CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761067Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td><strong>PDUFA Goal Date</strong></td>
<td>March 23, 2018</td>
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<td><strong>OSE RCM #</strong></td>
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**Reviewer Name(s)**
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**Team Leader**
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**Deputy Director**
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**Review Completion Date**
- March 7, 2018

**Subject**
- Evaluation of Need for a REMS

**Established Name**
- Tildrakizumab

**Trade Name**
- Ilumya

**Name of Applicant**
- Merck Sharp & Dohme Corp.

**Therapeutic Class**
- Human Interleukin 23 Antagonist

**Formulation(s)**
- 100 mg/ml single-dose prefilled syringe

**Dosing Regimen**
- 100mg 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 Ilumya (tildrakizumab) is necessary to ensure the benefits of this product outweigh its risks. Merck Sharp & Dohme Corp (MSD) submitted a Biologics Licensing Application (BLA 761067) for tildrakizumab with the proposed indication for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The risk associated with the use of tildrakizumab include infections. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Dermatology and Dental Products agree that a REMS is not needed to ensure the benefits of tildrakizumab outweigh its risks. Tildrakizumab has proven to reduce the severity of symptoms in patients with moderate-to-severe plaque psoriasis. 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. In general, healthcare providers who treat psoriasis should be familiar with the risk of infections.

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 (NME) Ilumya (tildrakizumab) is necessary to ensure the benefits of this product outweigh its risks. Merck Sharp & Dohme Corp (MSD) submitted a Biologics Licensing Application (BLA 761067) for tildrakizumab on March 23, 2017 for the proposed indication for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. This application is under review in the Division of Dermatology and Dental Products (DDDP). The Applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION
Tildrakizumab, a new molecular entity,\textsuperscript{a} is a fully human immunoglobulin G1 kappa (IgG1\(\kappa\)) monoclonal antibody (mAb) that binds to the p19 protein subunit of interleukin-23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Tildrakizumab inhibits the release of proinflammatory cytokines and chemokines. Tildrakizumab is proposed for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The blockade of the IL-23 cytokine pathway is how Tildrakizumab exerts clinical effects in plaque psoriasis.

Tildrakizumab is proposed to be available as 100 mg/ml prefilled syringes to be administered by subcutaneous route at week 0, week 4, and every 12 weeks thereafter.\textsuperscript{b} Due to the infrequent dosing

\textsuperscript{a} FDAAA factor (F): Whether the drug is a new molecular entity

\textsuperscript{b} FDAAA factor (D): The expected or actual duration of treatment with the drug
schedule, the Applicant proposes that tildrakizumab should be administered by a healthcare professional. Tildrakizumab is in the same class as Tremfya (guselkumab), approved on 7/13/2017, which does not have a REMS.

Tildrakizumab is not currently approved in any jurisdiction.

2.2 **REGULATORY HISTORY**
The following is a summary of the regulatory history for BLA 761067 relevant to this review:

- 3/23/2017: BLA 761067 submission for tildrakizumab injection indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy received.
- 9/13/2017: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tildrakizumab.
- 12/6/2017: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for tildrakizumab.

3 **Therapeutic Context and Treatment Options**

3.1 **DESCRIPTION OF THE MEDICAL CONDITION**
Psoriasis is a common, chronic, inflammatory, multi-system disease with predominantly skin and joint manifestations. It can present in many different patterns from the scalp to the feet and cause psychiatric distress and physical disabilities. Psoriasis affects approximately 2-3% of the U.S. population. It can begin at any age, but one population study of the age of onset revealed two peaks, at age 16 and at age 60. Risk factors may include family history, obesity, smoking and environmental smoke, and heavy alcohol use. Risk factors that may trigger or exacerbate psoriasis include stress, physical trauma to the skin, cold dry weather, sun exposure and hot weather, infections, and certain medications. Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has a substantial impact on patient’s lives.1,2

3.2 **DESCRIPTION OF CURRENT TREATMENT OPTIONS**
Multiple products are approved for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provide a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illness, there is a need for additional therapeutic options.

