CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761244Orig1s000

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	BLA
Application Number	761244
PDUFA Goal Date	September 1, 2022
OSE RCM #	2021-1961
Reviewer Name	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 19, 2022
Subject	Evaluation of Need for a REMS
Established Name	spesolimab
Trade Name	Spevigo
Name of Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Therapeutic Class	Interleukin-36 receptor antagonist; humanized IgG1 monoclonal antibody
Formulation	Injection: 450 mg/7.5 mL (60 mg/mL) in a single-dose vial
Dosing Regimen	Administer as a single 900 mg intravenous infusion over 90 minutes • If GPP flare symptoms persist, may administer an additional 900 mg dose one week after the initial dose

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Spevigo (spesolimab) is necessary to ensure the benefits outweigh its risks. Boehringer Ingelheim Pharmaceuticals, Inc. submitted a Biologics Licensing Application (BLA) 761244 for spesolimab with the proposed indication for the treatment of flares in adult patients with generalized pustular psoriasis. The Applicant did not submit a REMS with this application.

DRM and the Division of Dermatology and Dentistry (DDD) have determined that a REMS is not needed to ensure the benefits of spesolimab outweigh its risks. Generalized pustular psoriasis (GPP) is a rare, severe, dermatologic disease. Flares may be associated with life-threatening complications (e.g., sepsis, renal, hepatic, and cardiorespiratory failure, or death) and patients may require hospitalization for treatment. As there are no approved treatments for the treatment of GPP flares or for flare prevention, there is an unmet need for treatment options for GPP. The benefit of spesolimab for the treatment of acute GPP flares of moderate-to-severe severity was demonstrated in one phase 2 pivotal trial, Study 1368-0013. The revised indication is for the treatment of generalized pustular psoriasis flares in adults. Although the clinical team determined the safety data was adequate, it is limited due to the small number of trial subjects and the short duration (1 week) of randomized, placebo-controlled period for the pivotal trial.

Based on the safety and efficacy data available, a risk evaluation and mitigation strategy (REMS) is not necessary to ensure the benefits outweigh the risks. The risks associated with spesolimab include infections and hypersensitivity reactions including drug reaction with eosinophilia and systemic symptoms (DRESS). Several biologic agents approved for other types of psoriasis share similar risks; therefore, prescribers are likely to be familiar with the risks and appropriate monitoring and management. These risks will be communicated through labeling (Section 5 - Warnings and Precautions and a Medication Guide).

During the review cycle, the Applicant submitted new safety information regarding suspected spesolimab-associated Guillain-Barré Syndrome (GBS) cases in ongoing clinical trials with spesolimab for non-GPP indications. The risk of GBS will be included in Section 6 of labeling.

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) Spevigo (spesolimab) is necessary to ensure the benefits outweigh its risks. Boehringer Ingelheim Pharmaceuticals, Inc. (hereafter referred to as the Applicant) submitted a Biologics Licensing Application (BLA) 761244 for spesolimab with the proposed indication for the treatment of flares in adult patients with generalized pustular psoriasis.[1] This application is under review in the Division of Dermatology and Dentistry. The Applicant did not submit a REMS with this application.

2. Background

2.1. Product Information

Spevigo (spesolimab-sbzo, hereafter referred to as spesolimab), a new molecular entity[a], is a humanized monoclonal immunoglobulin G1 (IgG1) antibody that inhibits interleukin-36 (IL-36) signaling by binding to the IL-36 receptor. Spesolimab, an IL-36 receptor antagonist, prevents downstream activation of pro-inflammatory and pro-fibrotic pathways.[2] Spesolimab is proposed for the treatment of flares in adult patients with generalized pustular psoriasis.[3]

Spesolimab is proposed to be supplied as a 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial for intravenous (IV) injection.[3] Spesolimab must be diluted in 100 mL of sterile 0.9% sodium chloride solution for injection prior to administration. The proposed dose of spesolimab is a single 900 mg dose administered as an IV infusion over 90 minutes. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose.[3] Spesolimab is proposed for the treatment of acute GPP flares only.[b] Spesolimab is likely to be administered in a healthcare setting (e.g. inpatient or infusion clinic) by a healthcare provider for the treatment of acute GPP flares. Spesolimab was granted orphan drug designation and breakthrough therapy designation. Spesolimab is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761224 relevant to this review:

