Spevigo IV

PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Spevigo IV

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 450mg spesolimab.
Each mL of concentrate for solution for infusion contains 60 mg spesolimab. After dilution, each mL of the solution contains 9 mg spesolimab.
For the full list of excipients, see section 11.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

4. INDICATIONS AND USAGE

SPEVIGO is indicated for the treatment of generalized pustular psoriasis (GPP) flares in adults.

5. DOSAGE AND ADMINISTRATION

5.1 Testing and Procedures Prior to Treatment Initiation

Evaluate 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 *[see Warnings and Precautions (8.2)]*.

5.2 Important Administration Information

- SPEVIGO vials are for intravenous use for treatment of GPP flare.
- Intravenous infusion of SPEVIGO is only to be administered by a healthcare professional in a healthcare setting.
- Prepare SPEVIGO intravenous infusion by diluting SPEVIGO single-dose vials *[see Dosage and Administration (5.4)]*.
- Do not mix SPEVIGO with other medicinal products.

5.3 Recommended Intravenous Dosage for Treatment of GPP Flare Dose

The recommended dosage of SPEVIGO for treatment of GPP flare in adults is a a single 900 mg dose administered by intravenous infusion over 90 minutes.
If GPP flare symptoms persist, an additional intravenous 900 mg dose (over 90 minutes) may be administered one week after the initial dose.

5.4 Preparation and Administration Instructions

SPEVIGO must be diluted before use.

Parenteral drug products should be inspected visually for particulate matter and discoloration, whenever solution and container permits. SPEVIGO is a colorless to slightly brownish-yellow, clear to slightly opalescent solution. The solution is practically free from particles. Do not use if the solution is cloudy, discolored, or contains large or colored particulates.

Preparation

- SPEVIGO solution for intravenous infusion must be diluted before use.
- Use aseptic technique to prepare the solution for infusion.
- Draw and discard 15 mL from a 100 mL container of sterile 0.9% Sodium Chloride Injection.
- Slowly replace with 15 mL of SPEVIGO (two vials of 450 mg/7.5 mL).
- Mix gently before use.
- Use the diluted SPEVIGO solution immediately.

Administration

- Administer SPEVIGO as a continuous intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron) over 90 minutes.
- A pre-existing intravenous line may be used for administration of SPEVIGO. The line must be flushed with sterile 0.9% Sodium Chloride Injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.
- If the infusion is slowed or temporarily stopped, the total infusion time (including stop time) should not exceed 180 minutes *[see Warnings and Precautions (8.3)]*.
- No incompatibilities have been observed between SPEVIGO and infusion sets composed of polyvinylchloride (PVC), polyethylene (PE), polypropylene (PP), polybutadiene and polyurethane (PUR), and in-line filter membranes composed of polyethersulfone (PES, neutral and positively charged) and positively charged polyamide (PA).

Storage of Diluted Solution

Use the diluted solution immediately.
Protect from light.

6. DOSAGE FORMS AND STRENGTHS

SPEVIGO is a, colorless to slightly brownish-yellow, clear to slightly opalescent solution. The solution is practically free from particles.
Each vial contains: 450 mg/7.5 mL (60 mg/mL)in a single-dose vial for dilution prior to intravenous infusion

7. CONTRAINDICATIONS

SPEVIGO is contraindicated in patients with hypersensitivity to spesolimab or to any of the excipients in SPEVIGO. Reported hypersensitivity reactions have included drug reaction with eosinophilia and systemic symptoms (DRESS) *[see Warnings and Precautions (8.3) and Adverse Reactions (9.1)]*. For the full list of ingredients, see section 11.

8. WARNINGS AND PRECAUTIONS

8.1 Infections

SPEVIGO may increase the risk of infections. During the one-week placebo-controlled period in the Effisayil-1 trial, infections were reported in 14% of subjects treated with SPEVIGO compared with 6% of subjects treated with placebo *[see Adverse Reactions (9.1)]*.

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 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.

8.2 Risk of Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SPEVIGO. Avoid use of SPEVIGO in patients with active TB infection.

Consider initiating anti-TB therapy prior to initiating 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.

8.3 Hypersensitivity and Infusion-Related Reactions

SPEVIGO-associated hypersensitivity reactions may include immediate reactions such as anaphylaxis and delayed reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in clinical trials with SPEVIGO in subjects with GPP *[see Adverse Reactions (9.1)]*.

