CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217900
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Nexus TTT #	2023-5773
Reviewer Name(s)	Donella Fitzgerald, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 23, 2024
Subject	Evaluation of Need for a REMS
Established Name	deuruxolitinib
Trade Name	Leqselvi
Name of Applicant	Sun Pharmaceutical Industries, Inc.
Therapeutic Class	Janus kinase inhibitor
Formulation(s)	8 mg tablet
Dosing Regimen	One 8 mg tablet twice daily

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1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Leqselvi (deuruxolitinib) is necessary to ensure the benefits outweigh its risks. Sun Pharmaceuticals, Inc. (Applicant) submitted a New Drug Application (NDA) 217900 for deuruxolitinib with the proposed indication for the treatment of moderate to severe alopecia areata in adults. This application is under review in the Division of Dermatology and Dentistry (DDD). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Deuruxolitinib, a new molecular entity,[a] is a janus kinase (JAK) inhibitor proposed for the treatment of moderate to severe alopecia areata (AA) in adults. Janus kinases are a family of tyrosine kinases that play an important role in cytokine signal transduction. Cytokines are thought to contribute to AA pathogenesis as 'the mechanism of hair loss in alopecia areata appears to be mediated by cytotoxic T cell attack of the hair follicle after loss of immune privilege, regulated by upstream JAK signaling".[1] The Applicant reports that deuruxolitinib modulates upstream JAK signaling, ultimately helping to slow the progression or reverse AA. Deuruxolitinib is proposed as an 8 mg tablet to be taken orally twice daily for chronic treatment.[b] It is not approved in other jurisdictions.

2.2. Regulatory History

- 07/28/2023: NDA 217900 submission for moderate to severe alopecia areata in adults received
- 01/24/2024: A post 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 deuruxolitinib

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Alopecia areata (AA) is a chronic, relapsing, immune-mediated disease that targets anagen hair follicles and causes non-scarring hair loss.[2] The affected area can range from loss in well-defined patches to total hair loss that can affect all hair bearing sites on the body. Patchy alopecia affecting the scalp is the most common presentation. In addition to the clinical manifestations of the disease, patients may also

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

experience significant psychosocial effects including anxiety, depression, and social phobia.[3] Disease onset can occur at any age; however, most patients develop AA before age forty with the mean onset between twenty-five and thirty-six years of age.[4] Prevalence in the general population is 0.1-0.2%. The lifetime risk of developing AA is estimated to be 1.7%.[5]

3.2. Description of Current Treatment Options

There is no preventative therapy or cure for AA. A variety of topical, intralesional, systemic agents and devices have been used for treatment with patient response varying widely. Treatment selection is typically based on patient age, disease duration, and extent of hair loss. For patients with limited patchy hair loss, topical or intralesional corticosteroids are typically the initial treatment approach. For patients experiencing extensive hair loss (>50%) the preferred initial treatment is with an oral JAK inhibitor, typically baricitinib or ritlecitinib,[6] which are the only FDA-approved pharmacologic treatments for AA (see Table 1 for additional details). Other JAK inhibitors (tofacitinib, ruxolitinib), along with various drug therapies such as minoxidil, anthralin and methotrexate are also used off-label for AA treatment.[7] Effectiveness of the various pharmacological therapies varies widely and use may be limited by their associated adverse effects. Intralesional and topical corticosteroids may cause skin atrophy, pruritis, telangiectasias, acne, and striae. Oral corticosteroid use is generally limited to short courses due to safety concerns associated with chronic use including adrenal suppression, effects on bone growth and integrity, and worsening of hypertension and diabetes mellitus. JAK inhibitors have been associated with serious adverse events and include Boxed Warnings in their labels for serious infections, mortality, malignancies, major adverse cardiovascular events, and thrombosis. Given the variable effectiveness of available treatment options for AA and potential risks with therapy, there is an unmet medical need for treatment of AA.