Currently approved drugs for the treatment of moderate-to-severe psoriasis include the anti-metabolite methotrexate (MTX), tumor necrosis factor (TNF) inhibitors, such as etanercept, adalimumab and infliximab, IL-12+23 antagonist ustekinumab, IL-23 antagonist guselkumab, IL-17A antagonist...
secukinumab and ixekizumab, IL-17A receptor antagonist brodalumab, T-cell inhibitor cyclosporine (CSA), retinoid acitretin, and phosphodiesterase-4 (PDE-4) inhibitor apremilast (see Appendix 11.1). Phototherapy, with either PUVA (UVA light combined with the psoralen methoxsalen) or UVB light therapy, is also a standard of care treatment for moderate-to-severe psoriasis patients. The efficacy of these products is generally measured on the Psoriasis Area and Severity Index (PASI), with the change from baseline as the most common primary efficacy endpoint. The PASI 75 (75% reduction in the PASI score compared to baseline) for currently available drug therapies varies from highly efficacious (PASI 75 \geq 70\%) for cyclosporine, infliximab, adalimumab, ustekinumab and secukinumab to moderately efficacious (PASI 75 \geq 40\%) for methotrexate and etanercept, to somewhat efficacious (PASI 75 \geq 20\%) for acitretin and apremilast.²

Infliximab, etanercept, adalimumab, 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 only. Infliximab, etanercept, and adalimumab were released from the CP 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. Siliq (brodalumab), an IL-17A receptor antagonist, was approved on February 15, 2017 with a REMS consisting of elements to assure safe use (ETASU) and a timetable for submission of assessments. A MG is also included as part of the approved labeling. The ETASU includes 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. The goal of the Siliq REMS is to mitigate the observed risk of suicidal ideation and behavior (SIB) including completed suicides, which occurred in subjects treated with Siliq by 1) ensuring that prescribers are educated about the risk of SIB observed with Siliq therapy and the need to counsel patients about this risk and 2) ensuring that patients are informed about the risk of SIB observed with Siliq therapy and the need to seek medical attention for manifestations of SIB, new onset or worsening depression, or other mood changes.

4 Benefit Assessment

Evidence of the effectiveness of tildrakizumab for the treatment of moderate-to-severe plaque psoriasis in adult patients was derived from two pivotal Phase 3 trials (P010 and P011). Patients 18 years of age and older with moderate-to-severe plaque psoriasis who were candidates for phototherapy or systemic therapy were eligible for enrollment. Moderate-to-severe plaque psoriasis was defined by \geq 10\% body surface area (BSA) involvement, Physician’s Global Assessment\(^c\) (PGA) score \geq 3 (“moderate”), and PASI\(^d\)

\(^c\) Physician’s Global Assessment (PGA) is used to determine the overall severity of a subject’s psoriasis lesions at a given time point. The lesions are graded on a 6-point scale from 0 = no evidence to 5 = severe for thickness, erythema, and scaling. The PGA endpoint is defined as the proportion of subjects with PGA score of 0 “clear” or 1 “minimal” with at least a 2-grade reduction from baseline for the Phase 3 trials at the time of assessment.
score \geq 12 at baseline. In addition, no more than 40% of subjects were to have prior exposure to biological therapies for psoriasis and no more than 30% of subjects were to have a diagnosis of psoriatic arthritis at baseline. The investigators used both US-licensed and non-US-licensed etanercept in the studies, but did not provide bioequivalence data for the non-US-licensed product. Therefore, only data from US-licensed etanercept will be considered by the clinical review team.

Safety data was also included from Phase 2 study, P003.

Both trials, P010 and P011, were randomized, multicenter, double blind, placebo-controlled, parallel-group trials with an optional long-term safety extension at Week 64. Trial P011 also included an active-comparator arm using etanercept up to week 28. Both trials had an initial 28-week treatment period during which, subjects initially assigned to placebo were subsequently re-randomized to tildrakizumab 200 mg or 100 mg at Week 12. Trial P010 included a randomized withdrawal and retreatment period from Week 28 to Week 64. The primary objective for both trials was to assess the efficacy of tildrakizumab compared to placebo in the treatment of moderate-to-severe chronic plaque psoriasis as measured by the co-primary endpoints of PASI 75 response and PGA score of “clear” or “minimal” with at least a 2-grade reduction from baseline assessed at Week 12.