If a patient develops signs of anaphylaxis or other serious hypersensitivity, discontinue SPEVIGO immediately and initiate appropriate treatment. SPEVIGO is contraindicated in patients with hypersensitivity to spesolimab or to any of the excipients in SPEVIGO *[see Contraindications (7)]*.

If a patient develops mild or moderate hypersensitivity during an intravenous infusion or other infusion-related reactions, stop SPEVIGO infusion and consider appropriate medical therapy (e.g., systemic antihistamines and/or corticosteroids). Upon resolution of the reaction, the infusion may be restarted at a slower infusion rate with gradual increase to complete the infusion.

8.4 Vaccinations

Avoid 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.

8.5 Effects on ability to drive and use machines

Spevigo has no or negligible influence on the ability to drive and use machines.

9. ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Infections *[see Warnings and Precautions (8.1)]*
- Hypersensitivity and Infusion-Related Reactions *[see Warnings and Precautions (8.3)]*

9.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions with Intravenous SPEVIGO for Treatment of GPP Flare (Study Effisayil-1)

SPEVIGO was studied in Study Effisayil-1, a randomized, double-blind, placebo-controlled study comparing a single intravenous 900 mg dose of SPEVIGO (n=35) with placebo (n=18) in subjects with generalized pustular psoriasis (GPP) flare. 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. After Week 1 to Week 12, subjects in either treatment group whose GPP flare reoccurred after achieving a clinical response were eligible to receive a single open-label rescue intravenous dose of 900 mg of SPEVIGO, with a maximum of 3 total doses of SPEVIGO throughout the study. Six subjects received a single open-label rescue dose of SPEVIGO. Thirty-six subjects received 1 dose of SPEVIGO, 13 subjects received 2 doses of SPEVIGO, and 2 subjects received 3 doses of SPEVIGO throughout the study *[see Clinical Studies (14)]*.

Subjects ranged in age from 21 to 69 years (mean age of 43 years); 45% were White and 55% were Asian; and 68% were female.

Table 1 summarizes selected adverse reactions that occurred at a rate of at least 1% and at a higher rate in the intravenous SPEVIGO group than in the placebo group through Week 1.

Table 1 Selected Adverse Reactions Occurring in ≥1% of the Intravenous SPEVIGO Group and More Frequently than in the Placebo Group through Week 1 in Subjects with GPP Flare ((Study Effisayil-1)

Adverse Reaction	Intravenous SPEVIGO N = 35 n (%)	Placebo N = 18 n (%)
Asthenia and Fatigue	3 (9)	1 (6)
Headache	3 (9)	1 (6)
Nausea	2 (6)	0
Pruritus and prurigo	2 (6)	0
Infusion site hematoma and bruising	2 (6)	0
Urinary tract infection	2 (6)	0
Bacteremia	1 (3)	0
Bacteriuria	1 (3)	0
Cellulitis	1 (3)	0
Herpes dermatitis and oral herpes	1 (3)	0
Upper respiratory tract infection	1 (3)	0
Dyspnea	1 (3)	0
Eye edema	1 (3)	0
Urticaria	1 (3)	0

Specific Adverse Reactions

Infections

The most frequent adverse reactions that occurred in subjects treated with intravenous SPEVIGO were infections. During the 1-week placebo-controlled period in Study Effisayil-1, infections were reported in 14% of subjects treated with SPEVIGO compared with 6% of subjects treated with placebo. Serious infection (urinary tract infection) was reported in 1 subject (3%) treated with SPEVIGO and no subjects treated with placebo. Infections observed through Week 1 in Study Effisayil-1 in subjects treated with SPEVIGO were mild (29%) to moderate (71%).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Two cases of DRESS were reported in Study Effisayil-1 in subjects with GPP who were treated with intravenous SPEVIGO. RegiSCAR DRESS validation scoring (with the following categories: “no”, “possible”, “probable”, or “definite” DRESS) was applied to the reported cases. Reported cases were assessed as “no DRESS” and “possible DRESS”.

Safety through Week 12 and 17

In Study Effisayil-1, additional adverse reactions that occurred through Week 12 in subjects treated with 1 single intravenous dose of randomized SPEVIGO were mild to moderate infections: device-related infection (3%), subcutaneous abscess (3%), furuncle (3%), and influenza (3%).