Table 1: FDA Approved Treatments for Alopecia Areata

Product Trade Name (Generic) **Year of Approval**	**Indication**	**Formulation/ Administration**	**Risk Management Approaches/ Boxed Warning, Medication Guide**
Olumiant (baricitinib) 2018	• Rheumatoid arthritis • COVID-19 • Alopecia areata	4 mg, 2 mg, and 1 mg oral tablet	Boxed warning for serious infections, mortality, malignancy, major cardiovascular events (MACE), thrombosis
Litfulo (ritlecitinib) 2023	• Alopecia areata	50 mg oral capsule	Boxed warning for serious infections, mortality, malignancy, MACE, thrombosis

In addition to pharmacological treatments for AA, phototherapy, topical immunotherapy and injection of platelet-rich plasma has been used to help stimulate hair growth. Patients may also use wigs and weaves to hide hair loss.

4. Benefit Assessment

The efficacy of deuruxolitinib for the treatment of AA was demonstrated in two Phase 3 studies (CP543.3001, NCT04518995; CP543.3002, NCT04797650) conducted in North America and the European Union (EU). The studies were multicenter, randomized, double-blind, placebo-controlled studies in adult subjects with a definitive diagnosis of AA and at least 50% hair loss, with a current episode of scalp hair loss lasting at least 6 months and not exceeding 10 years. In Study CP543.3001, 706 subjects were randomized in a 3:5:2 ratio (deuruxolitinib 12 mg BID: deuruxolitinib 8 mg BID: placebo). In Study CP543.3002, 517 subjects were randomized in a 1:2:1 ratio (deuruxolitinib 12 mg BID: deuruxolitinib 8 mg BID: placebo). After completion of 24 weeks of treatment, subjects were eligible to enroll in one of the open-label extension (OLE) studies (CP543.5001, NCT03898479 [North America]; CP543.5002, NCT05041803 [EU]). Due to the thrombotic events that occurred in the OLE trials at the 12 mg BID dose, the Applicant is currently seeking approval of only the deuruxolitinib 8 mg BID dose.[8]

Efficacy was evaluated using the Severity of Alopecia Tool (SALT) which assesses the percentage of missing scalp hair (from 0 to 100). The Applicant reported that deuruxolitinib 8 mg and 12 mg were superior to placebo ($p<0.001$) in both trials for the primary endpoint of SALT ≤20 response (i.e., no more than 20% missing hair) at Week 24. The results for the primary efficacy endpoint were consistent across the two trials:

- CP543.3001 SALT ≤20 response: 39.8% (12 mg) vs. 29.2% (8 mg) vs. 0.8% (placebo)
- CP543.3002 SALT ≤20 response: 36.7% (12 mg) vs. 32.1% (8 mg) vs. 0.8% (placebo)

Four key secondary endpoints (hair satisfaction patient reported outcome (SPRO) responders at Week 24, absolute SALT scores ≤ 20 at Week 12, Week 16 and Week 20) were also statistically significant across both trials.[9]

The medical officer concluded that the Applicant provided substantial evidence of effectiveness based on deuruxolitinib's superiority to placebo in both trials; however, the approved indication will be for the treatment of severe AA, instead of moderate to severe as the Applicant proposed.[10c] This determination was made because deuruxolitinib was studied in patients with at least 50% hair loss (SALT≥50). DDD stated that literature indicates that patients and clinicians consider SALT ≥50 to represent severe disease, not moderate to severe.[11] Therefore, the clinical review team concluded the indication will be for the treatment of severe AA.

[c] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

5. Risk Assessment & Safe-Use Conditions

The primary safety analysis consists of data from 1319 subjects (380 deuruxolitinib 12 mg BID, 640 deuruxolitinib 8mg BID, 299 placebo) who participated in the 24-week placebo-controlled portion of the Phase 3 trials, with supportive data from the first 52 weeks of the OLE trials (CP543.5001 and CP543.5002) and the Phase 2 Trial CP543.2001 [NCT02777008].

