Tildrakizumab-asmn (Ilumya™) New Drug Update

April 2018

<table>
<thead>
<tr>
<th>Drug Name:</th>
<th>tildrakizumab-asmn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade Name (Manufacturer):</td>
<td>Ilumya (Sun)</td>
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<tr>
<td>Form:</td>
<td>Subcutaneous (SC) injection in single-patient-use pen</td>
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<tr>
<td>Strength:</td>
<td>100 mg/mL solution in a single-dose prefilled syringe</td>
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<tr>
<td>FDA Approval:</td>
<td>March 20, 2018</td>
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<tr>
<td>Market Availability:</td>
<td>To be determined (TBD)</td>
</tr>
<tr>
<td>FDA Approval Classification:</td>
<td>Standard</td>
</tr>
<tr>
<td>Classification:</td>
<td>Specific Therapeutic Class (HIC3): Antipsoriatic Agents, Systemic (L1A) (anticipated)</td>
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**INDICATION**¹

Tildrakizumab-asmn (Ilumya), a high affinity, humanized IgG1 kappa monoclonal antibody that targets the p19 subunit of interleukin 23 (IL-23), is indicated for the treatment of adults with moderate-to-severe plaque psoriasis (PSO) who are candidates for systemic therapy or phototherapy.

**PHARMACOKINETICS**

The absolute bioavailability of SC tildrakizumab-asmn is estimated to be 73% to 80% and the peak concentration \((C_{\text{max}})\) is reached at approximately 6 days. The volume of distribution is 10.8 L. The method of metabolism of tildrakizumab-asmn has not been determined, but it is thought to be degraded into small peptides and amino acids via catabolic pathways. Steady-state is reached by week 16 following approved dosing of tildrakizumab-asmn, its systemic clearance is 0.32 L/day, and the half-life of tildrakizumab-asmn is approximately 23 days.

**CONTRAINDICATIONS/WARNINGS**

Tildrakizumab-asmn is contraindicated in patients with a known serious hypersensitivity reaction to it or any of the excipients. Cases of angioedema and urticaria have occurred with tildrakizumab-asmn. It should be discontinued immediately if serious hypersensitivity occurs.

Tildrakizumab-asmn can increase the risk of infection. Treatment with tildrakizumab-asmn should not be initiated in patients with any significant active infection until the infection resolves or is adequately treated. The risks and benefits of tildrakizumab-asmn should be considered prior to initiating therapy in patients with a chronic infection of a history of recurrent infection. Discontinuation may be required in patients with a serious infection until infection resolution. Patients should be evaluated for tuberculosis (TB) prior to beginning therapy, and treatment of latent TB should occur prior to initiation of tildrakizumab-asmn; it should not be administered to patients with active TB.
All age appropriate immunizations according to current immunization guidelines should be administered prior to initiating therapy with tildrakizumab-asmn. Live vaccines should be avoided in patients treated with tildrakizumab-asmn.

**DRUG INTERACTIONS**

There are no known drug interactions with tildrakizumab-asmn; however, as mentioned previously, avoid use with live vaccines.

**COMMON ADVERSE EFFECTS**

The most common (≥ 1%) adverse reactions reported with tildrakizumab-asmn treatment in clinical trials were upper respiratory infections (14%; 12% with placebo), injection site reactions (3%; 2% with placebo), and diarrhea (2%; 1% with placebo).

As a therapeutic protein, there is the potential for immunogenicity with tildrakizumab-asmn. In clinical trials, 6.5% of tildrakizumab-asmn-treated patients developed anti-drug antibodies, and of those, 40% developed neutralizing antibodies.

**SPECIAL POPULATIONS**

**Pregnancy**

Data on tildrakizumab-asmn use in pregnant women are insufficient to inform a drug-associated risk for adverse developmental outcomes.

**Pediatrics**

Safety and efficacy of tildrakizumab-asmn have not been established in pediatric patients.

**Geriatrics**

No overall differences in safety or efficacy of tildrakizumab-asmn were found between these geriatric patients and younger adults; however, greater sensitivity in this population cannot be ruled out.

**DOSAGES**

Tildrakizumab-asmn is dosed as 100 mg SC at weeks 0, 4, and every 12 weeks thereafter by a healthcare provider (HCP). The injection site should be on clear skin and easy access (e.g., abdomen, thigh, upper arm); do not administer 2 inches around the navel or tender, bruised, erythematous, indurated, or psoriasis-affected skin or into scars, stretch marks, or blood vessels.

**CLINICAL TRIALS**<sup>2,3</sup>

A literature search was performed using “tildrakizumab-asmn” and “psoriasis.”

Two, multinational, 3-part, parallel group, double-blind, randomized, placebo-controlled studies assessed the safety and efficacy of tildrakizumab-asmn for the treatment of moderate-to-severe chronic PSO in patients ≥ 18 years (reSURFACE 1 and reSURFACE 2). In both trials, moderate-to-severe chronic PSO was defined as body surface area (BSA) involvement ≥ 10%, Physician’s Global Assessment (PGA) score ≥ 3, and Psoriasis Area and Severity Index (PASI) score ≥ 12. In the first part, participants were randomized to active treatments or placebo. The co-primary endpoints were the proportion of
patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 grade score reduction from baseline) at week 12.

