SPEVIGO

1. NAME OF THE MEDICINAL PRODUCT

Spevigo 450 mg concentrate for solution for infusion

2. QUALTITATIVE AND QUANTITATVE COMPOSITION

Each vial contains 450 mg spesolimab in 7.5 mL.

Each mL of concentrate for solution for infusion contains 60 mg spesolimab.

After dilution, each mL of the solution contains 9 mg spesolimab (see section 6.6).

Spesolimab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to slightly brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spevigo is indicated for the treatment of flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.

4.2 Posology and method of administration

Treatment should be initiated and supervised by physicians experienced in the management of patients with inflammatory skin diseases.

Posology

The recommended dose is a single dose of 900 mg (two 450 mg/7.5 mL vials) administered as an intravenous infusion.

If flare symptoms persist, an additional 900 mg dose (two 450 mg/7.5 mL vials) may be administered 1 week after the initial dose.
Clinical data for treatment of subsequent flares is very limited (see section 4.4).

Clinical data for concomitant use of other GPP treatments with spesolimab is limited. Spesolimab should not be used in combination with other GPP treatments, e.g. systemic immunosuppressants, to treat a flare (see sections 4.4 and 4.5).

Elderly
No dose adjustment is required.

Renal and/or hepatic impairment
SPEVIGO has not been studied in these patient populations. These conditions are generally not expected to have any clinically relevant impact on the pharmacokinetics of monoclonal antibodies and no dose adjustments are considered necessary.

Paediatric population
The safety and efficacy of spesolimab in adolescents aged 12 to 18 years have not been established. No data are available.
There is no relevant use of spesolimab in children below the age of 12 years.

Method of administration

This medicinal product is for intravenous infusion only. It should not be administered as an intravenous push or bolus.

Following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, it is administered 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. No other infusion should be administered in parallel via the same intravenous access.

In the event that the infusion is slowed or temporarily stopped, the total infusion time (including stop time) should not exceed 180 minutes (see section 4.4).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

Clinically important active infections (e.g. active tuberculosis, see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infections

Spesolimab may increase the risk of infections (see section 4.8).

In patients with a chronic infection or a history of recurrent infection, the potential risks and expected clinical benefits of treatment should be considered prior to prescribing spesolimab. Treatment with spesolimab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Patients should be instructed to seek medical advice if signs or symptoms of clinically important infection occur after treatment with spesolimab.

Pre-treatment evaluation for tuberculosis

Prior to initiating treatment with spesolimab, patients should be evaluated for tuberculosis (TB) infection. Spesolimab is contraindicated to patients with active TB infection (see section 4.3).

Anti-TB therapy should be considered prior to initiating spesolimab treatment in patients with latent TB, a history of TB or possible previous exposure to people with active tuberculosis in whom an adequate course of treatment cannot be confirmed. After spesolimab treatment, patients should be monitored for signs and symptoms of active TB.

Hypersensitivity and infusion-related reactions

Hypersensitivity and infusion-related reactions may occur with monoclonal antibodies such as spesolimab. Hypersensitivity may include immediate reactions such as anaphylaxis and delayed reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS).

Immediate hypersensitivity reactions, including anaphylactic reactions have been reported in patients treated with SPEVIGO (see section 4.8).

If a patient develops signs of anaphylaxis or other serious hypersensitivity, spesolimab treatment should be discontinued immediately and appropriate treatment should be initiated (see section 4.3).

If a patient develops mild or moderate hypersensitivity during the infusion, treatment should be stopped and appropriate medical therapy should be considered (e.g., systemic anti-histamines 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 (see section 4.2).

Use in patients with an immediate, life-threatening GPP flare

There is no experience from the use of spesolimab in patients with an immediate, life-threatening flare of GPP or a flare requiring intensive care treatment.

Concomitant use with other GPP treatments

The safety and efficacy of spesolimab in combination with immunosuppressants, including biologics, have not been evaluated systematically (see section 4.5). In the GPP flare treatment clinical study, there was a washout period for most other treatments (biologics, other systemic immunomodulating treatments), while some treatments were discontinued before initiation of spesolimab treatment with no washout period required (methotrexate, cyclosporine, retinoids, topical treatments) (see section 5.1).

Concomitant use of other immunosuppressants and spesolimab is not recommended. At initiation of spesolimab treatment, other GPP treatments should be stopped and other treatments (e.g. with systemic

immunosuppressants) should not be used concomitantly to treat the flare.

Re-treatment

Very limited efficacy and safety data are available for re-treatment with spesolimab for a subsequent new flare. Data are available for five patients with GPP who received re-treatment at a subsequent new flare and followed up for a minimum of 8 weeks.

Immunisations

It is unknown whether spesolimab affects the efficacy of vaccines.

