 (1.0)</td>
<td>0 (0)</td>
<td>1 (1.3)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4 (1.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Source: Integrated Summary of Safety Table 2.2.1.11; PY=patient-years

### 5.2 Adverse Events of Special Interest

#### 5.2.1 Infections

In the primary safety analysis, 5 (0.4%) patients in the risankizumab 150-180 mg group experienced a total of 7 serious infections compared to one (0.3%) patient in the placebo group; 4 (1.7%) patients in the ustekinumab group; and one (0.3%) patient who experienced 2 serious infections in the adalimumab group. Cellulitis was the only serious infection reported in more than one patient in the risankizumab group. There were no serious fungal infections in any group and no active or latent cases of tuberculosis reported with risankizumab, ustekinumab, or adalimumab treatment in the primary safety analysis; a single report of Mycobacterium tuberculosis complex in the placebo group represented a case of latent tuberculosis.

In the full safety analysis set, there were no cases of serious fungal infections or active tuberculosis among risankizumab-treated patients; a total of 8 patients reported latent tuberculosis or Mycobacterium tuberculosis complex. In these cases, the event represented positive tests without clinical symptoms.
5.2.2 Malignancies

There were 11 malignancies other than non-melanoma skin cancer (NMSC) in the risankizumab full safety analysis set, including breast cancer (4), hepatic cancer (1), intestinal adenocarcinoma (1), malignant melanoma (2), esophageal carcinoma (1), and prostate cancer (2). The overall rate for malignancy events other than NMSC was 0.5 per 100 patient-years (PY), which is similar to the rates for adalimumab (0.7 per 100 PY), ustekinumab (0.6 per 100 PY), ixekizumab (0.5 per 100 PY), or secukinumab (0.48 per 100 PY).

The 120-day safety update reported that 10 additional malignancies other than NMSC have occurred, for a total of 21 cases. Including these data, the overall rate for malignancy (excluding NMSC) was 0.62 per 100 PY. The review team noted that the limited duration of observation during the drug development program did not allow for detection of rare events with a long latency such as malignancy. Therefore, a postmarketing observational study will be required to collect long-term safety data including malignancy.6

5.2.3 Major Adverse Cardiovascular Events

In the 52-week ustekinumab-controlled studies (M15-995, M16-008), 8 (1.3%) of 598 patients in the risankizumab group reported SAEs in the cardiac disorders SOC compared with 1 (0.5%) of 199 patients in the ustekinumab group. A consult review by the Division of Cardiovascular and Renal Products (DCRP) noted the incidence of cardiovascular events was low in number and similar across all the arms of the trials. The estimated annualized event rates were as follows: risankizumab 150 mg–180 mg (2%); placebo (5%); ustekinumab (5%); and adalimumab (4%). In the subset of ustekinumab-controlled studies, there were 8 adjudicated cardiovascular events in 7 patients in the risankizumab-treated group compared with 0 events in the ustekinumab group; the adverse events included 4 events of supraventricular arrhythmia and 4 events of congestive heart failure. The consult noted that, in the absence of imbalances in the larger sample size of the primary pooled safety population, this low incidence observation was likely due to chance.

6 Expected Postmarket Use

Risankizumab is likely to be prescribed by dermatologists and is expected to be used mainly by patients in the outpatient setting. The product will be administered subcutaneously by self-injection or injection by a caregiver. Healthcare professionals will need to provide proper training to patients and/or caregivers on preparation and administration according to the Instructions for Use included in the labeling.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS or risk management plan with the application.

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1 The clinical reviewer identified one case of breast cancer in addition to the three cases reported by the Applicant.
8 Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the review team recommends approval of risankizumab for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Psoriasis is a common, chronic, inflammatory skin disease that, depending on disease severity, can have a significant effect on the patient’s quality of life. The benefits of treatment with risankizumab were demonstrated by meeting the co-primary endpoints of the proportion of patients who simultaneously achieved ≥90% reduction from baseline in the PASI score at Week 16 and a static physician global assessment of clear or almost clear at Week 16 compared to placebo or active control.

The safety profile demonstrated for risankizumab appears to be similar to other products in the class of systemic agents used for the treatment of moderate-to-severe psoriasis. The most important safety concern is the risk of serious infections, including reactivation of tuberculosis. The proposed label includes a warning and precaution that risankizumab may increase the risk for infections and to evaluate patients for tuberculosis infection and consider treatment for latent infection prior to initiating risankizumab. Additionally, a theoretical risk of malignancy for biologics used to treat psoriasis exists due to their immunosuppressive effects. A long-term prospective observational study of risankizumab will be a post-marketing requirement (PMR) to assess the risk of malignancy and other secondary outcomes such as serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, cardiovascular events, and other adverse events.

The healthcare providers who are likely to prescribe risankizumab should be familiar with treatment regimens that include immunomodulator agents that block cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23, and the risks associated with these treatments. Additionally, the biologics infliximab, adalimumab, etanercept, and ustekinumab, which had REMS programs to mitigate the risks of infections and malignancies, had their REMS released after the REMS communication plan activities were completed and the assessments showed that healthcare professionals understood the key messages. Since the likely prescribers of risankizumab and these products are the same, prescribers should be aware and knowledgeable about the risks. Therefore, based on the data currently available, DRISK and DDDP agree that a REMS is not necessary to ensure the benefits outweigh the risks of risankizumab.

9 Conclusion & Recommendations

Based on the available information a REMS is not necessary to ensure the benefits of risankizumab outweigh the risks. In general, healthcare providers who treat psoriasis are familiar with the risks associated with the class of biologic immunomodulators available to treat psoriasis.

Should DDDP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.
## 10 Appendices

### 10.1 Supplementary Table 1

<table>
<thead>
<tr>
<th>Product Name (Trade Name) Year of Approval</th>
<th>Mechanism of action</th>
<th>REMS History</th>
<th>Boxed Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ustekinumab (Stelara) 2009</td>
<td>IL-12 and IL-23 inhibitor</td>
<td>Medication Guide Communication Plan REMS released February 2017</td>
<td>None</td>
</tr>
<tr>
<td>Secukinumab (Cosentyx) 2015</td>
<td>IL-17A inhibitor</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ixekizumab (Taltz) 2016</td>
<td>IL-17A inhibitor</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Brodalumab (Siliq) 2017</td>
<td>IL-17A receptor antagonist</td>
<td>Elements to Assure Safe Use</td>
<td>Suicidal ideation and behavior</td>
</tr>
<tr>
<td>Guselkumab (Tremfya) 2017</td>
<td>IL-23 inhibitor</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Tildrakizumab (Ilumya) 2018</td>
<td>IL-23 inhibitor</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

TNF=tumor necrosis factor; IL=interleukin

Reference ID: 4420469
10.2 REFERENCES


3 Feldman SR. Epidemiology, clinical manifestations, and diagnosis of psoriasis. In:UpToDate, Dellavalle RP, Callis Duffin K, and Ofori AO (Eds), UpToDate, Waltham, MA 2018.


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ROBERT G PRATT
04/17/2019 10:06:17 AM

DONELLA A FITZGERALD
04/17/2019 10:12:43 AM

JAMIE C WILKINS PARKER
04/17/2019 10:36:04 AM