

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Spevigo 450 mg concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE 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).

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

Excipients with known effect

Each vial contains 3 mg polysorbate 20 (E432).

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 generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age 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.

Treatment can be initiated with the pre-filled syringe as a subcutaneous injection to prevent GPP flares (please refer to the Summary of Product Characteristics for Spevigo 150 mg and 300 mg solution for injection in pre-filled syringe) or with an intravenous dose of spesolimab to treat a GPP flare.

Posology

The recommended dose for GPP flare treatment in adults and adolescents from 12 years of age and weighing at least 40 kg is a single dose of 900 mg (two vials of 450 mg) administered as an intravenous infusion. If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose.

Spevigo has not been studied in patients weighing less than 40 kg. Based on pharmacokinetic modelling and simulation, the recommended dose for adolescents from 12 years of age weighing ≥ 30 and < 40 kg is a single dose of 450 mg (one vial of 450 mg) administered as an intravenous infusion (see section 5.2). If flare symptoms persist, an additional 450 mg dose (one vial of 450 mg) 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).

Special populations

Elderly

No dose adjustment is required.

Renal or hepatic impairment

Spevigo has not been formally 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 children less than 12 years of age has not been established. No data are available.

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 spesolimab (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 an intravenous infusion or other infusion-related reactions, 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. In Effisayil 1, five patients received re-treatment for a subsequent new flare and were 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.

For additional information regarding immunisation prior starting the treatment for preventing GPP flares, see Spevigo 150 mg solution for injection in pre-filled syringe Summary of Product Characteristics.

Peripheral neuropathy

The potential for peripheral neuropathy with spesolimab 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 with known effect

Polysorbates

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

Sodium

This medicinal product 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. In GPP patients, spesolimab is not expected to cause cytokine-mediated CYP interactions as a perpetrator.

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

There is limited experience from the concomitant use of spesolimab 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. If treatment was discontinued before the last trimester 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 frequently reported adverse reactions are infections (17.1%) with urinary tract infection reported as serious in 1 patient (2.9%) (see Description of selected adverse reactions).

Tabulated list of adverse reactions

Table 1 provides a list of the adverse reactions reported in clinical trials as well as in the post-marketing setting. The adverse reactions are listed by

MedDRA System Organ Class (SOC) and frequency category using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\ 000$ to $< 1/100$), rare ($\geq 1/10\ 000$ 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
<i>Infections and infestations</i>	Infection ^{a)}	Very common
<i>Immune system disorders</i>	Hypersensitivity ^{b)}	Not known
<i>Skin and subcutaneous tissue disorders</i>	Pruritus	Common
<i>General disorders and administration site conditions</i>	Injection site reactions	Very common ^{c)}
	Fatigue	Common

a) The most commonly reported infections were Urinary tract infection (Common) and Upper respiratory tract infection (Very 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. In Effisayil 1, serious infection (urinary tract infection) was reported in 1 patient (2.9%) in the spesolimab group and no patient in the placebo group. During the placebo-controlled period of up to 48 weeks in Effisayil 2, infections were reported in 33.3% of patients treated with Spevigo and 33.3% of patients treated with placebo. In Effisayil 2, serious infections were reported in 3 patients (3.2%) in the Spevigo group and no patient 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 erythema, swelling, pain, induration, warmth, exfoliation, papule, pruritus, rash, and urticaria at the injection site. Injection site reactions were typically mild to moderate in severity.

Paediatric population

The available data for adolescents are limited. 8 adolescent patients with GPP, 14 to 17 years of age, were enrolled in trial Effisayil 2 (see section 5.1).

Overall, the safety profile in adolescents treated with spesolimab (n = 6) was consistent with the safety profile in adults and no new safety concerns have been identified.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the **Google Play** or **Apple App Store**.

4.9 Overdose

The highest dose of spesolimab administered in clinical trials was 1 200 mg intravenously or subcutaneously. 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 interleukin 36 receptor (IL36R) signalling. Binding of spesolimab to IL36R prevents the subsequent activation of IL36R by its ligands (IL36 α , β and γ) and downstream activation of pro-inflammatory pathways.

Pharmacodynamic effects

Following treatment with intravenous spesolimab in patients with GPP, reduced levels of C-reactive protein (CRP), IL6, T helper cell (Th1/Th17) mediated cytokines, keratinocyte-mediated inflammation markers, neutrophilic mediators, and proinflammatory cytokines were observed in serum and skin at week 1 compared to baseline and were 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 (Effisayil 1)*

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; other systemic psoriasis treatments (e.g. fumarates), any investigational device or product (excluding psoriasis products); photochemotherapy (e.g. PUVA); granulocytes and monocytes adsorptive apheresis
7 days	anakinra

* No treatment initiation 1 week prior to randomisation: 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); no treatment initiation 2 weeks prior to randomisation, no dose escalation within 2 weeks prior to randomisation, and had to be discontinued prior to receiving the first dose: methotrexate, cyclosporine, retinoids.

** 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 and the GPPGA total score of 0/1, 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 flare 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 (Effisayil 1)

	Placebo	Spesolimab 900 mg i.v.
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 = Generalised Pustular Psoriasis Physician Global Assessment; i.v. = 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.