- **10/03/2018:** Orphan drug designation granted for the treatment of patients with generalized pustular psoriasis.
- **04/30/2021:** Breakthrough therapy designation granted for IND 131311.
- **10/01/2021:** BLA 761244 submission for the treatment of flares in adult patients with generalized pustular psoriasis received.[1]
- **01/21/2022:** A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the REMS determination was ongoing but based on the available safety information at this time, labeling may be sufficient to communicate the risks of spesolimab.[4]
- **03/29/2022:** A Late-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that labeling and pharmacovigilance will likely be adequate for risk management of spesolimab.[5]

[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.*

- **04/25/2022:** The Applicant submitted new safety information describing cases of GBS in ongoing clinical trials with spesolimab for other indications.
- **05/09/2022:** The Agency issued a Major Amendment Acknowledgement Letter to the Applicant extending the PDUFA goal date by 3 months due to the new safety information.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Generalized pustular psoriasis (GPP) is a rare, severe, dermatologic disease characterized by acute episodes of widespread eruption of sterile pustules that occurs with or without systemic symptoms.[6-8] GPP is a subtype of pustular psoriasis and may develop independently or in association with pre-existing plaque psoriasis.[9] The pathophysiology is complex and not fully understood, but involves cellular components and cytokines of the immune system. Sustained activation of the pro-inflammatory cytokines, IL-1 and IL-36 are observed in GPP and thought to be a major driver of pathology.[9] Several genetic mutations are associated with an increased risk of developing GPP.[10] Acute flares may be idiopathic or may be triggered by infection, withdrawal or administration of certain medications (including those used in the treatment of GPP such as corticosteroids or methotrexate), pregnancy, or stress.[6,9]

The exact prevalence of GPP is unknown. It is rare and accounts for about 1% of all types of psoriasis.[11] The estimated prevalence has been reported as 1-9/1,000,000.[12,c] The prevalence of GPP is higher in Asians compared to Caucasians.[13] Claims based data provides an estimated GPP prevalence of 0.9-1 per 10,000 persons in the United States, with an approximate number of individuals with GPP between 29,000-32,000.[2,14] GPP most commonly presents in middle-age adults with onset typically between ages 40-60 years; however, it has also been reported in children.

The European Rare and Severe Psoriasis Network (ERASPEN) consensus definition[15] for the diagnosis of GPP is primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques) with three sub-classifiers:

- With or without systemic inflammation (using the American Society of Chest Physicians definition of fever >38 ^{o}C and leukocytosis (WBC >12x10^{9}/L))
- With or without psoriasis vulgaris
- Either relapsing (>1 episode) or persistent (>3 months)

GPP may be further subtyped into acute generalized pustular psoriasis (also known as generalized pustular psoriasis of von Zumbusch) and generalized annular pustular psoriasis. Acute GPP is characterized by an abrupt onset of rapidly disseminating, widespread eruption of superficial, sterile

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

pustules on erythematous and inflamed skin with systemic symptoms.[6,9,13] Pustules frequently occur on the trunk and limbs and may merge forming "lakes of pus". The skin lesions are painful, and patients often experience systemic inflammatory symptoms such as high fever, chills, fatigue, malaise, and nausea.[6] Extracutaneous symptoms including arthralgias, edema, jaundice, and ocular abnormalities may also occur. Pustules resolves within days to weeks, but residual edema and scaling improve over a longer period of time. Generalized annular psoriasis presents as a recurring, subacute eruption with peripheral pustules and scaling.[9]

GPP is a heterogenous disease with a variable clinical course.[16] The frequency of flares varies widely between patients. The extent and severity of symptoms varies between patients and even between flare events experienced by a patient. Life-threatening complications such as sepsis, renal, hepatic, and cardiorespiratory failure or death may occur with acute GPP. Patients may require hospitalization for management and monitoring.[13] The all-cause mortality for patients hospitalized with a GPP flare was 2.5% within 4 weeks after flare.[13] The reported mortality rates due to GPP or associated treatment have ranged from 2-16%.[13,16,d]

3.2. Description of Current Treatment Options

There are no agents approved for the prevention or treatment of GPP flares. Agents used for treatment are all off-label with limited evidence supporting use.