Deaths

There was one death (completed suicide) reported in the clinical development program in a 34-year-old male receiving deuruxolitinib 8 mg BID. The subject received 8 mg deuruxolitinib BID in Trial CP543.3001 for 24 weeks, followed by the same dose for approximately 44 days in the OLE Trial CP543.5001. The subject committed suicide approximately 2 weeks after study drug discontinuation due to a COVID-19 infection. The clinical investigator concluded that the suicide was considered not related to study drug, but possibly due to paranoia, relationship issues, and an ongoing lawsuit, as noted in the autopsy report. The Division of Psychiatry analyzed the suicide case report and determined that there was no evidence that deuruxolitinib played a direct causal role in the subject's death by suicide.[12]

Serious adverse events

Serious adverse events (SAEs) were reported at a similar rate in subjects who received deuruxolitinib compared to placebo during the placebo-controlled portion (24 weeks) of the trials. SAEs were reported in 7/640 (1.1%) of subjects who received deuruxolitinib 8 mg BID, 4/380 (0.9%) of subjects treated with deuruxolitinib 12 mg BID, and 4/299 (1.5%) of subjects who received placebo.[13] Table 1 below details the SAEs as presented by system organ class (SOC).

Table 1: SAEs by SOC and PT, 24-Week Placebo-Controlled Period[d]

System Organ Class	Preferred Term	PBO n (adj%) (N = 299)	DEURUX 8 mg BID n (adj%) (N = 640)	DEURUX 12 mg BID n (adj%) (N = 380)
Total SAEs		4	9	5
Number of subjects with any SAE		4 (1.5)	7 (1.1)	4 (0.9)
Infections and infestations	Appendicitis	1 (0.4)	2 (0.3)	1 (0.3)
	COVID-19	0	1 (0.2)	0
	Cellulitis	0	0	1 (0.3)
	Meningitis	0	1 (0.2)	0
	Pneumonia influenza	0	1 (0.2)	0
General disorders and administration site conditions	Chest pain	0	1 (0.2)	0
	Pyrexia	0	1 (0.2)	0

[d] Section 505-1 (a) of the FD&C Act: *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.*

Gastrointestinal disorders	Ileus	0	0	1 (0.2)
Injury, poisoning and procedural complications	Radius fracture	0	0	1 (0.3)
Musculoskeletal and connective tissue disorders	Osteoarthritis	0	0	1 (0.3)
Nervous system disorders	Migraine with aura	0	1 (0.2)	0
	Epilepsy	1 (0.4)	0	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	0	1 (0.2)	0
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	1 (0.4)	0	0
Psychiatric disorders	Adjustment disorder	1 (0.4)	0	0

PBO- placebo, DEURUX- deuruxolitinib, n = number of subjects with event
Source: Division of Dermatology and Dentistry. Multidisciplinary Review and Evaluation for deuruxolitinib, NDA 217900, July 1, 2024
NOTE: Percentages are adjusted for study size.

The Infections and Infestations SOC had the most SAEs reported and will be discussed in section 5.3 of this review. The remaining SOCs each had a single subject report in either the placebo or study drug treatment groups.

5.1. Malignancy

Malignancy is a known class effect of JAK inhibitors and was observed during the deuruxolitinib clinical development program. In the Overall Exposure Pool that included all subjects exposed to deuruxolitinib in the Phase 2 and 3 trials (n=1730), 10 subjects reported malignancies. The types of malignancies are outlined below in Table 2.

Table 2: Malignancies Reported in the Deuruxolitinib Overall Exposure Pool (subjects exposed to deuruxolitinib in Phase 2 and 3 trials)

Malignancies Possibly Related to Deuruxolitinib[e]	Malignancies unlikely related to Deuruxolitinib[f]
Malignant melanoma in situ (2)	Colon cancer
Basal cell carcinoma	Signet-ring cell carcinoma
Nasal neoplasm	Metastatic pancreatic carcinoma
Testicular cancer	Clear cell renal cell carcinoma
Salivary gland tumor	

[e,f] As determined by the DDD deuruxolitinib Clinical Reviewer

Five additional reports of malignancy were included in the application's 120-day Safety Update. Three cases were considered possibly related to study drug (basal cell carcinoma [2], gastric cancer) and two were not (planoepithelia cancer of tongue, squamous cell carcinoma of skin). The clinical reviewer concluded that:

> "*Overall, the incidence rates for malignancies were low. In addition, a substantial number of the narratives lacked key information to allow a definitive causality assessment. Therefore, the number of events was not sufficient to draw meaningful conclusions regarding risk or dose-response for malignancies*".[14]

Because malignancy is a known class effect of JAK inhibitors and there were occurrences in the trials, the Prescribing Information will include a Boxed Warning for malignancy and lymphoproliferative disorders. Additional language regarding malignancies will be included in Section 5 Warnings and Precautions of the label.