Results for P010, and P011

A total of 1861 subjects were randomized in the two trials: 310 to placebo, 616 to 100 mg tildrakizumab, 622 to 200 mg tildrakizumab, 313 to 50 mg etanercept. A summary of clinical responses for Week 12 is provided in Table 1. The Applicant concluded that there were clinically meaningful improvements in psoriasis compared with placebo through Week 12 and that tildrakizumab demonstrated significant improvement in psoriasis as measured by PASI and IGA. The clinical reviewer agrees that tildrakizumab was superior to placebo in both IGA and PASI 75 at Week 12 in both trials. Comparisons between tildrakizumab and US licensed etanercept were assessed as secondary endpoints at Weeks 12 and 28 and the results are provided in Table 2. In the subgroup who received US-licensed etanercept, none of the secondary endpoints comparing tildrakizumab 100 mg and etanercept had p-values less than 0.05, therefore, labeling will not include data comparing tildrakizumab with etanercept. Examination of age, gender, race, and previous treatment with a biologic did not identify differences in response to tildrakizumab among these subgroups at Week 12.

To evaluate the maintenance and durability of response (P010), subjects originally randomized to tildrakizumab who were PASI 75 responders at Week 28 were re-randomized to either maintaining the same dose of tildrakizumab every 12 weeks or placebo for an additional 36 weeks. Subjects who relapsed, defined by reduction in maximum PASI response by 50%, during treatment with placebo were restarted on their original dose of tildrakizumab. At Week 28, 87.5% of subjects continued on tildrakizumab 100 mg and 93.9% of subjects continued on tildrakizumab 200 mg maintained a response.

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. PASI 75, PASI 90, and PASI 100 stand for the status of achieving \geq 75%, \geq 90%, and \geq 100% reduction from baseline in PASI score, respectively. Responders were defined as subjects who achieve PASI \geq 75.
(PASI 75) at Week 64. Of the subjects who were initially randomized to tildrakizumab 100mg or 200mg, 114 and 119 subjects, respectively, were re-randomized to placebo at Week 28. Of these subjects, a total of 62 (54.4%) and 58 (48.7%) subjects in the 100 mg and 200 mg treatment groups, respectively, relapsed between Weeks 32 through 64. Among subjects who relapsed, 35 (30.7%) and 30 (25.2%) were re-treated for at least 12 weeks with the same dose of tildrakizumab to which they had initially been randomized. Of those subjects, 30 (85.7%) and 25 (83.3%) subjects had regained a PASI 75 response at Week 64.

The clinical pharmacology reviewer notes that the Phase 3 efficacy results overall support the proposed tildrakizumab 100 mg dosage regimen, however, Efficacy results and dose-response at Week 12 shows that the tildrakizumab 200 mg dosage regimen did not consistently demonstrate a higher response rate than the 100 mg dosage regimen for the co-primary efficacy endpoints of PGA of “clear” or “minimal” and PASI 75. The review team concluded that as there was no additional benefit to the use of the 200 mg dose over the 100 mg dose in any subgroup, only tildrakizumab 100 mg will be recommended in labeling.

The review team agrees with the Applicant that tildrakizumab was statistically superior to placebo on the co-primary endpoints (p < 0.001) in trials P010 and P011 and has concluded that the Applicant has demonstrated that tildrakizumab is effective for its intended use in the target population.

### Table 1: Efficacy Results at Week 12 in Adults with Plaque Psoriasis

<table>
<thead>
<tr>
<th>Clinical Endpoint</th>
<th>Tildrakizumab</th>
<th>Placebo</th>
<th>Tildrakizumab</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>100 mg</td>
<td>200 mg</td>
<td>100 mg</td>
<td>200 mg</td>
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<td></td>
<td>N = 309</td>
<td>N = 308</td>
<td>N = 307</td>
<td>N = 314</td>
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<td></td>
<td>n (%)</td>
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<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>PASI 75 p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>188 (61)</td>
<td>206 (66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 (6)</td>
<td></td>
</tr>
<tr>
<td>PGA of “clear” or “minimal” p-value</td>
<td>179 (58)</td>
<td>182 (59)</td>
<td>168 (55)</td>
<td>185 (59)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 (5)</td>
<td></td>
</tr>
<tr>
<td>PASI 90 p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>119 (39)</td>
<td>115 (37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 (1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PASI 100 p-value</td>
<td>43 (14)</td>
<td>43 (14)</td>
<td>38 (12)</td>
<td>37 (12)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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4.2 Table 2: Results for the Secondary Efficacy Endpoints against Etanercept in Trial P011