Effisayil 2 (1368-0027)

A randomised, double-blind, placebo-controlled phase II b study (Effisayil 2) evaluated the efficacy and safety of spesolimab for subcutaneous administration in adult and adolescent patients with a history of GPP, as diagnosed per ERASPEN criteria, regardless of IL36RN mutation status, and with at least two GPP flares of moderate-to-severe intensity in the past. Patients were randomised if they had a GPPGA total score of 0 or 1 at screening and randomisation. Patients were required to discontinue systemic and topical therapy for GPP prior to or at randomisation. These patients 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.

The primary endpoint of the study was the time to the first GPP flare up to week 48 (defined by a GPPGA pustulation subscore of ≥ 2 and an increase in GPPGA total score by ≥ 2 from baseline). The key secondary endpoint of the study was the occurrence of at least one GPP flare up to week 48. Additional secondary endpoints at week 48 were the time to the first worsening of Psoriasis Symptom Scale (PSS) and Dermatology Quality of Life Index (DLQI) defined as a 4-point increase in total score from baseline.

A total of 123 patients were randomised (1:1:1:1) to receive one of the four treatments (see Table 4).

Table 4: Treatment arms in Effisayil 2

	<i>Loading dose</i>	<i>Subsequent doses</i>
spesolimab	600 mg subcutaneously	300 mg subcutaneously every 4 weeks
spesolimab	600 mg subcutaneously	300 mg subcutaneously every 12 weeks
spesolimab	300 mg subcutaneously	150 mg subcutaneously every 12 weeks
Placebo	subcutaneous treatment	subcutaneous treatment every 4 weeks

The study population consisted of 38.2% men and 61.8% women. The mean age was 40.4 (range: 14 to 75) years with 8 (6.5%) adolescent patients (2 per treatment arm); 64.2% of patients were Asian and 35.8% were Caucasian. Patients included in the study had a GPPGA pustulation sub score of 1 (28.5%) or 0 (71.5%), and patients had a GPPGA total score of 1 (86.2%) or 0 (13.8%). At the time of randomisation, 74.8% of patients were treated with systemic therapy for GPP, which was discontinued at the start of the randomised study treatment.

While 3 dosing regimens were studied in Effisayil 2, the recommended dosing regimen for GPP flare prevention is a subcutaneous loading dose of 600 mg spesolimab followed by 300 mg subcutaneous treatment administered every 4 weeks (see section 4.2). The results summarised below are those for the recommended dosing regimen.

Patients who experienced a flare were eligible to receive up to two open-label, intravenous doses of 900 mg spesolimab (see section 4.2). 2 (6.7%) patients in the spesolimab arm for the recommended dose and 15 (48.4%) patients in the placebo arm received intravenous flare treatment.

Treatment with the recommended spesolimab dose compared to placebo resulted in statistically significant improvement based on the primary and key secondary endpoint (see Table 5).

Table 5: Time to the first GPP flare and occurrence of at least one GPP flare up to week 48 (Effisayil 2)

	Placebo	Recommended spesolimab dose
Number of patients analysed, N	31	30
Patients with GPP flares, N (%)*	16 (51.6)	3 (10.0)
Hazard ratio (HR)** for the time to the first flare vs placebo (95% CI)	0.16 (0.05, 0.54)	
p-value***	0.0005	
Risk difference for GPP flare occurrence vs placebo (95% CI)	-39.0% (-62.1, -15.9)	
p-value****	0.0013	

* The use of intravenous spesolimab treatment or investigator-prescribed standard of care to treat GPP worsening were considered as onset of GPP flare

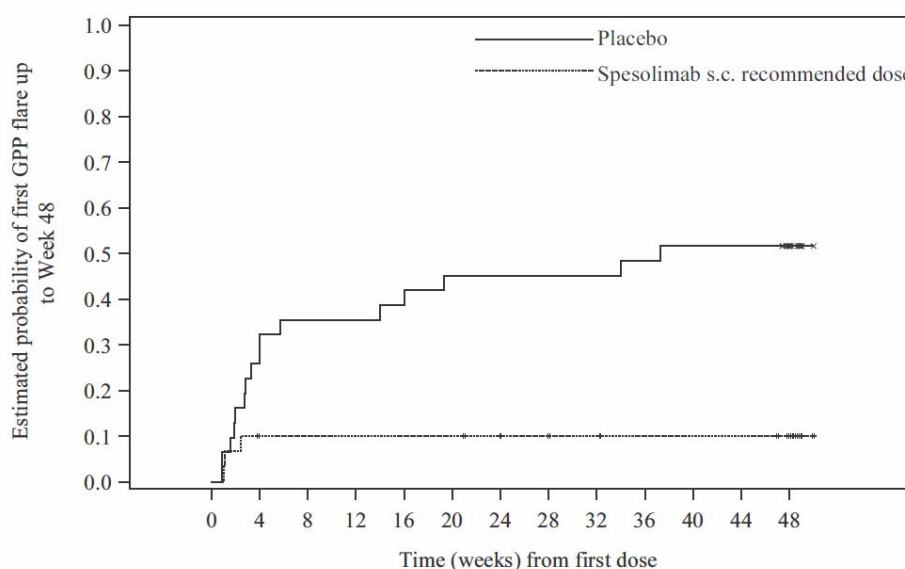
** Cox regression model stratified by the use of systemic GPP medications at randomisation

*** Log-rank test stratified by the use of systemic GPP medications at randomisation, one-sided p-value

**** Cochran-Mantel-Haenszel test after multiple imputation, stratified by the use of systemic GPP medications at randomisation, one-sided p-value

The efficacy of the subcutaneous recommended spesolimab dose compared with placebo was observed shortly after randomisation and was maintained up to week 48 (see Figure 1).