No data are available on the potential secondary transmission of infection by live vaccines in patients receiving spesolimab (see section 4.5). The interval between live vaccinations and initiation of spesolimab therapy should be at least 4 weeks. Live vaccines should not be administered for at least 16 weeks after treatment with spesolimab.

Peripheral neuropathy

The potential for peripheral neuropathy with SPEVIGO is unknown. Cases of peripheral neuropathy have been reported in clinical trials with spesolimab. Physicians should be vigilant for symptoms potentially indicative of new-onset peripheral neuropathy.

Excipients

SPEVIGO contains polysorbate 20
This medicine contains 3 mg of polysorbate 20 in each 7.5 ml vial. Polysorbates may cause allergic reactions.

SPEVIGO contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. For the treatment of GPP flares, spesolimab is not expected to cause cytokine mediated CYP interaction as a perpetrator.

Live vaccines should not be given concurrently with spesolimab (see section 4.4).

There is limited experience from the use of spesolimab in combination with immunosuppressants in GPP patients (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of spesolimab in pregnant women. Non-clinical studies using a surrogate, mouse specific anti-IL36R monoclonal antibody do not indicate direct or indirect harmful

effects with respect to reproductive toxicity (see section 5.3). Human immunoglobulin (IgG) is known to cross the placental barrier. As a precautionary measure, it is preferable to avoid the use of spesolimab during pregnancy.

Breast-feeding

No data are present on excretion of spesolimab in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, transfer of IgG antibodies to the newborns through milk, may happen during the first few days. In this short period, a risk to the breastfed child cannot be excluded. Afterwards, spesolimab can be used during breastfeeding if clinically needed. When treatment has occurred up to the last few months of pregnancy, breastfeeding can be started immediately after birth.

Fertility

There are no data available on the effect of spesolimab on human fertility. Studies in mice using a surrogate, mouse specific anti-IL36R monoclonal antibody, do not indicate direct or indirect harmful effects with respect to fertility from antagonism of IL36R (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions are infections (17.1%) with urinary tract infection reported as serious in 1 patient (2.9%).

Tabulated summary of adverse reactions

Table 1 provides a list of the adverse reactions reported from clinical trials. The adverse reactions are listed by MedDRA System Organ Class (SOC) an d. frequency category using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (frequency cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Adverse reactions	Frequencies
Infections and infestations	Infection[a)]	Very common
Immune system disorders	Hypersensitivity[b)]	Not known
Skin and subcutaneous tissue	Pruritus	Common
General disorders and administration site conditions	Injection site reactions	Very common[c)]
	Fatigue	Common

[a)] The most commonly reported infections were Urinary tract infection (Common) and Upper respiratory tract infection (Common)
[b)] derived from open-label extension trials and post-marketing experience
[c)] Not reported in Effisayil 1

Description of selected adverse reactions

Infections
During the 1-week placebo-controlled period in Effisayil 1, infections were reported in 17.1% of patients treated with spesolimab compared with 5.6% of patients treated with placebo. Serious infection (urinary tract infection) was reported in 1 patient (2.9%) in the spesolimab group and no patients in the placebo group. Infections observed in clinical trials with spesolimab were generally mild to moderate with no distinct pattern regarding pathogen or type of infection.

Hypersensitivity
Hypersensitivity comprises immediate systemic hypersensitivity reactions, including anaphylactic reaction. Immediate systemic hypersensitivity reactions have been reported in open-label extension trials and the post-marketing setting.

Injection site reactions
Injection site reactions include injection site erythema, injection site swelling, injection site pain, injection site induration, and injection site warmth. Injection site reactions were typically mild to moderate in severity.

Immunogenicity
In patients with GPP treated with spesolimab in Effisayil 1, anti-drug antibodies (ADA) formed with a median onset of 2.3 weeks. Following intravenous administration of spesolimab 900 mg, 24% of patients had a maximum ADA titer greater than 4 000 and were Neutralising antibody-positive by end of the trial (weeks 12 to 17). Females appeared to have higher immunogenicity response; the percentage of patients with ADA titer greater than 4 000 was 30% in females, and 12% in males, respectively.

In some patients with ADA titer values > 4 000, plasma spesolimab concentrations were reduced, with no apparent impact on pharmacokinetics at ADA titers below 4 000.

As the majority of patients did not experience a subsequent new flare in Effisayil 1, the data on re-treatment of patients with ADA (n = 4) is limited. It is currently unknown if there is a correlation between the presence of ADA to spesolimab and maintenance of efficacy or hypersensitivity reactions upon re-treatment.

4.9 Overdose

The highest dose of spesolimab administered in clinical trials was 1 200 mg. Adverse reactions observed in subjects receiving single or repeated doses up to 1 200 mg were consistent with the known safety profile of spesolimab.