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Tildrakizumab</th>
<th>Etanercept</th>
<th>p-value</th>
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<tr>
<td></td>
<td>200 mg n=314</td>
<td>100 mg n=301</td>
<td>Etanercept n=313</td>
</tr>
<tr>
<td>PGA of &quot;clear&quot; or &quot;minimal&quot; at Week 12</td>
<td>186 (59%)</td>
<td>168 (55%)</td>
<td>149 (48%)</td>
</tr>
<tr>
<td>US</td>
<td>45 (52%)</td>
<td>41 (48%)</td>
<td>41 (47%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>141 (62%)</td>
<td>127 (57%)</td>
<td>108 (48%)</td>
</tr>
<tr>
<td>PASI 75 at Week 12</td>
<td>206 (66%)</td>
<td>188 (61%)</td>
<td>151 (48%)</td>
</tr>
<tr>
<td>US</td>
<td>48 (56%)</td>
<td>45 (53%)</td>
<td>44 (51%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>158 (60%)</td>
<td>143 (64%)</td>
<td>107 (47%)</td>
</tr>
<tr>
<td>PGA of &quot;clear&quot; or &quot;minimal&quot; at Week 28</td>
<td>207 (66%)</td>
<td>190 (62%)</td>
<td>131 (42%)</td>
</tr>
<tr>
<td>US</td>
<td>54 (62%)</td>
<td>38 (45%)</td>
<td>38 (44%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>154 (68%)</td>
<td>132 (68%)</td>
<td>93 (41%)</td>
</tr>
<tr>
<td>PASI 75 at Week 28</td>
<td>217 (69%)</td>
<td>216 (70%)</td>
<td>155 (50%)</td>
</tr>
<tr>
<td>US</td>
<td>58 (67%)</td>
<td>51 (60%)</td>
<td>45 (52%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>159 (70%)</td>
<td>165 (74%)</td>
<td>110 (49%)</td>
</tr>
<tr>
<td>PASI 90 at Week 12</td>
<td>115 (37%)</td>
<td>119 (39%)</td>
<td>67 (21%)</td>
</tr>
<tr>
<td>US</td>
<td>23 (27%)</td>
<td>26 (31%)</td>
<td>24 (28%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>92 (40%)</td>
<td>93 (42%)</td>
<td>43 (19%)</td>
</tr>
<tr>
<td>PASI 100 at Week 12</td>
<td>37 (12%)</td>
<td>38 (12%)</td>
<td>15 (5%)</td>
</tr>
<tr>
<td>US</td>
<td>4 (5%)</td>
<td>9 (11%)</td>
<td>6 (7%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>33 (14%)</td>
<td>29 (13%)</td>
<td>9 (4%)</td>
</tr>
</tbody>
</table>

US sample sizes = (N_{200}, N_{100}, N_{E}) = (86, 85, 87)
Non-US sample sizes = (N_{200}, N_{100}, N_{E}) = (228, 222, 226)

5 Risk Assessment & Safe-Use Conditions

The primary analysis dataset for the review of the safety included pooled data from Phase 2 trial P003 and Phase 3 trials P010 and P011. Data from subjects enrolled in Trial P003 who received doses (100 mg or 200 mg) or placebo was pooled with data from the Phase 3 trials. A total of 1994 subjects with moderate-to-severe plaque psoriasis were treated with tildrakizumab in controlled phase 2 and phase 3 clinical trials, 1083 subjects were treated with tildrakizumab 100 mg. In the placebo controlled period of the pooled clinical trials, adverse events occurred in 48.2% of subjects in the tildrakizumab 100 mg and 47.9% of subjects in the tildrakizumab 200 mg groups compared with 53.8% of subjects in the placebo group and 54% of subjects in the etanercept group. Common AEs that occurred at a rate of at least 1% and at a higher rate in the tildrakizumab group than in the placebo group include upper respiratory infections, injection-site reactions, fatigue, diarrhea, back pain, abdominal pain, and nausea. Through Week 52 (P003, P011) and Week 64 (P010), no new adverse reactions were identified with tildrakizumab use and the frequency of the adverse reactions was similar to that observed during the placebo-controlled period.

Safety parameters or AEs of interest were identified based on the tildrakizumab mechanism of action and specific risks in the target subject population and were considered as Tier 1. Tier 1 AEs included the
percentage of subjects with severe infections, malignancies, non-melanoma skin cancer (NMSC), melanoma skin cancer, confirmed extended major adverse cardiovascular event (MACE), and drug-related hypersensitivity reactions. Commonly occurring AEs (defined as at least four subjects in any treatment group) were considered as Tier 2. When comparing placebo, 100 mg and 200 mg in all subjects in Part 1 of P010 and P011, no specific safety difference was observed in adverse event categories of infections/infestations, severe infections/infestations, upper respiratory tract infections, and nasopharyngitis, basal/squamous cell carcinoma, melanoma, MI/ischemia, cardiac failure, or drug hypersensitivity.