Treatment options for stable GPP may include use of methotrexate or oral retinoids (e.g., acitretin).[17] These agents may be considered as maintenance therapies due to their slower onset of action, however, these agents are associated with risks including embryo-fetal toxicity (both), liver and bone marrow toxicity (for methotrexate), and renal and hepatic dysfunction (for acitretin).

Treatment options for more severe, acute GPP, include cyclosporine; TNF-alpha inhibitors (infliximab, adalimumab, etanercept); IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), IL-23 inhibitors (risankizumab, guselkumab), corticosteroids, and anakinra.[17] Risks associated with cyclosporine include renal and hepatic toxicity, infections, and malignancies which limit long-term use and risks for biologics include infections and other risks depending on agent selected.

There is an unmet need for targeted therapies for GPP flares and maintenance.

4. Benefit Assessment

The primary evidence for efficacy and safety of spesolimab for the treatment of GPP flares is supported by one phase 2 pivotal trial, Study 1368-0013 (National Controlled Trial 03782792). Study 1368-0013

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study in subjects[e] ages 18 to 75 years with an acute GPP flare of moderate-to-severe severity.[18] Flare severity was defined by a Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score[f] of at least 3 (moderate), presence of fresh pustules (new appearance or worsening of pustules), GPPPGA pustulation sub-score of at least 2 (mild), and at least 5% of body surface area (BSA) covered with erythema and the presence of pustules.

During the double-blind period, subjects were randomized in a 2:1 ratio to receive a single dose of spesolimab on day 1 or placebo. Subjects in both arms with persistent symptoms[g] were eligible for an open-label dose of spesolimab 900 mg on day 8. After day 8 to week 12, rescue treatment with a single spesolimab dose could be administered if subjects experienced a flare reoccurrence. A maximum of three doses of spesolimab were allowed throughout the randomized and open-label parts of the trial. Subjects with worsening GPP flare severity or progression could receive a standard of care therapy (escape medication) at the discretion of the investigator during the study. At week 12, subjects who completed the trial with clinical improvement and no flare symptoms were eligible for entering a 5-year open-label-extension trial.

The primary endpoint was the proportion of subjects with a GPPPGA pustulation sub-score of 0 (indicating no visible pustules) at Week 1 (Day 8) after treatment.

Results:

In the double-blind period, 53 subjects were randomized to receive a single dose of spesolimab 900 mg on day 1 (N=35) or placebo (N=18). At week 1, a statistically significant higher proportion of subjects in the spesolimab-treated group met the primary endpoint of a GPPPGA pustulation sub-score of 0 at Week 1 (Day 8) compared to placebo (see Table 1).

[e] Eligible subjects for screening included those with a documented history of GPP based on the European Rare and Severe Psoriasis Expert Network (ERASPEN) diagnostic criteria as well as subjects with a first episode of acute GPP flare.

[f] Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score (which ranges from 0 [clear] to 4 [severe])

[g] Persistent symptoms was defined by a GPPGA total score of 2 or higher at the end of week 1 and a clinician assessment of GPP severity based on a modified Physician Global Assessment and a GPPGA pustulation sub-score of 2 or higher at week 1.

