PDL DRUG REVIEW

Proprietary Name: Spevigo® Prefilled Syringe
Common Name: spesolimab-sbzo
PDL Category: Anti-Inflammatories, Non-NSAID

Pharmacology/Usage: Spesolimab-sbzo, the active ingredient of Spevigo®, is an interleukin-36 receptor antagonist. It is a humanized monoclonal IgG1 antibody (mAb) against human IL-36R, produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. It inhibits interleukin-36 (IL-36) signaling by specifically binding to the IL36R. Binding of spesolimab-sbzo to IL36R prevents the subsequent activation of IL36R by its ligands (IL-36 α, β, and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways. The precise mechanism linking reduced IL36R activity and treatment of flares of GPP is unclear.

Indication: For the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients 12 years of age and older and weighing at least 40kg.

There is no pregnancy category for this medication; however, the risk summary indicates the limited data on use in pregnant women are not sufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. Human IgG is known to cross the placental barrier; thus, Spevigo® may be transmitted from the mother to the developing fetus. The safety and efficacy of use in the pediatric population younger than 12 years of age or in pediatric patients weighing less than 40kg have not been established.

Dosage Form: Solution for Injection, preservative-free, available as:

- For subcutaneous (SC) use: 150mg/ml in a single-dose prefilled syringe.
- For intravenous (IV) use: 450mg/7.5ml (60mg/ml) in a single-dose vial for dilution prior to IV infusion.

Recommended Dosage: Assess patients for active or latent tuberculosis (TB) infection. Spevigo® initiation is not recommended in patients with active TB infection. Consider initiating treatment of latent TB prior to initiation of Spevigo®.

Complete all age-appropriate vaccinations per current immunization guidelines prior to starting Spevigo®.

Spevigo® prefilled syringes are for SC use for treatment of GPP when not experiencing a flare. If required, the 600mg SC loading dose of Spevigo® is to be administered by a healthcare professional. For subsequent 300mg doses, if the healthcare professional determines that it is appropriate, a patient 12 years of age and older may self-inject or the caregiver may administer Spevigo® after proper training in SC injection technique. In pediatric patients 12 to 17 years of age, administer Spevigo® under the supervision of an adult. If a patient experiences a GPP flare while receiving SC Spevigo®, the GPP flare may be treated with IV Spevigo®.

Spevigo® vials are for IV use for treatment of GPP flare. IV infusion of Spevigo® is only to be administered by a healthcare professional in a healthcare setting. Prepare Spevigo® IV infusion by diluting Spevigo® single-dose vials. Do not mix Spevigo® with other medicinal products.

The recommended SC dosage for treatment of GPP when not experiencing a flare: The recommended dosage of Spevigo® for treatment of GPP when not experiencing a flare in adults and pediatric patients 12 years of age and older and weighing at least 40kg is a loading dose of 600mg (four 150mg injections), followed by 300mg (two 150mg injections) administered SC 4 weeks later and every 4 weeks thereafter. Administer in the upper thighs or abdomen, rotating the injection site. Allow SC injections to reach room temperature (15-30 minutes) before injection.

For initiating or reinitiating SC Spevigo® after treatment of a GPP flare with IV Spevigo®: Four weeks after treatment of a GPP flare with IV Spevigo®, initiate or reinitiate SC Spevigo® for treatment of GPP at a dose of 300mg administered Q4W. A SC loading dose is not required following treatment of a GPP flare with IV Spevigo®.

Recommended IV dosage for treatment of GPP flare: The recommended dosage of Spevigo® for treatment of GPP flare in adults and pediatric patients 12 years of age and older and weighing at least 40kg is a single 900mg dose administered by IV infusion over 90 minutes. If GPP flare symptoms persist, an additional IV 900mg dose (over 90 minutes) may be administered one week after the initial dose.

As a monoclonal antibody, spesolimab-sbzo is not expected to undergo hepatic or renal elimination. No formal study of the effect of hepatic or renal impairment on the pharmacokinetics of spesolimab-sbzo was conducted.

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Spevigo® IV) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included asthenia and fatigue (9%), nausea and vomiting (3%), headache (3%), pruritus and prurigo (6%), infusion site hematoma and bruising (6%), urinary tract infection (6%), bacteremia (3%), bacteriuria (3%), cellulitis (3%), herpes dermatitis and oral herpes (3%), upper respiratory tract infection (3%), dyspnea (3%), eye edema (3%), and urticaria (3%).