Psychiatric AEs, including three suicidal ideation and behavior (SIB) events, were identified by DDP from the Applicant’s initial submission. DDP requested that the Division of Psychiatry Products (DPP) review the psychiatric AE study data and the requested results of a retrospective Columbia Classification and Assessment of Suicidal Adverse Events (C-CASA) tabulation analysis to provide input on whether there are any concerns about a psychiatric or SIB AE signal, and if so, what follow-up and labeling guidance should be provided. The DPP reviewer concluded that overall, the rates of psychiatric AEs found in the studies during the placebo-controlled phase was around 2% on study drug compared to 1% on placebo, and did not demonstrate nominally statistically significant differences between the study drug population and placebo. Based on the data provided, there is no clear association between tildrakizumab and SIB or other psychiatric conditions.5 The clinical reviewer concurs with DPP’s conclusion and stated that one case had insufficient information to reach a conclusion and the other was not related.

5.1 DEATHS
Ten deaths were reported across the development program. Five subjects randomized to tildrakizumab 100mg (alcoholic cardiomyopathy and steatohepatitis, acute myeloid leukemia, respiratory arrest, myocardial infarction, and unknown cause), one subject randomized to tildrakizumab 200 mg (aneurysm), and one subject randomized to etanercept in Part 1 who was switched to tildrakizumab 200 mg in Part 3 (sepsis). All fatal AEs were considered to be severe except for acute myeloid leukemia which was moderate in intensity. Three additional deaths occurred in the Phase 3 extension: one subject randomized to tildrakizumab 100 mg experienced a fatal AE of unknown cause, one subject randomized to tildrakizumab 200 mg who switched to 100 mg experienced a fatal AE due to “intoxication by the combined effects of fluoxetine and cyclobenzaprine,” and one patient randomized to placebo who switched to tildrakizumab 200 mg experienced a fatal SAE of asphyxiation due to immobilization of the chest. None of the fatal events were considered causally related to trial medication by either the investigator or the Applicant. The clinical reviewer concurs.

5.2 SERIOUS ADVERSE EVENTS (SAEs)
In the placebo-controlled safety pool, 6 (1.7%) placebo subjects, 26 (1.8%) tildrakizumab 100 mg or 200 mg subjects, and 2 (2.3%) US-licensed etanercept subjects had one or more SAEs. In tildrakizumab patients, cardiac disorders (acute myocardial infarction, atrial fibrillation, alcoholic cardiomyopathy, coronary artery disease, and tachycardia) were the most commonly reported SAE, which occurred in 5 (0.4%) subjects, followed by gastrointestinal disorders, which occurred in 4 (0.3%) subjects and infections, which occurred in 3 (0.2%) subjects. Cardiac disorders occurred in 1 (0.3%) placebo subject
and 1 (1.1%) US-licensed etanercept patients. Gastrointestinal disorders did not occur in any placebo or etanercept subjects. Infections occurred in 1 (0.3%) placebo subject and no etanercept subjects.

The clinical reviewer agrees that all SAEs occurred in single subjects and no system organ class had an incidence of SAEs > 1% in any treatment group.

5.3 Infections
In clinical trials, infections occurred in 22.6% of subjects in the tildrakizumab 100 mg group and 21.6% of subjects in the tildrakizumab 200 mg group compared to 22% of subjects in the placebo group and 23.6% of subjects in the etanercept group during the placebo-controlled period. In the exposure-adjusted placebo-controlled safety pool, 1 (0.03%) placebo subject, 2 (0.6%) subjects who received placebo and transitioned to tildrakizumab 100 mg or 200 mg, 22 (1.5%) subjects who received only tildrakizumab 100 mg or 200 mg, and no subjects who received etanercept, experienced a severe infection. The most common severe infection experienced by subjects exposed to tildrakizumab was cellulitis, followed by diverticulitis and sinusitis. Opportunistic infections including tuberculosis (TB) and re-activation of TB were also included as adverse events of special interest. There was one case of a 58-year-old male with a history of abnormal chest x-ray, chronic cough, and tobacco usage that experienced TB of the vertebral column. The Applicant proposes to include the infection, as well as evaluation for TB prior to initiating treatment with tildrakizumab, in the Warnings and Precautions section of the labeling. The review team concurs that tildrakizumab may increase the risk of infection and screening for TB should be included in the Warnings and Precautions section of the Prescribing Information as well as in the Medication Guide.