Table 1. Primary Efficacy Endpoint Results[2,18]

	Spesolimab (N=35)	Placebo (N=18)
GPPPGA pustulation sub-score of 0 at Day 8, n (%)	19 (54.3)	1 (5.6)
Risk difference versus placebo, % (95% CI)	48.7 (21.5, 67.2)	
P-value	0.0004	

Source: Adapted from Unireview, Statistical Reviewer analysis

The clinical reviewer concluded that the available efficacy data supports approval of spesolimab for the treatment of GPP flares in adults.[h,2]

5. Risk Assessment & Safe-Use Conditions

A total of 80 subjects with GPP were treated with at least 1 dose of spesolimab IV for the treatment of a flare.[2] The primary safety population consists of all subjects in the randomized population who received at least one study drug dose in the pivotal phase 2 trial, 1368-0013. Data from trials[i] 1368-0011, 1368-0027 (ongoing), and 1368-0025 (ongoing) and data from spesolimab clinical development programs for other indications provided additional supportive safety data.

The primary safety population includes a total of 53 subjects with 35 subjects randomized to spesolimab treatment and 18 randomized to placebo. The clinical reviewer notes that there is limited safety data compared to placebo as the duration of the randomized, double-blind period for trial 1368-0013 was only 1 week.[2] Subjects in either treatment group who continued to experience flare symptoms at week 1 were eligible for a single, open-label dose of spesolimab. At week 1, 12 (34%) subjects in the spesolimab group and 15 (83%) subjects in the placebo group received open label spesolimab. After week 1 through week 12, subjects were eligible to receive a single, open-label dose of spesolimab if they experienced a GPP flare reoccurrence after achieving a clinical response. A maximum of 3 doses of spesolimab were allowed throughout the trial. Throughout the trial, 36 subjects received 1 dose, 13 subjects received 2

[h] 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.*

[i] Trial 1368-0011 was a single-dose, open-label, proof-of-concept study in 7 subjects with active GPP. Trial 1368-0027 is an ongoing randomized, double-blind, placebo-controlled dose-finding study evaluating the efficacy and safety of spesolimab IV followed by subcutaneously for GPP flare prevention. Trial 1368-0025 is an ongoing open-label extension trial for subjects who completed trials 1368-0013 or 1368-0027 to continue open-label spesolimab subcutaneous treatment

doses, and 2 subjects received 3 doses. Safety was evaluated through week 12; however, this data was considered open-label due to the use of open-label spesolimab in the majority of placebo subjects.

The most common adverse events (≥5% in the spesolimab group and more common than placebo in week 1) were asthenia and fatigue, nausea and vomiting, headache, pruritis, infusion site bruising, and urinary tract infections.[3] Adverse events through week 12 were similar compared to the first week of randomized spesolimab treatment.[2]

Similar to other biologics, spesolimab may increase the risk of infections. Infections were reported in 14% of subjects treated with spesolimab compared to 6% on placebo. The risk of infections and avoidance of treatment initiation in patients with an active infection will be communicated in labeling in Section 5 – Warnings and Precautions.[3] There were no cases of active tuberculosis in the development program; there was one case of latent TB in trial 1368-0013 in a patient who received open label spesolimab. The risk of TB and recommendations for screening and monitoring will be included in Section 5 – Warnings and Precautions.[3]

5.1. Serious Adverse Events

5.1.1. Serious Adverse Events

There were no deaths in the clinical development program for GPP.[j,2,19] During the pivotal study[k], there were 12 serious adverse reactions[l] (SAEs) reported in 9 subjects.[m] The most frequently reported SAE was pustular psoriasis in both the spesolimab group (N=4, 11.4%) and placebo group (N=3, 16.7%).[2] The clinical reviewer concluded that no factors suggest a causal

[j] There was one death reported in trial 1368-0017 which was evaluating spesolimab for the treatment of ulcerative colitis. The subject was reported with SARS-CoV-2 pneumonia and Guillain-Barre syndrome 20 days after last administration of trial medication. The subject was hospitalized and died 12 days later. The Applicant concluded the fatal outcome was not related to spesolimab.

[k] Covers treatment phase including residual effect period (REP) (16 weeks after drug administration) of randomized treatment at Day 1 and censored at the time of any non-randomized Spesolimab administration (either OL at day 8 or OL rescue after day 8).