5.2. Thrombosis

Thrombosis is a known class effect of JAK inhibitors. Thrombotic events were not observed with the 8 mg BID dosing of deuruxolitinib but were reported for the 12 mg BID dosing. During the Phase 3 trials one subject who received deuruxolitinib 12 mg BID developed non-fatal bilateral pulmonary embolism. During the OLE trials 4 subjects (0.3% overall) receiving deuruxolitinib 12 mg BID developed 7 non-fatal thrombotic events (0.2 per 100 patient years), including deep vein thrombosis, bilateral pulmonary embolism, pulmonary embolism, and cerebral venous thrombosis. Due to the reports of thromboses occurring in subjects receiving the 12 mg strength during the Phase 3 trials, the Agency placed the trials on partial clinical hold to prohibit further administration of that dosage. The Applicant subsequently decided to seek approval for the 8 mg dose only. Since the NDA submission, two additional reports of thrombotic events (thrombophlebitis, transient ischemic attack) were included in the 120-day Safety Update. Both of the events occurred in subjects receiving the 12 mg BID dosage.

As is consistent with other JAK inhibitors, the Prescribing Information will include a Boxed Warning that thrombosis has occurred in patients treated with deuruxolitinib and that there is increased incidence of pulmonary embolism, venous and arterial thrombosis when used with another JAK inhibitor vs. TNF blockers. Additional language regarding thrombosis is proposed for Section 5 Warnings and Precautions and Section 6 Adverse Reactions.

5.3. Serious Infections

Serious infections are a known class effect of JAK inhibitors and were the most frequently observed SAE during the deuruxolitinib clinical development program. The exposure-adjusted incidence rate (EAIR) for serious infections during the 26-week placebo-controlled period was 0.8/100 patient-years for the placebo group, 1.8/100 patient-years in the deuruxolitinib 8 mg group, and 1.2/100 patient-years in the deuruxolitinib 12 mg group. Table 1 in this review lists the serious infections that occurred during this period. The medical officer concluded that most were possibly related to study drug. Draft labeling includes a Boxed Warning for the risk of serious bacterial, fungal, viral, and opportunistic infections

including tuberculosis. Section 5 Warnings and Precautions includes language to avoid use in patients with an active, serious infection and instructions for healthcare providers to closely monitor patients for the development of signs and symptoms of infection during and after treatment. Providers are also cautioned to avoid use of live vaccines during or immediately prior to deuruxolitinib treatment.

5.4. Use in CYP2C9 Poor Metabolizers or Moderate or Strong CYP2C9 Inhibitors

Drug Interactions: Coadministration of deuruxolitinib with multiple doses of a strong CYP2C9 inhibitor resulted in a 200% increase of deuruxolitinib total exposure. When co-administered with a dual CYP3A4/CYP2C9 inhibitor, the increased deuruxolitinib total exposure was 140%. Due to the potential for dose-dependent SAEs such as thrombosis, deuruxolitinib will be contraindicated in patients who are using moderate or strong CYP2C9 inhibitors. Labeling will also include a Warning and Precaution about this risk as well as language in Section 7 Drug Interactions.

Pharmacogenomics: CYP2C9 activity is expected to be decreased in individuals with genetic variants such as CYP2C9*2 and CYP2C9*3 alleles.[15] The impact of CYP2C9 genetic variants on the pharmacokinetics of deuruxolitinib has not been directly evaluated in a clinical trial, but based on simulations using physiologically-based PK modeling, it is predicted that CYP2C9 poor metabolizers will have a 2-fold increase in deuruxolitinib total exposure compared to normal metabolizers.[16] Due to the potential for dose-dependent SAEs, deuruxolitinib will be contraindicated in patients who are CYP2C9 poor metabolizers. The label will also include a Warning and Precaution regarding the increased risk of serious adverse reactions in these patients. DDD also plans to require the Applicant to conduct a post marketing study to assess systemic deuruxolitinib exposure in CYP2C9 poor metabolizers, and will direct the Applicant to establish an in-vitro diagnostic genotyping assay to determine CYP2C9 genotype status, as there is currently no FDA approved companion diagnostic. DDD stated that "prescribers can utilize other commercially available assays to determine genotyping prior to initiating treatment with deuruxolitinib while awaiting development of an assay from the Applicant."[17]