5.4 Major Adverse Cardiovascular Events (MACE)
Given the epidemiologic associations between psoriasis and cardiovascular (CV) events, and the potential association between anti-cytokine therapies used in the treatment of moderate-to-severe psoriasis and CV events, the Applicant conducted additional analyses on CV events. CV event data was analyzed from Phase 2 (P003) and Phase 3 trials (P010 and P011). MACE was defined as nonfatal myocardial infarction (MI), and nonfatal stroke, and cardiovascular deaths that were confirmed as “cardiovascular” or “sudden.” Extended MACE was defined as MACE, unstable angina, coronary revascularization, and resuscitated cardiac arrest. Fatal and nonfatal thrombotic, embolic or ischemic events included MACE, extended MACE, transient ischemic attack, pulmonary embolism, peripheral arterial thrombosis or thromboembolism, and venous thrombosis.

DDDP requested input from the Division of Cardiovascular and Renal Products (DCRP) on the cardiovascular findings including MACE and the potential for QT prolongation. The cardiology reviewer found 6 cases of adjudicated MACE from the pooled sample of the Phase 2/Phase 3 safety database. One subject had an adjudicated event while on placebo (ischemic stroke), three subjects had an adjudicated event while on tildrakizumab 100 mg (two deaths, one non-ST-elevated MI), and two subjects had an adjudicated event while on tildrakizumab 200 mg (one death, one ischemic stroke). No MACE was identified in the etanercept arm. All subjects in the tildrakizumab arms experienced MACE after drug was discontinued and all had cardiovascular risk factors. The cardiology reviewer concluded that the incidence of adjudicated MACE was low (0.3-0.4%) which approximates the annualized
incidence, thereby precluding a clinical concern. Similarly, the review of potential for QT prolongation concluded that based on analysis of the data sets, tildrakizumab does not appear to prolong TQc, PR, or QRS. The clinical reviewer concurs with the reviews by DCRP.

6 Expected Postmarket Use

Tildrakizumab is likely to be prescribed by dermatologists. The Applicant proposes that tildrakizumab should only be administered by a healthcare professional. The Applicant’s rationale for administration only by a healthcare professional is to improve patient adherence and satisfaction. Patients with moderate-to-severe plaque psoriasis who are both experienced biologics users and biologic naïve prefer longer dosing intervals such as every 12 weeks. However, with infrequent dosing, patients may have difficulty in establishing a regular self-injection routine, unlike other products that are dosed more frequently. For a drug that is administered every 12 weeks, maintaining proper adherence to dosing is critical, as any lack of compliance may have an effect on clinical benefit. Should a patient miss a single injection or incorrectly administer a dose, that patient will have underdosed by 25% for the treatment year. Therefore, incorrect administration or inconsistent dosing will have a larger impact on the patient’s outcome than for a drug that is more frequently dosed. Because patients with moderate-to-severe plaque psoriasis should be receiving regular follow-up visits, the Applicant does not anticipate that this regimen will result in additional burden to the healthcare system and may improve patient adherence due to the long lag time between doses. The clinical reviewer has not identified a safety concern that would require tildrakizumab to only be administered by a healthcare provider. The Dosage and Administration portion of the labeling includes a section of important administration instructions that states Ilumya should only be administered by a healthcare provider. It is DRISK’s opinion that due to the route of administration of this product, and no identified safety issues associated with administration to differentiate this product from others that are safely administered via the subcutaneous route with this device, that although the label will state that the product should be administered by a healthcare provider, there is no safety reason to require doing so.

Healthcare providers who are likely to prescribe tildrakizumab should be familiar with treatment regimens that include immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23. Other medications used to treat psoriasis, including infliximab, adalimumab, etanercept, and ustekinumab, which had REMS to mitigate the risks of infections and malignancies, have been released. Their REMS assessments showed that healthcare professionals understood the key messages regarding immunomodulating agents and risk of infection. Since the likely prescribers of tildrakizumab and these products are the same, it is likely that prescribers are aware and knowledgeable about the risks of immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tildrakizumab beyond routine pharmacovigilance and labeling.
8  Discussion of Need for a REMS

The Clinical Reviewer recommends approval of tildrakizumab based on the efficacy and safety information currently available.