Additional adverse reactions that occurred through Week 17 in subjects treated with a single intravenous dose of open-label SPEVIGO at Week 1 (second dose and first dose for subjects in the SPEVIGO and placebo groups, respectively) were mild to moderate infections: otitis externa (7%), vulvovaginal candidiasis (4%), vulvovaginal mycotic infection (4%), latent tuberculosis (4%), diarrhea (11%), and gastritis (4%). No new adverse reactions were identified for up to 16 weeks in subjects treated with a single intravenous dose of open-label rescue SPEVIGO from Week 1 to Week 12 (range 1-3 total doses).

Clinical Development of Spesolimab

Guillain-Barre syndrome

Among approximately 835 subjects exposed to spesolimab during clinical development, Guillain-Barre syndrome (GBS) was reported in 3 subjects who received various doses of spesolimab via various methods of administration in clinical trials for unapproved indications.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important.
It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

10. USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

The limited data on the use of SPEVIGO in pregnant women are insufficient to inform a drug-associated risk of adverse pregnancy-related outcomes. Human IgG is known to cross the placental barrier; therefore, SPEVIGO may be transmitted from the mother to the developing fetus. In an animal reproduction study, intravenous administration of a surrogate antibody against IL36R in mice during the period of organogenesis did not elicit any reproductive toxicity *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Embryo-fetal development and pre- and postnatal development toxicity studies were performed in mice using a surrogate mouse specific IL36R antagonist monoclonal antibody. In the embryo-fetal development study, the surrogate was administered intravenously at doses up to 50 mg/kg to pregnant female mice twice weekly during the period of organogenesis. The surrogate was not associated with embryo-fetal lethality or fetal malformations. In the pre- and postnatal development toxicity study, the surrogate was administered intravenously at doses up to 50 mg/kg to pregnant female mice twice weekly from gestation day 6 through lactation day 18. There were no maternal effects observed. There were no treatment-related effects observed on postnatal developmental, neurobehavioral, or reproductive performance of offspring.

10.2 Lactation

Risk Summary

There are no data on the presence of spesolimab in human milk, the effects on the breastfed infant, or the effects on milk production. Spesolimab is a monoclonal antibody and is expected to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SPEVIGO and any potential adverse effects on the breastfed infant from SPEVIGO or from the underlying maternal condition.

10.3 Pediatric Use

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

10.4 Geriatric Use
There were 2 (6%) intravenous SPEVIGO-treated subjects 65 to 74 years of age and no subjects 75 years of age or older in Study Effisayil-1. Clinical studies of SPEVIGO did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

11. DESCRIPTION
Spesolimab, an interleukin-36 receptor antagonist, is a humanized monoclonal IgG1 antibody (mAb) against human IL-36R produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Spesolimab has a molecular weight of approximately 146 kDa.

SPEVIGO (spesolimab) injection is a sterile, preservative-free, colorless to slightly brownish-yellow, clear to slightly opalescent solution supplied in a single-dose vial for intravenous use. The solution is practically free from particles. Each 7.5 mL vial contains 450 mg spesolimab, sucrose, arginine hydrochloride, sodium acetate, polysorbate 20, glacial acetic acid, and Water for Injection.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Spesolimab is a humanized monoclonal immunoglobulin G1 antibody that inhibits interleukin-36 (IL-36) signaling by specifically binding to the IL36R. Binding of spesolimab 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 the treatment of flares of GPP is unclear.

12.2 Pharmacodynamics
The pharmacodynamics of SPEVIGO in the treatment of patients with GPP have not been fully characterized.

12.3 Pharmacokinetics
A population pharmacokinetic model was developed based on data collected from healthy subjects, patients with GPP, and patients with other diseases. After a single intravenous dose of 900 mg of SPEVIGO, the population PK model-estimated $AUC_{0-\infty}$ (95% CI) and C_{max} (95% CI) in a typical anti-drug antibody (ADA)-negative patient with GPP were 4750 (4510, 4970) mcg·day/mL and 238 (218, 256) mcg/mL, respectively.

When administered intravenously, spesolimab AUC increased dose-proportionally from 0.3 to 20 mg/kg, and CL and terminal half-life were independent of dose.

Distribution
Based on the population pharmacokinetic analysis, the typical total volume of distribution at steady state was 6.4 L.

Elimination
Metabolism
The metabolic pathway of spesolimab has not been characterized. As a humanized IgG1 monoclonal antibody, spesolimab is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner

similar to endogenous IgG.