In the event of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and symptomatic treatment be instituted as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors. ATC code: L04AC22

Mechanism of action

Spesolimab is a humanised antagonistic monoclonal immunoglobulin G1 (IgG1) antibody blocking human IL36R signalling. Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory pathways.

Pharmacodynamic effects

Following treatment with spesolimab in patients with GPP, reduced levels of C-reactive protein (CRP), IL6, T helper cell (Th1/Th17) mediated cytokines, keratinocyte-mediated inflammation, neutrophilic mediators, and proinflammatory cytokines were observed in serum and skin at week 1 compared to baseline and was associated with a decrease in clinical severity. These reductions in biomarkers became more pronounced at the last measurement at week 8 in Effisayil 1.

Clinical efficacy and safety

Effisayil 1 (1368-0013)
A randomised, double-blind, placebo-controlled study (Effisayil 1) was conducted to evaluate the clinical efficacy and safety of spesolimab in adult patients with flares of Generalised Pustular Psoriasis (GPP), as diagnosed per European Rare And Severe Psoriasis Expert Network (ERASPEN) criteria, regardless of IL36RN mutation status. Patients were randomised if they had a flare of GPP of moderate-to-severe intensity, as defined by a Generalised Pustular Psoriasis Physician Global Assessment (GPPGA) total score (which ranges from 0 [clear] to 4 [severe]) of at least 3 (moderate), presence of fresh pustules (new appearance or worsening of pustules), GPPGA pustulation sub score of at least 2 (mild), and at least 5% of body surface area covered with erythema and the presence of pustules. Patients were required to discontinue systemic and topical therapy for GPP prior to randomisation (see Table 2). Patients with an immediate life-threatening flare of GPP or requiring intensive care treatment were excluded from the study.

Table 2: Minimum time between discontinuation of restricted medications for GPP treatment and randomisation

Duration of washout period	Medications or class of medications
2 months	adalimumab, alemtuzumab, briakinumab, brodalumab, efalizumab, guselkumab, infliximab, ixekizumab, natalizumab, risankizumab, rituximab, secukinumab, tildrakizumab, ustekinumab, visilizumab, investigational products for psoriasis (non biologics)
6 weeks	etanercept
30 days	systemic immunomodulatory treatments (e.g. corticosteroids*, cyclophosphamide), tofacitinib, apremilast; systemic psoriasis treatments (e.g. fumarates); photochemotherapy (e.g. PUVA); granulocytes and monocytes adsorptive apharesis
7 days	phototherapy (e.g. UVA, UVB), topical treatment for psoriasis or any other skin condition (e.g. topical corticosteroids, topical vitamin D analogues, tar, anthralin, topical retinoids), anakinra

* No restriction on inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear.

The primary endpoint of the study was the proportion of patients with a GPPGA pustulation sub score of 0 (indicating no visible pustules) at week 1 after treatment. The key secondary endpoint of the study was the proportion of patients with a GPPGA total score of 0 or 1 (clear or almost clear skin) at week 1. For the GPPGA pustulation sub score of 0, the GPPGA total score of 0/1 and the GPPASI 75, non-responder imputation was used to handle the occurrence of escape (treatment at the investigator's choice if the

disease worsened) and rescue (single 900 mg dose of intravenous spesolimab) medication use and missing data.

A total of 53 patients were randomised (2:1) to receive a single intravenous dose of 900 mg spesolimab (n = 35) or placebo (n = 18). Patients in either treatment arm who still experienced flare symptoms at week 1 were eligible to receive a single intravenous dose of open-label 900 mg spesolimab, resulting in 12 patients (34%) in the spesolimab arm receiving a second dose of spesolimab and 15 patients (83%) in the placebo arm receiving one dose of spesolimab on day 8. In addition, 6 patients (4 spesolimab arm; 2 placebo arm) received rescue treatment with a single 900 mg dose of intravenous spesolimab for reoccurrence of a flare after day 8.

The study population consisted of 32% men and 68% women. The mean age was 43 (range: 21 to 69) years; 55% of patients were Asian and 45% were Caucasian. Most patients included in the study had a GPPGA pustulation sub score of 3 (43%) or 4 (36%), and patients had a GPPGA total score of 3 (81%) or 4 (19%). 24.5% of patients had been previously treated with biologic therapy for GPP.

Primary and key secondary efficacy
At week 1, there was a statistically significant difference in the proportion of patients achieving a GPPGA pustulation sub score of 0 (indicating no visible pustules) and GPPGA total score of 0 or 1 (clear or almost clear skin) in the spesolimab arm compared with placebo (see Table 3).