[l] 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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[m] 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.*

link between pustular psoriasis to the study drug.[2] There were two reported cases of drug reaction with eosinophilia and systemic symptoms (DRESS) in trial 1368-0013. One of the subjects with DRESS also reported two additional two additional SAEs, moderate urinary tract infection and moderate drug-induced liver injury. See Section 5.2.1 for additional discussion on the cases of DRESS. There was one SAE of severe arthritis starting 6 days after study drug administration The investigator assessed the arthritis to be probable septic arthritis and assessed it as related to study treatment.[19] The clinical reviewer concluded a causal link between the SAE of arthritis and the study drug is inconclusive. The clinical reviewer notes that both sepsis and arthritis are associated complications of GPP which could potentially confound the link between the reported SAE and study drug.[2]

5.2. Adverse Events of Special Interest

5.2.1. Hypersensitivity and Infusion-Related Reactions

Hypersensitivity reactions associated with spesolimab may include immediate reactions such as anaphylaxis and delayed reactions such as DRESS. There were no cases of anaphylaxis reported in the clinical development program. There were two reported cases of DRESS in trial 1368-0013.[19]

The first case involved a 40-year-old female with SAEs of DRESS, drug-induced liver injury, and urinary tract infection. The patient with a history of cephalosporine allergy was administered acetaminophen and cefuroxime/cefepime a few days before spesolimab administration. Two days after spesolimab administration, the patient was reported to have DRESS and elevated aminotransferases which peaked at >10-fold the upper limit of normal three days after study drug was administered. No therapy was administered for DILI and DRESS and the antibiotics were discontinued. The Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score was 1, which is not consistent with DRESS related to spesolimab. The clinical reviewer commented that DRESS was less likely as the onset of liver enzyme elevations, fever, and other symptoms was too soon for DRESS related to spesolimab. The clinical reviewer noted that while DILI due to spesolimab cannot be entirely ruled out, it is more likely that the cephalosporin induced both the drug eruption and liver injury given the history of cephalosporin allergy.[2]

The second case involved a 34-year-old female who was documented to have DRESS and worsening GPP flare 35 days after spesolimab was administered. The subject received a rescue dose of spesolimab 36 days after the initial dose. The infusion was interrupted due to reported adverse events; however, the full dose was eventually administered. Six days after the second study drug administration (and 42 days after initial study drug administration), her eosinophils remained elevated, and she had further episodes of pustular psoriasis, upper abdominal pain, and extremity pain. No therapy was documented for DRESS and symptoms resolved 41 days after the initial report. In addition to spesolimab, the patient received spiramycin therapy for a

tooth infection and for inflamed skin folds during the study timeframe. Months later, the subject was re-exposed to spiramycin and developed generalized erythema, scales, and desquamation; lack of pustules; and involvement of palms and soles but without systemic symptoms. The RegiSCAR score for this case was 2 which indicates "possible" case of DRESS. Both spiramycin and the study drug were considered possible drug culprits. The clinical reviewer commented that although it was unusual that the spiramycin rechallenge did not result in systemic symptoms, cases have been reported of sensitization to antibiotics during DRESS with re-exposure resulting in drug eruption without systemic symptoms.[2,20]

No other cases of DRESS have been reported in other studies for GPP or other spesolimab clinical development programs.

The clinical reviewer recommends the risk of DRESS be communicated in labeling in Section 4 – Contraindications, Section 5 – Warning and Precautions, and 6 – Clinical Trial Experience/6 Adverse Reactions and the Medication Guide.

5.2.2. Guillain-Barre Syndrome

During the course of the review, the Applicant submitted new safety data including three reported cases of suspected Guillain-Barre Syndrome (GBS) from three clinical trials for non-GPP indications (ulcerative colitis, palmoplantar psoriasis, and hidradenitis suppurativa). (b) (4)

DDD consulted the Division of Neurology I (DN1) to review the GBS case reports and to provide labeling recommendations.[21] The DN1 reviewer reviewed the three cases and concluded that there were two cases of probable GBS. He concluded that these few cases represent a relatively high frequency of GBS in a small safety population (2 cases/747 exposures) and this may represent a higher frequency than background. Biologic plausibility remains unclear.