Moderate-to-severe psoriasis is a serious and, at times, disabling condition that has substantial impact on patients’ lives. The benefits of treatment with tildrakizumab were demonstrated by meeting the primary endpoints of the clinical trials. Based on these results, tildrakizumab was found to be highly efficacious with an acceptable safety profile for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Safety concerns associated with the use of tildrakizumab for moderate-to-severe psoriasis are well documented. The safety profile demonstrated for tildrakizumab is consistent with the known safety profiles of other systemic agents used for the treatment of moderate-to-severe psoriasis and includes the risk of immunosuppression with the associated risks of serious infections and reactivation of tuberculosis. Healthcare providers who are likely to prescribe tildrakizumab should be familiar with treatment regimens that include immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23. Labeling will include infections, pre-treatment evaluation of tuberculosis, and avoidance of live immunizations in the Warnings and Precautions section.

A theoretical risk of malignancy exists due to immunosuppressive effects, and is hypothesized to be a potential risk for all psoriasis biologics. A long-term prospective observational study will be a post-marketing requirement (PMR) to assess long-term malignancy risk and other secondary outcomes such as serious infections, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal and hematologic adverse events among tildrakizumab users. Similar biologics such as Tremfya (guselkumab), Taltz (ixekizumab), Siliq (brodalumab), and Cosentyx (secukinumab), were issued PMRs to examine the risk of long-term malignancy and other secondary outcomes.

Additionally, the medications 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 complete and the assessments showed that healthcare professionals understood the key messages. Since the likely prescribers of tildrakizumab and these products are the same, it is likely that prescribers are aware and knowledgeable about the risks of immunomodulating agents involving blockade of cytokines in the psoriasis pathogenesis pathway, including inhibition of IL-23. 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 tildrakizumab.
9 Conclusion & Recommendations

Based on the available data, it is this reviewer’s opinion that a REMS is not necessary to ensure the benefits outweigh the risks. Tildrakizumab has proven to reduce the severity of symptoms in patients with moderate-to-severe plaque psoriasis. Based on the known safety profile for similar medications and the risks associated with tildrakizumab from the clinical trials, the benefit-risk profile is acceptable and will be communicated through labeling. In general, healthcare providers who treat psoriasis should be familiar with the risk of serious infection.

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

10 Materials Reviewed

The following is a list of materials informing this review:


11 Appendices

11.1 FDA Approved Drugs for Treatment of Plaque Psoriasis

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>Route</th>
<th>REMS/Boxed Warning/MG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin (retinoid)</td>
<td>Oral</td>
<td>RiskMAP, Boxed Warning (Pregnancy/teratogen, hepatotoxicity), MG</td>
</tr>
<tr>
<td>Adalimumab (TNF blocker)</td>
<td>Inject</td>
<td>REMS Removed, Boxed Warning (Serious Infections, Malignancy), MG</td>
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<tr>
<td>Apremilast (PDE4 inhibitor)</td>
<td>Oral</td>
<td>None</td>
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<tr>
<td>Brodalumab (IL-17A receptor antagonist)</td>
<td>Injectable</td>
<td>REMS w/ETASU (SIB), Boxed Warning, MG</td>
</tr>
<tr>
<td>Calcipotriene (Vit D derivate)</td>
<td>Topical</td>
<td>None</td>
</tr>
<tr>
<td>Calcipotriene/betamethasone dipropionate (Vit D derivative + corticosteroid)</td>
<td>Topical</td>
<td>None</td>
</tr>
<tr>
<td>Calcitriol (Vit D analog)</td>
<td>Topical</td>
<td>None</td>
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<tr>
<td>Cyclosporine (immunosuppressant)</td>
<td>Oral</td>
<td>Boxed Warning (Infections, malignancy [skin], brands are not bioequivalent, hypertension, nephrotoxicity)</td>
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<tr>
<td>Desoximetasone (corticosteroid)</td>
<td>Oral</td>
<td>None</td>
</tr>
</tbody>
</table>
11.2 References


4. Guerra, Matthew. 7.2.4 Results for the Co-Primary Efficacy Endpoints. DRAFT Unireview for Tildrakizumab, dated 10/31/17.


7. CDER Division of Cardiovascular and Renal Products QT Interdisciplinary Review Team. QT-IRT Consult to BLA 761067, dated September 29, 2017.


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/s/

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03/07/2018

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