Spevigo® may increase the risk of infections. In patients with a chronic infection or a history of recurrent infection, consider the potential risks and expected clinical benefits of treatment prior to prescribing Spevigo®. Treatment with Spevigo® is not recommended for use in patients with any clinically important active infection until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur during or after treatment with Spevigo®. If a patient develops a clinically important active infection, discontinue Spevigo® therapy until the infection resolves or is adequately treated.

Assess patients for TB infection prior to starting treatment with Spevigo®. Avoid use of Spevigo® in patients with active TB infection. Consider starting anti-TB therapy prior to starting Spevigo® in patients with latent TB or a history of TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after Spevigo® treatment.

Spevigo®-associated hypersensitivity reactions may include immediate reactions such as anaphylaxis and delayed reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS has been reported in clinical trials with spesolimab-sbzo in subjects with GPP. If a patient develops signs of anaphylaxis or other serious hypersensitivity, discontinue Spevigo® immediately and start appropriate treatment. Spevigo® is contraindicated in patients with severe or life-threatening hypersensitivity to spesolimab-sbzo or any of the excipients of the product. If a patient develops mild or moderate hypersensitivity reactions during an infusion or other infusion-related reactions, stop Spevigo® infusion and consider appropriate medical therapy. Upon resolution of the reaction, the infusion may be restarted at a slower infusion rate with gradual increase to complete the infusion.

Prior to starting Spevigo®, complete all age-appropriate vaccinations per current immunization guidelines. Avoid the use of live vaccines in patients during and for at least 16 weeks after treatment with Spevigo®. No specific studies have been conducted in Spevigo®-treated patients who have recently received live viral or live bacterial vaccines.

Contraindications: In patients with severe or life-threatening hypersensitivity to spesolimab-sbzo or to any of the excipients of the product.

Manufacturer: Boehringer Ingelheim Pharmaceuticals.

Analysis: The safety and efficacy of intravenous Spevigo® were assessed in a randomized, double-blind, placebo-controlled study (Effisayil-1) that included adult subjects with flares of generalized pustular psoriasis (GPP). Subjects were randomized if they had a flare of GPP of moderate-to-severe intensity, as defined by:

- A Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score of at least 3 (moderate) [the total GPPPGA score ranges from 0 (clear) to 4 (severe)],
- The 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.

Subjects were required to discontinue systemic and topical therapy for GPP prior to receiving study drug. Patients (N=53) were randomized to receive a single IV dose of 900mg Spevigo® or placebo during the double-blind portion of the study. The mean age of the study population was 43 years (range 21 to 69), while 68% were female and 55% were Asian. Most subjects had a GPPPGA pustulation sub score of 3 (43%) or 4 (36%), and subjects had a GPPPGA total score of 3 (81%) or 4 (19%). In this study, 25% of subjects had been previously treated with biologic therapy for GPP. At baseline acute flare, of the subjects with white blood cell count (WBC) assessments, 45% and 31% of subjects in the Spevigo® and placebo groups, respectively, had WBC >12 X 10^9/L. Of subjects with WBC assessments, 12% and 6% of subjects in the Spevigo® and placebo groups, respectively, had both WBC >12 X 10^9/L and temperature >38° Celsius.

The primary endpoint was the proportion of subjects with a GPPPGA pustulation sub score of 0 (indicating no visible pustules) at week 1 after treatment. The results are presented in the table below, which was adapted from the prescribing information.

	Spevigo® IV (N=35)	Placebo (N=18)
Subjects achieving a GPPPGA pustulation sub score of 0, n (%)	19 (54%)	1 (6%)
Risk difference vs placebo, %	49%	
NNT *calculated by CHC*	3	

In this study, subjects in either treatment group who continued to experience flare symptoms at week 1 were eligible to receive a single open-label IV dose of 900mg of Spevigo® (second dose and first dose for subjects in the Spevigo® and placebo groups, respectively). At week 1, 12 subjects (34%) in the IV Spevigo® group and 15 subjects (83%) in the placebo group received open-label Spevigo®. In subjects who were randomized to IV Spevigo® and received an open-label dose of Spevigo® at week 1, 5 subjects (42%) had a GPPPGA pustulation sub score of 0 at week 2 (one week after their second dose of Spevigo®).