Figure 1: Time to the first GPP flare up to week 48 (Effisayil 2)



Patients at risk

Placebo	31	23	20	20	19	17	17	17	17	16	15	15	11
Spesolimab s.c. recommended dose	30	26	26	26	26	26	25	24	23	22	22	22	18

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

One adolescent patient in the placebo arm received investigator-prescribed standard of care to treat GPP worsening and was considered to have a GPP flare. No adolescent patient in the recommended spesolimab dose arm experienced a GPP flare.

The prevention of GPP worsening in terms of PSS, and DLQI was also observed, as shown by the hazard ratios for PSS 0.42 (95% CI 0.20, 0.91) and for DLQI 0.26 (95% CI 0.11, 0.62).

Immunogenicity

In patients with GPP treated with intravenous spesolimab in Effisayil 1, 46% of patients developed ADAs. A majority of ADA-positive subjects also developed neutralising antibodies. In Effisayil 2, following multiple subcutaneous doses of spesolimab, 41% of the patients developed ADAs. A majority of ADA-positive subjects also developed neutralising antibodies. Clearance of spesolimab increased along with increasing ADA titers. 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 for flare treatment. After subcutaneous administration of spesolimab in Effisayil 2, there was no apparent impact of ADA presence on efficacy or safety.

Paediatric population

The MHRA has waived the obligation to submit the results of studies with Spevigo in the paediatric population younger than 12 years of age in the treatment of generalised pustular psoriasis (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited. The MHRA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic 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 $AUC_{0-\infty}$ (95% CI) and C_{max} (95% CI) in a typical ADA-negative patient with GPP were 4 750 (4 510, 4 970) $\mu\text{g}\cdot\text{day}/\text{mL}$ and 238 (218, 256) $\mu\text{g}/\text{mL}$, respectively. After a 600 mg subcutaneous loading dose of spesolimab followed by 300 mg spesolimab subcutaneously every 4 weeks, the mean (CV%) steady-state trough concentration ranged from 33.4 $\mu\text{g}/\text{mL}$ (37.6%) to 42.3 $\mu\text{g}/\text{mL}$ (43.0%).

Absorption

Following subcutaneous single dose administration of spesolimab in healthy volunteers, peak plasma concentrations were achieved between 5.5 to 7.0 days after dosing. After subcutaneous administration in the abdomen, absolute bioavailability was slightly higher at higher doses with estimated values of 58%, 65%, and 72% at 150 mg, 300 mg, and 600 mg, respectively. Based on limited data, absolute bioavailability in the thigh was approximately 85% following a subcutaneous dose of 300 mg spesolimab.

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 characterised. As a humanised 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 to 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.

Linearity/non-linearity

When administered intravenously, spesolimab exhibited linear pharmacokinetics with dose-proportional increase in exposure across single dose ranges of 0.3 to 20 mg/kg. Both clearance (CL) and terminal half-life were independent of dose. Following subcutaneous single dose administration, spesolimab exposure increased slightly more than dose-proportionally across the dose range of 150 mg to 600 mg due to slightly increased bioavailability at higher doses.

Body weight

Spesolimab concentrations were lower in subjects with higher body weight and higher in subjects with lower body weight. Spesolimab has not been studied in patients with GPP weighing more than 164 kg. Based on pharmacokinetic modelling and simulation, the recommended dose for adolescents from 12 years of age weighing ≥ 30 and < 40 kg is half the recommended dose than for adults and adolescents from 12 years of age and weighing at least 40 kg (see section 4.2). The exposure in patients weighing ≥ 30 and < 40 kg receiving the reduced dosing regimen is expected to be comparable with those observed in GPP

studies.

Elderly / gender / race

Based on population pharmacokinetic analyses, age, gender and race do not have a clinically relevant 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 below the age of 14 years have not been studied.

The plasma pharmacokinetics of spesolimab observed in adolescents were consistent with that observed in adults.

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

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

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

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:
 - For the recommended dose of 900 mg, 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).
 - For the recommended dose of 450 mg, draw and discard 7.5 mL from a 100 mL container of sodium chloride 9 mg/mL (0.9%) solution for injection and replace slowly with 7.5 mL spesolimab sterile concentrate (one vial 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 MARKETING AUTHORISATION HOLDER

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Industriparken 55
DK-2750 Ballerup
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PL 05293/0193

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

27/10/2025

10 DATE OF REVISION OF THE TEXT

30/03/2026