DN1 recommends communicating this risk in Section 6 and including specific language about GBS (b) (4) The consult reviewer states that although there was a temporal association for GBS cases and spesolimab, there was no other causal evidence to support placement in Section 5, Warnings and Precautions.[21] The review team, including the DN1 consultant, recommend enhanced pharmacovigilance for this risk in the post-marketing setting to improve understanding of the safety signal.[2]

6. Expected Postmarket Use

Spesolimab is proposed for the treatment of acute GPP flares and is likely to be prescribed by dermatologists as well as hospitalists or general practitioners. Spesolimab is likely to be administered in a healthcare setting (e.g., inpatient or infusion clinic) by a healthcare provider where monitoring can occur during the infusion.

7. Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application.

7.1. Other Proposed Risk Management Activities

The Applicant proposed the following risk management activities:

- Voluntary Risk Management Plan which describes additional pharmacovigilance activities including a voluntary post-marketing safety study to assess rates of selected safety events of interest including infections, systemic hypersensitivity reactions including DRESS, and malignancy.[22]

Reviewer's Comments: *We note that these other activities proposed by the Applicant are voluntary risk management activities, we defer to Division of Pharmacovigilance and Division of Epidemiology for review and input. At the time of this review, discussions related to post-marketing requirements and pharmacovigilance plans were ongoing.*

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of spesolimab on the basis of the efficacy and safety information currently available. The revised indication is for the treatment of generalized pustular psoriasis flares in adults.

Generalized pustular psoriasis (GPP) is a rare, severe, dermatologic disease characterized by acute episodes of widespread eruption of sterile pustules that occurs with or without systemic symptoms. The frequency and severity of flares varies between patients. Flares may be associated with life-threatening complications such as sepsis, renal, hepatic, and cardiorespiratory failure or death. Patients may require hospitalization for management and monitoring. There are no approved treatments for the treatment or prevention of GPP flares. There is an unmet need for treatment options for GPP.

The benefit of spesolimab for the treatment of acute GPP flares of moderate-to-severe severity was demonstrated in one phase 2 pivotal trial, Study 1368-0013. At Week 1, a statistically significant higher

proportion of subjects in the spesolimab-treated group met the primary endpoint of a GPPPGA pustulation sub-score of 0 at Week 1 compared to placebo.

The most important risks associated with spesolimab include infections (including the risk of tuberculosis) and systemic hypersensitivity reactions including DRESS. Additionally, a few cases of suspected spesolimab GBS were reported in trials for non-GPP indications. The clinical review team notes the safety of spesolimab is limited due to the small number of trial subjects and the short duration (1 week) of randomized, placebo-controlled period for the pivotal trial. However, there are currently no approved therapies for GPP flares, and flares can be associated with severe or life-threatening complications. The clinical reviewer concluded that based on the available data, no significant safety concerns were identified that preclude approval. The risk of infections will be communicated in Section 5, Warning and Precautions. Labeling will also include a Warning on the risk of tuberculosis and recommendations for screening and monitoring. Healthcare providers who treat GPP are likely to be familiar with the risk of infections as this risk is common for biologic agents used for the treatment of other types of psoriasis. Two cases of DRESS were reported in the pivotal trial. This risk will be communicated in labeling. The likely prescribing population includes dermatologists who should be familiar with identifying and monitoring for hypersensitivity reactions, including DRESS. However, it is important to note that GPP flares and DRESS have overlapping symptoms and will require clinical evaluation to make a diagnosis. The Applicant submitted new safety information that included possible spesolimab-associated GBS cases reported in non-GPP clinical trials. A DN1 consult concluded that two cases were probable GBS and had a temporal association with spesolimab. The risk of GBS will be communicated in Section 6. The review team recommends enhanced pharmacovigilance for GBS to monitor this risk in the post marketing setting.