The safety and efficacy of subcutaneous (SC) Spevigo® were assessed in a randomized, double-blind, placebo-controlled study (Effisayil-2) that included adults and pediatric subjects 12 years of age and older and weighing at least 40kg who had a history of at least two GPP flares of moderate-to-severe intensity. Subjects were randomized if they had a GPPPGA total score of 0 or 1 at screening and randomization, and they were required to discontinue systemic and topical therapy for GPP prior to or at randomization. In addition, subjects must have had a history of flaring while on concomitant treatment for GPP or a history of flaring upon dose reduction or discontinuation of these concomitant medications. Subjects (N=123) were randomized to one of four treatment arms, including Spevigo® 600mg SC loading dose (LD) followed by 300mg SC Q4W; Spevigo® 600mg SC LD followed by 300mg SC Q12W; Spevigo® 300mg SC LD followed by 150mg SC Q12W; or placebo SC LD followed by SC treatment Q4W.

While a 600mg LD of Spevigo® followed by 300mg Q12W dosage and a 300mg LD of Spevigo® followed by 150mg Q12W dosage were studied in this study, these dosages are not approved. The recommended dosage of Spevigo® for the treatment of GPP when not experiencing a flare is a SC LD of 600mg followed by 300mg SC Q4W. The results summarized here are those for the recommended dosage regimen.

The study population had a mean age of 40 years (range 14 to 75), with 8 pediatric patients (7%), while 38% were male, 64% were Asian, 28% had a GPPPGA pustulation subscore of 1, 72% had a GPPPGA pustulation subscore of 0, 86% had a GPPPGA total score of 1, and 14% had a GPPPGA total score of 0. At the time of randomization, 75% were treated with systemic therapy for GPP, which was discontinued at the start of the randomized study treatment.

Subjects who experienced a GPP flare were eligible to receive up to two open-label IV doses of 900mg Spevigo®. Two subjects in the SC Spevigo® 600mg LD/300mg Q4W arm and 48% in the placebo arm received IV Spevigo® for treatment of GPP flare.

The primary endpoint of this study was the time to the first GPP flare up to week 48 (defined by a GPPPGA pustulation subscore of ≥2 and an increase in GPPPGA total score by ≥2 from baseline). The key secondary endpoint was the occurrence of at least one GPP flare up to week 48. The number of subjects who experienced at least one GPP flare are presented in the table below, which was adapted from the prescribing information.

	Spevigo® SC (N=30)	Placebo (N=31)
Subjects with GPP flares n (%)	3 (10%)	16 (52%)
Risk difference for GPP flare occurrence vs placebo, %	-39%	
NNT *calculated by CHC*	3	

The estimated probability of first GPP flare up to week 48 was 0.1 for Spevigo® vs 0.5 for placebo.

Place in Therapy: Spevigo® is an interleukin-36 receptor antagonist indicated for the treatment of generalized pustular psoriasis (GPP) in adults and pediatric patients 12 years of age and older and weighing at least 40kg. It is to be administered as a single IV infusion for treatment of GPP flare; however, if GPP flare symptoms persist, an additional IV dose may be administered one week after the initial dose. It is to be used as a SC injection for treatment of GPP when not experiencing a flare. A loading dose should be administered by a healthcare professional, but subsequent doses may be self-injected or injected by caregiver once the healthcare professional determines it is appropriate. Assess patients for active or latent TB infection prior to treatment initiation, and Spevigo® initiation is not recommended in patients with active TB infection. In addition, complete all age-appropriate vaccinations per current immunization guidelines prior to starting Spevigo® for treatment of GPP.

The safety and efficacy of IV Spevigo® were assessed in a randomized, double-blind, placebo-controlled trial that included adults with flares of GPP of moderate-to-severe intensity. Results suggested that a greater number in the Spevigo® group achieved a GPPPGA pustulation sub score of 0 than in the placebo group (NNT 3). Per the full-text study by Bachelez et al[2], the difference between Spevigo® and placebo for this primary endpoint was statistically significant ($p<0.001$). The safety and efficacy of SC Spevigo® were assessed in a randomized, double-blind study that included subjects with a history of at least 2 GPP flares of moderate-to-severe intensity. More subjects in the placebo group experienced at least one GPP flare as compared with the Spevigo® group. Spevigo® is currently the only FDA approved treatment for GPP.

Summary

It is recommended that Spevigo® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Spevigo® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2024.
[2] Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. NEJM; 2021; 385(26): 2431-2440.

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