In reSURFACE 1, 772 patients were randomized 2:2:1 to tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo administered at weeks 0 and 4 during part 1 and at week 16 during part 2 (weeks 12 and 16 for participants re-randomized from placebo to tildrakizumab-asmn). At week 12, 62% of patients in the 200 mg group and 64% patients in the 100 mg group achieved PASI 75 versus 6% in the placebo group (p<0.0001 for both active dosing regimens versus placebo), and 59% of the 200 mg group and 58% of the 100 mg group achieved PGA responses versus 7% in the placebo group (p<0.0001 for both active dosing regimens versus placebo). Serious adverse events were similar between groups.

In reSURFACE 2, 1,090 patients were randomized 2:2:1:2 to tildrakizumab-asmn 200 mg or tildrakizumab-asmn 100 mg administered at weeks 0 and 4 during part 1 and at week 16 during part 2 (weeks 12 and 16 for participants re-randomized from placebo to tildrakizumab-asmn), placebo, or etanercept 50 mg given twice weekly in part 1 (once weekly during part 2). At week 12, 66% of patients the 200 mg tildrakizumab-asmn group, 61% in the 100 mg tildrakizumab-asmn group, 6% in the placebo group, and 48% in the etanercept group achieved PASI 75 (p<0.0001 for both tildrakizumab-asmn versus placebo and p≤0.001 for tildrakizumab-asmn versus etanercept). Likewise, 59% of patients in the 200 mg tildrakizumab-asmn group, 55% in the 100 mg tildrakizumab-asmn, 4% in the placebo group, and 48% in the etanercept group achieved a PGA response (p<0.0001 for both tildrakizumab-asmn versus placebo, p=0.0031 for tildrakizumab-asmn 200 mg versus etanercept, p=0.0663 for tildrakizumab-asmn 100 mg versus etanercept). Serious adverse events were similar between groups; however, 1 patient died (cause of death undetermined, but the patient did have alcoholic cardiomyopathy and steatohepatitis).

At week 12 in reSURFACE 1 (part 2), those assigned to placebo were reassigned to either active strength of tildrakizumab-asmn, and, by week 28, efficacy was similar to results seen with those who initiated active treatment at baseline. At week 28 (part 3), those who did not achieve a 50% improvement from baseline PASI (PASI 50) were removed from the study. Partial responders assigned tildrakizumab-asmn 200 mg continued treatment and partial responders assigned tildrakizumab-asmn 100 mg were re-randomized to 100 mg or 200 mg tildrakizumab-asmn. Participants assigned tildrakizumab-asmn who achieved PASI 75 were re-randomized to either continue treatment or to placebo until relapse (PASI maximum response reduction of 50%) and were then re-initiated on their active treatment. Those who were initially assigned placebo and randomized to active treatment at week 12 who then achieved PASI 50 continued their treatment. Response was generally maintained through part 3.

At week 12 in reSURFACE 2 (part 2), those assigned to placebo were reassigned to either active strength of tildrakizumab-asmn and, by week 28, efficacy was similar to results seen with those who initiated tildrakizumab-asmn at baseline. At week 28 (part 3), participants were also reassigned based on responder status. Nonresponders assigned tildrakizumab-asmn were discontinued from the study while those assigned to etanercept were switched to tildrakizumab-asmn 200 mg. Etanercept responders were discontinued from the study. Those assigned tildrakizumab-asmn 200 mg achieving PASI 75 were randomized to either continue treatment or to a lower dose of 100 mg, and partial responders continued treatment. Those assigned tildrakizumab-asmn 100 mg achieving PASI 75 continued treatment, and partial responders were randomized to either continue treatment or to an increased dose of 200 mg. Response was generally maintained through part 3.
OTHER DRUGS USED FOR CONDITION⁴

There are several biologic and topical medications available for the treatment of PSO. While several of these agents work by neutralizing inflammatory activity, guselkumab (Tremfya™) shares a common target with tildrakizumab-asmn (the p19 subunit of IL-23). Other biologic medications approved for psoriasis include adalimumab (Humira®), brodalumab (Siliq®), etanercept (Enbrel®), infliximab and its biosimilars (Remicade®, Inflectra®, Renflexis™), ixekizumab (Taltz®), secukinumab (Cosentyx®), and ustekinumab (Stelara®). Apremilast (Otezla®) and tofacitinib (Xeljanz®), Xeljanz XR), small molecule agents, is also approved for PSO. Topical therapies include corticosteroids, vitamin D analogs, tazarotene, salicylic acid, anthralin, and coal tar. There are also many traditional, non-biologic systemic therapies available including acitretin, cyclosporine, methotrexate, and methoxsalen. Phototherapy and photochemotherapy are also treatment options for patients with psoriasis.