Excretion
In the linear dose range (0.3 to 20 mg/kg), based on the population PK model, spesolimab clearance (95% CI) in a typical GPP patient without ADA, weighing 70 kg was 0.184 (0.175, 0.194) L/day. The terminal half- life was 25.5 (24.4, 26.3) days.

Specific Populations
Age, Gender, and Race
Based on population pharmacokinetic analyses, age, gender, and race did not have an effect on the pharmacokinetics of spesolimab.

Hepatic and Renal Impairment
As a monoclonal antibody, spesolimab 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 was conducted.

Body Weight
Spesolimab concentrations were increased in subjects with lower body weight and decreased in subjects with higher body weight. The clinical impact of body weight on spesolimab plasma concentrations is unknown.

Drug Interaction Studies
No formal drug interactions studies have been conducted with spesolimab. In patients with GPP, spesolimab is not expected to cause cytokine-mediated CYP interactions as a perpetrator.

12.4 Immunogenicity
The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of spesolimab or of other spesolimab products.

In subjects with GPP treated with intravenous SPEVIGO in Study Effisayil-1, ADAs formed with a median onset of 2.3 weeks. Following administration of 900 mg intravenous SPEVIGO, (12/50) 24% of subjects had a maximum ADA titer greater than 4000 and were neutralizing antibody (Nab)-positive by the end of the study (Weeks 12 to 17).
In Study Effisayil-1 following intravenous SPEVIGO, females appeared to have higher immunogenicity response; the percentage of subjects with ADA titer greater than 4000 was 30% in females, and 12% in males, respectively.

Anti-Drug Antibody Effects on Pharmacokinetics
In subjects with ADA titers below 4000, there was no apparent impact on spesolimab pharmacokinetics. In some subjects with ADA titer values greater than 4000, plasma spesolimab concentrations were significantly reduced after reaching this ADA titer.
In Study Effisayil-1, there are limited data on the impact of ADAs on safety and efficacy upon retreatment as the majority of subjects did not experience a subsequent, new flare in an open-label extension study.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity and mutagenicity studies have not been conducted with spesolimab.

No adverse effects on fertility were observed in male or female mice that were intravenously administered a surrogate antibody to IL36R at doses up to 50 mg/kg twice weekly.

14 CLINICAL STUDIES

Intravenous SPEVIGO for Treatment of GPP Flare (Study Effisayil-1)

A randomized, double-blind, placebo-controlled study (Study Effisayil-1) [NCT03782792] was conducted to evaluate the clinical efficacy and safety of intravenous 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% male and 68% female. The mean age was 43 years (range: 21 to 69 years); 55% of subjects were Asian and 45% were White. For ethnicity, there were no subjects that identified as Hispanic or Latino in the study. 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 intravenous SPEVIGO and placebo groups, respectively, had (WBC) >12 x 10^9/L. Seventeen percent and 11% of subjects in the intravenous 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 10^9/L and temperature >38º Celsius *[see Adverse Reactions (9.1)]*.

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.

Clinical Response

The results of the primary endpoint are presented in Table 2.

Table 2 GPPPGA Pustulation Sub Score at Week 1 in Adult Subjects with Flares of GPP in Study Effisayil-1 (Intravenous SPEVIGO)

	Intravenous 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 intravenous SPEVIGO and placebo groups, respectively, received open-label SPEVIGO. In subjects who were randomized to intravenous 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 sufficient numbers of 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.

15. HOW SUPPLIED/STORAGE AND HANDLING

How supplied:
SPEVIGO injection is a sterile, preservative-free, colorless to slightly brownish-yellow, clear to slightly opalescent concentrate for solution for intravenous infusion. The solution is practically free from particles.

Each carton contains two single-dose 450 mg/7.5 mL (60 mg/mL) glass vials.

Storage and Handling
The expiry date of the product is indicated on the packaging materials.
Must be refrigerated, store at 2°C to 8°C in original carton to protect from light. Do not freeze.

Prior to dilution, may store unopened SPEVIGO vials up to 30°C for up to 24 hours in the original carton to protect from light.

Storage of Diluted Solution: Use the diluted solution immediately.

16 MANUFACTURER

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17 MARKETING AUTHORISATION HOLDER

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18 MARKETING AUTHORISATION NUMBER(S)

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