Table 3: GPPGA pustulation sub score and GPPGA total score at week 1

	Placebo	Spesolimab 900mg iv
Number of Patients analysed	18	35
Patients achieving a GPPGA pustulation sub score of 0, n (%)	1 (5.6)	19 (54.3)
p-value*	0.0004	
Patients achieving a GPPGA total score of 0 or 1, n (%)	2 (11.1)	15 (42.9)
p-value*	0.0118	

GPPGA = Generalized Pustular Psoriasis Physician Global Assessment; iv = intravenous
*One-sided p-value

For both the primary and the key secondary endpoint, treatment effect was observed for all patients regardless of the IL36RN mutation status.

5.2 Pharmacokinetics properties

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, the population PK model-estimated AUC0-∞ (95% CI) and Cmax (95% CI) in a typical ADA-negative patient with GPP were 4 750 (4 510, 4 970) µg·day/mL and 238 (218, 256) µg/mL, respectively. In some patients with ADA titer values > 4 000, plasma spesolimab concentrations were reduced, with no apparent impact on pharmacokinetics at ADA titers below 4 000 (see section 4.8).

Distribution

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

Biotransformation

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.

Elimination

In the linear dose range (0.3-20 mg/kg), based on the population PK model, spesolimab clearance (95% CI) in a typical ADA-negative patient with GPP, weighing 70 kg was 0.184 L/day. The terminal-half-life was 25.5 days. Clearance of spesolimab was increased in some patients with ADA titer values > 4 000.

Linearity/non-linearity

At low doses, spesolimab exhibited target-mediated drug disposition (TMDD) kinetics after single intravenous dose administration. At doses from 0.01 to 0.3 mg/kg, both clearance (CL) and terminal half-life were dose dependent, and systemic exposure (AUC) increased more than dose proportionally with dose. The saturation of the nonlinear elimination pathway occurred at about 0.3 mg/kg as spesolimab AUC increased approximately linearly with dose from 0.3 to 20 mg/kg, and CL and terminal half-life were independent of dose.

Body weight
Spesolimab concentrations were lower in subjects with higher body weight. The impact of body weight on spesolimab exposure is not expected to be clinically meaningful up to approximately 130 kg. The clinical relevance of higher body weight greater than 130 kg is unknown.

Elderly / Gender / Race

Based on population pharmacokinetic analyses, age, gender and race do 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 trial of the effect of hepatic or renal impairment on the pharmacokinetics of spesolimab was conducted.

Population PK analysis did not identify mild hepatic impairment or mild or moderate renal impairment as having an influence on the systemic exposure of spesolimab.

Paediatric population

The pharmacokinetics of spesolimab in paediatric patients has not yet been studied.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity studies.

Developmental and reproductive toxicity

Non-clinical studies conducted in mice using a surrogate antibody directed towards murine IL36R do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development or fertility.

Genotoxicity

Genotoxicity studies have not been conducted with spesolimab.

Carcinogenicity

Carcinogenicity and mutagenicity studies have not been conducted with spesolimab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate (E262)
Glacial acetic acid (E260) (for pH adjustment)
Sucrose
Arginine hydrochloride
Polysorbate 20 (E432)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After opening

From a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately.

After preparation of infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2 °C to 30 °C.

From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in use storage conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions. For the time between preparation and start of administration the solution for infusion should be protected from light following

local standard procedures.

6.4 Special precautions for storage

SPEVIGO has to be stored in the refrigerator (2 °C – 8 °C).

SPEVIGO must not be frozen.

Store in the original package in order to protect from light.
Prior to use, the unopened vial may be kept at temperatures up to 30 °C for up to 24 hours, if stored in the original package in order to protect from light.

For storage conditions after opening and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

7.5 mL concentrate in a colourless 10 mL glass vial (type I glass), with a coated rubber stopper and aluminium crimp cap with blue plastic button.

Pack size of 2 vials.

6.6 Special precautions for disposal and other handling

This medicinal product is compatible with 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).

Handling instructions

- The vial should be visually inspected before use. If the solution is cloudy, discoloured, or contains large or coloured particulates, the vial should be discarded.
- Spevigo is for single use only.
- Aseptic technique must be used to prepare the solution for infusion. Draw and discard 15 mL from a 100 mL container of sodium chloride 9 mg/mL (0.9%) solution for injection and replace slowly with 15 mL spesolimab sterile concentrate (two vials of 450 mg/7.5 mL). Mix gently before use. The diluted spesolimab infusion solution should be used immediately.
- Spevigo must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of diluted spesolimab infusion solution, if the compatibility information above is considered. The line must be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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for

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8. PRODUCT REGISTRATION NUMBER

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9. DATE OF REVISION

15 May 2025