NEW DRUG APPROVAL

Brand Name	Spevigo®
Generic Name	spesolimab-sbzo
Drug Manufacturer	Boehringer Ingelheim Pharmaceuticals, Inc.

New Drug Approval

FDA approval date: September 01, 2022

Review designation: N/A; Orphan

Type of review: Biologic License Application (BLA): 761244

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Pustular psoriasis is a rare and extreme form of psoriasis characterized by the appearance of sterile pustules which can take many patterns. All the main pathological features of the disease are accentuated. Generalized pustular psoriasis is clinically heterogeneous in its age at onset, precipitants, severity, and natural history. Many overlapping clinical entities are recognized. There is a relationship between these entities and plaque psoriasis, as some individuals may have episodes of plaque psoriasis preceding or following the generalized pustular psoriasis, but in others generalized pustular psoriasis occurs as the sole phenotype without plaque psoriasis at any time.

Psoriasis is a relatively common disorder that occurs in children and adults worldwide, though the prevalence varies among populations. A systematic, worldwide review found the prevalence of psoriasis ranged from 0.5 to 11.4 percent in adults and 0 to 1.4 percent in children. The prevalence of psoriasis tends to increase with increasing distance from the equator.

There is no clear sex predilection for psoriasis. In addition, psoriasis can begin at any age, though it is less common in children than adults. Peak ages for the onset of psoriasis are between 30 and 39 years and between 50 and 69 years.

The incidence of psoriasis may be increasing. A population-based study in the United States found an increase in the incidence of psoriasis between the years 1970 to 1974 (50.8 cases per 100,000) and 1995 to 1999 (100.5 cases per 100,000). A rise in incidence was also detected among children, increasing from 29.6 cases per 100,000 to 62.7 cases per 100,000 during the same time periods. However, changes in diagnostic patterns over time may also contribute to increasing rates of diagnosis.

The male-to-female ratio for pustular psoriasis is 1:1 in the United States. Globally, a female predominance has been reported, with a female-to-male ratio of 1.5, 1.7, and 3.5, respectively, for individuals with acrodermatitis of Hallopeau, generalized pustular psoriasis, and palmoplantar pustulosis.

Efficacy

A randomized, double-blind, placebo-controlled study (Study Effisayil-1) [NCT03782792] was conducted to evaluate the clinical efficacy and safety of Spevigo® in 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 covered with erythema and the presence of pustules. Subjects were required to discontinue systemic and topical therapy for GPP prior to receiving study drug.

A total of 53 subjects were randomized (2:1) to receive a single intravenous dose of 900 mg Spevigo® (N=35) or placebo (N=18) (administered over 90 minutes) during the double-blind portion of the study.
The study population consisted of 32% men and 68% women. The mean age was 43 years (range: 21 to 69 years); 55% of subjects were Asian and 45% were White. Most subjects included in the study 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 109 /L. Seventeen percent and 11% of subjects in the Spevigo® and placebo groups, respectively, had temperature >38o Celsius. Of the subjects with WBC assessments, 12% and 6% of subjects in the Spevigo® and placebo groups, respectively, had both WBC >12 x 109 /L and temperature >38o Celsius.
The primary endpoint of the study was the proportion of subjects with a GPPPGA pustulation sub score of 0 (indicating no visible pustules) at Week 1 after treatment. The results of the primary endpoint are presented in Table 1.

Table 1 GPPPGA Pustulation Sub Score at Week 1 in Study Effisayil-1

	Spevigo® (N=35)	Placebo (N=18)
Subjects achieving a GPPPGA pustulation sub score of 0, n (%)	19 (54)	1 (6)
Risk difference versus placebo, % (95% CI)	49 (21, 67	

GPPPGA = Generalized Pustular Psoriasis Physician Global Assessment

In Study Effisayil-1, subjects in either treatment group who continued to experience flare symptoms at Week 1 were eligible to receive a single open-label intravenous dose of 900 mg of Spevigo® (second dose and first dose for subjects in the Spevigo® and placebo groups, respectively). At Week 1, 12 (34%) subjects and 15 subjects (83%) in the Spevigo® and placebo groups, respectively, received open-label Spevigo®. In subjects who were randomized to Spevigo® and received an open-label dose of Spevigo® at Week 1, 5 (42%) subjects had a GPPPGA pustulation sub score of 0 at Week 2 (one week after their second dose of Spevigo®). This study did not include enough subjects to determine if there are differences in response according to biological sex, age, race, baseline GPPPGA pustulation sub score, and baseline GPPPGA total score.

Safety

ADVERSE EVENTS

Most common adverse reactions (≥5%) are asthenia and fatigue, nausea and vomiting, headache, pruritus and prurigo, infusion site hematoma and bruising, and urinary tract infection.

WARNINGS & PRECAUTIONS

- Infections: Spevigo® may increase the risk of infections. Do not initiate Spevigo® during any clinically important active infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur after treatment with Spevigo®.
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with Spevigo®.

- Hypersensitivity and Infusion-Related Reactions: Hypersensitivity including drug reaction with eosinophilia and systemic symptoms (DRESS) and infusion-related reactions may occur. If a serious hypersensitivity reaction occurs, discontinue Spevigo® immediately and initiate appropriate treatment.
- Vaccinations: Do not administer live vaccines concurrently with Spevigo®.

CONTRAINDICATIONS

Severe or life-threatening hypersensitivity to spesolimab-sbzo or to any of the excipients in Spevigo®.

Clinical Pharmacology

MECHANISMS OF ACTION

Spesolimab-sbzo is a humanized monoclonal immunoglobulin G1 antibody that 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 cognate 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 the treatment of flares of GPP is unclear.

Dose & Administration

ADULTS

Administer as a single 900 mg dose by intravenous infusion over 90 minutes. If flare symptoms persist, may administer an additional intravenous 900 mg dose one week after the initial dose.

PEDIATRICS

The safety and effectiveness of Spevigo® in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

No dosage adjustments required.

HEPATIC IMPAIRMENT

No dosage adjustments required.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 450 mg/7.5 mL (60 mg/mL) solution in a single-dose vial.