6. Expected Postmarket Use

Deuruxolitinib is proposed as an oral tablet that will likely be prescribed and self-administered in the outpatient setting. The most likely prescribers are dermatologists who are experienced with managing patients with AA. These prescribers are likely familiar with the risks associated with the JAK inhibitor drug class given there are other agents in this class approved for treatment of dermatologic conditions, including AA and atopic dermatitis.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for deuruxolitinib beyond routine pharmacovigilance and labeling. Draft labeling includes the Prescribing Information and a Medication Guide (MG) to inform patients of important safety information.

8. Discussion of Need for a REMS

Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of deuruxolitinib with the revised indication for the treatment of severe AA in adults.

Alopecia areata is a chronic, relapsing, immune-mediated disease that targets anagen hair follicles and causes non-scarring hair loss that can lead to significant psychosocial effects. There is no cure for AA, but there are two FDA-approved pharmacologic treatments for severe AA: baricitinib and ritlecitinib, which are both oral JAK inhibitors. The DDD stated that there is a significant unmet medical need for effective treatment for patients with severe AA because the existing approved therapies do not adequately manage the condition for all patients.

Efficacy of deuruxolitinib was demonstrated in two Phase 3 double-blind, placebo-controlled trials by meeting the primary endpoint of SALT ≤20 response at Week 24 compared to placebo. The serious risks observed with deuruxolitinib include malignancy, thrombosis, serious infections and CYP2C9 drug interactions. Potential risks of treatment include elevated deuruxolitinib plasma concentrations in patients who are CYP2C9 poor metabolizers. Because deuruxolitinib is a JAK inhibitor, most of the observed risks were expected; the Applicant submitted the application with a boxed warning for risks consistent with the drug class: serious infections, mortality, malignancy, major adverse cardiovascular events and thrombosis. Like other JAK inhibitors, deuruxolitinib labeling also includes Limitations of Use language recommending that it not be used in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants.

Unlike other JAK inhibitors approved to treat severe AA, deuruxolitinib will be contraindicated with concurrent use of moderate or strong CYP2C9 inhibitors and in patients who are CYP2C9 poor metabolizers. Labeling will include a recommendation for healthcare providers to conduct CYP2C9 genetic testing prior to treatment initiation. Additionally, the DDD plans to require a post-marketing study to assess systemic deuruxolitinib exposure in CYP2C9 poor metabolizers and will direct the Applicant to establish a companion in-vitro diagnostic genotyping assay to determine CYP2C9 genotype.

The clinical reviewer concluded that based on the safety profile of deuruxolitinib, which is consistent with other JAK inhibitors, the proposed labeling (PI, MG) and routine pharmacovigilance are considered adequate to manage risks of this product in the treatment of severe AA. Based on the data currently available, this reviewer agrees with the medical officer's assessment. Draft labeling for deuruxolitinib is consistent with that of JAK inhibitors that are approved for AA and other dermatologic conditions. Therefore, prescribers of deuruxolitinib should be familiar with these risks and how to manage them. The contraindication for use with CYP2C9 inhibitors and use in CYP2C9 poor metabolizers is unique to deuruxolitinib and should help to mitigate potential adverse events in these patient populations.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The proposed risk management approach for deuruxolitinib is similar to other JAK inhibitors approved for AA and other dermatological conditions, with the exception of risks associated with concomitant use with CYP2C9 inhibitors and use in CYP2C9 poor metabolizers, which will be contraindicated in the label. We expect healthcare providers to be familiar with the common JAK inhibitor safety concerns and knowledgeable about appropriate monitoring and risk management. At the time of this review, labeling was ongoing. Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

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