PLACE IN THERAPY⁵,⁶,⁷

The evidence-based clinical practice guidelines of the American Academy of Dermatology (AAD) published in sections from 2008 to 2011 indicate that approximately 80% of patients affected with psoriasis have a mild to moderate form of the disease that can be managed with topical agents. Furthermore, the AAD suggests biologics should be used in patients with systemic disease or those who have experienced a lack of effect from topicals and targeted phototherapy. Section 6 states there is no specific sequence in which tumor necrosis factor (TNF) antagonists should be used in patients with moderate to severe chronic PSO without psoriatic arthritis.⁵¹,⁵² Monotherapy with adalimumab, etanercept, infliximab, and ustekinumab are listed as acceptable first-line agents after failure of topical therapy alone when phototherapy is not available. However, the guidelines note that in non head-to-head phase 3 trials of the individual agents, infliximab clears cutaneous psoriasis in the highest proportion of patients and with the greatest rapidity, followed by adalimumab and then etanercept. These guidelines were published prior to the approval of multiple medications within this class for these indications.

The 2012 Consensus Guidelines for the Management of Plaque Psoriasis from the National Psoriasis Foundation recommend monotherapy with adalimumab, etanercept, and ustekinumab as acceptable first-line agents after failure of topicals alone when phototherapy is not available. This was also published prior to the availability of multiple other agents approved for PSO treatment.

Tildrakizumab-asmn (Ilumya) offers an additional treatment option for adults with moderate-to-severe PSO who are candidates for systemic therapy or phototherapy. Although it is a SC formulation, administration by an HCP is required. It will likely compete with guselkumab (Tremfya), which shares a pharmacologic target and indication but can be administered by a trained patient, as well as the several other biologic and traditional agents indicated for PSO. Tildrakizumab-asmn is approved for PSO only; thus, an agent approved to treat additional conditions may be more appropriate in patients who have PSO and other autoimmune disorders (e.g., psoriatic arthritis).
### SUGGESTED UTILIZATION MANAGEMENT

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<thead>
<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Cytokine and CAM Antagonists</th>
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<tbody>
<tr>
<td><strong>Clinical Edit</strong></td>
<td>Prior authorization will be required if product is determined to be non-preferred.</td>
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</table>

**Initial**

Patient must:
- Be aged ≥ 18 years; **AND**
- Have been evaluated and screened for the presence of latent TB infection prior to initiating treatment; **AND**
- Not have an active infection, including clinically important localized infections; **AND**
- Not receive live vaccines during therapy; **AND**
- Not be on concurrent treatment with another TNF inhibitor, anakinra, abatacept, or other biologic response modifier; **AND**
- Have physician-assessed baseline disease severity utilizing an objective measure/tool; **AND**
- Have moderate to severe plaque psoriasis for at least 6 months with at least 1 of the following:
  - Involvement of at least 10% of body surface area (BSA); **OR**
  - Psoriasis Area and Severity Index (PASI) score of 10 or greater; **OR**
  - Incapacitation due to plaque location (e.g., head and neck, palms, soles or genitalia); **AND**
- Have not responded adequately (or is not a candidate) to a 3 month minimum trial of topical agents (e.g., anthralin, coal tar preparations, corticosteroids, emollients, immunosuppressives, keratolytics, retinoic acid derivatives, and/or Vitamin D analogues); **AND**
- Have not responded adequately (or is not a candidate) to a 3 month minimum trial of at least 1 systemic agent (e.g., immunosuppressives, retinoic acid derivatives, and/or methotrexate); **AND**
- Have not responded adequately (or is not a candidate) to a 3 month minimum trial of phototherapy (e.g., Psoralens with UVA light (PUVA) OR UVB with coal tar or dithranol).
**Suggested Utilization Management (continued)**

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<tr>
<th>Clinical Edit (continued)</th>
<th>Renewal</th>
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<td>Patient must:</td>
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<tr>
<td></td>
<td>• Continue to meet above criteria; <strong>AND</strong></td>
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<td></td>
<td>• Has absence of unacceptable toxicity from the drug. (e.g., severe infections, severe hypersensitivity reactions, etc); <strong>AND</strong></td>
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<td></td>
<td>• Receive ongoing monitoring for presence of TB or other active infections; <strong>AND</strong></td>
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<td>• Have disease response as indicated by improvement in signs and symptoms compared to baseline such as redness, thickness, scaliness, and/or the amount of surface area involvement, and/or an improvement on a disease activity scoring tool [e.g. a 75% reduction in the PASI score from when treatment started (PASI 75) or a 50% reduction in the PASI score (PASI 50) and a 4-point reduction in the DLQI from when treatment started.</td>
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<tr>
<th>Quantity Limit</th>
<th>100 mg/mL at week 0 and week 4, then 100 mg/mL every 12 weeks thereafter</th>
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<tbody>
<tr>
<td>Duration of Approval</td>
<td>6 months (initial), 6 months (renewal)</td>
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<tr>
<td>Drug to Disease Hard Edit</td>
<td>None</td>
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</tbody>
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**REFERENCES**

1. Ilumya [package insert]. Whitehouse Station, NJ; Merck; March 2018.