Based on the data currently available, this reviewer is not recommending a REMS for the risks of spesolimab. The risks of spesolimab will be conveyed with labeling, including a Medication Guide.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. Labeling is sufficient for communicating the risks. At the time of this review, labeling negotiations were 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

1. Boehringer Ingelheim Pharmaceuticals, Inc. Original Submission (Orig-1) for spesolimab, BLA 761244. October 1, 2021.

2. Food and Drug Administration. Center for Drug Evaluation and Research. Division of Dermatology and Dentistry. NDA/BLA Multi-Disciplinary Review and Evaluation, Spesolimab, BLA 761224, DRAFT as of July 8, 2022.
3. Boehringer Ingelheim Pharmaceuticals, Inc. DRAFT Labeling for spesolimab, BLA 761244. Agency edits as of June 2022.
4. Marcus K. Food and Drug Administration. Division of Dermatology and Dentistry. Midcycle Communication for spesolimab, BLA 761244. February 23, 2022.
5. Marcus K. Food and Drug Administration. Division of Dermatology and Dentistry. Late-Cycle Meeting Background Package for spesolimab, BLA 761244. March 22, 2022.
6. Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Expert Rev Clin Immunol.* 2019;15(9):907-919.
7. National Center for Advancing Translational Sciences [Internet]. Genetic and Rare Diseases Information Center. Generalized Pustular Psoriasis. Last Updated Nov 8, 2021. https://beta.rarediseases.info.nih.gov/diseases/12819/generalized-pustular-psoriasis. Accessed December 14, 2021.
8. Crowley JJ, Pariser DM, Yamauchi PS. A brief guide to pustular psoriasis for primary care providers. *Postgrad Med.* 2021;133(3):330-344.
9. Kalb RE. Pustular psoriasis: Pathogenesis, clinical manifestations, and diagnosis. In: Duffin K, Ofori A, eds. *UptoDate.* UptoDate, Waltham, MA. Accessed December 14, 2021.
10. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine. Generalized pustular psoriasis. Updated August 18, 2020. https://medlineplus.gov/genetics/condition/generalized-pustular-psoriasis/#references. Accessed December 14, 2021.
11. Boehner A, Navarini AA, Eyerich K. Generalized pustular psoriasis – a model disease for specific targeted immunotherapy, systematic review. *Experimental Dermatology.* 2018;27(10):1067-1077.
12. Generalized Pustular Psoriasis. Orphanet encylopedia. Available at: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=19519&Disease_Disease_Search_diseaseGroup=Generalized-pustular-psoriasis&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Generalized-pustular-psoriasis&title=Generalized%20pustular%20psoriasis&search=Disease_Search_Simple. Accessed January 28, 2022.
13. Boehringer Ingelheim Pharmaceuticals, Inc. Clinical Overview for spesolimab, BLA 761244. October 1, 2021.
14. US Truven MarketScan administrative claims from 01 Oct 2015 to 30 Sep 2016 and Optum US claims database using data from 01 Oct 2015 to 30 Jun 2017.
15. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. *J Eur Acad Dermatol Venereol.* 2017;31(11):1792-1799.
16. Choon SE, Navarini AA, Pinter A. Clinical Course and Characteristics of Generalized Pustular Psoriasis. *Am J Clin Dermatol.* 2022;23(Suppl 1):21-29.
17. Kalb RE. Pustular psoriasis: Management. In: Duffin K, Ofori A, eds. *UptoDate.* UptoDate, Waltham, MA. Accessed December 15, 2021.
18. Boehringer Ingelheim Pharmaceuticals, Inc. Summary of Clinical Efficacy for spesolimab, BLA 761244. October 1, 2021.
19. Boehringer Ingelheim Pharmaceuticals, Inc. Summary of Clinical Safety for spesolimab, BLA 761244. October 1, 2021.

20. Santiago LG, Morgado FJ, Baptista MS, Gonçalo M. Hypersensitivity to antibiotics in drug reaction with eosinophilia and systemic symptoms (DRESS) from other culprits. *Contact Dermatitis.* 2020;82(5):290-296.
21. Foster D. Division of Neurology 1. Neurology Consult regarding spesolimab, BLA 761244. June 16, 2022.
22. Boehringer Ingelheim Pharmaceuticals, Inc. EU Risk Management Plan for Spevigo (spesolimab), BLA 761244. October 1, 2021.

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