ANNEX I

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).

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 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 (see Spevigo 150 mg solution for injection in pre-filled syringe Summary of Product Characteristics) 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
Spesolimab 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

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 (≥ 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 disorders	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 (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 national reporting system listed in Appendix V.

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 apharesis
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 Caucasian and 45% were Asian. 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

	Loading dose	*Subsequent doses*
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).

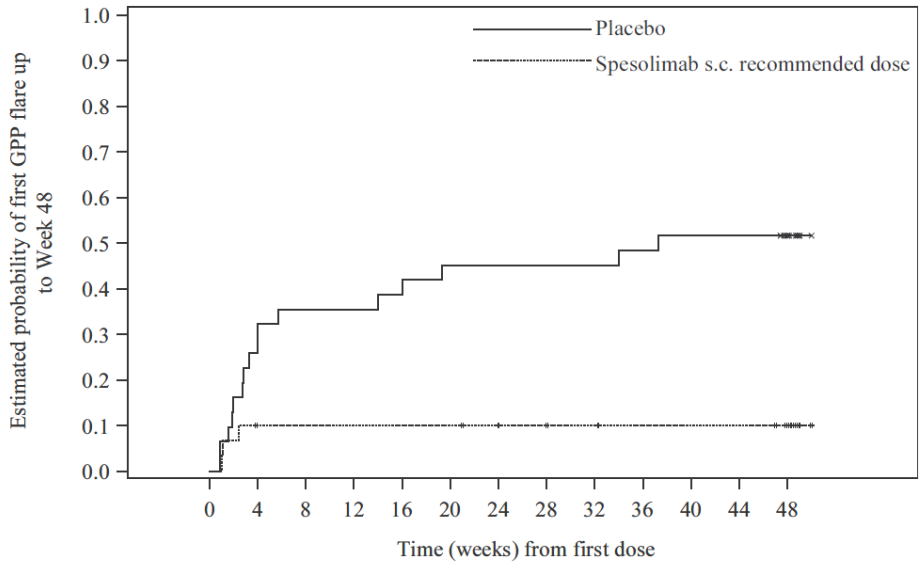
Table 5: Time to the first GPP flare and occurrence of at least one GPP flare up to week 48 (Effisayil 2)

	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 European Medicines Agency 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 European Medicines Agency 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) µg·day/mL and 238 (218, 256) µg/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 µg/mL (37.6%) to 42.3 µg/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 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:
    - 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

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/22/1688/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 December 2022

Date of latest renewal: 14 November 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼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 150 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 150 mg spesolimab in 1 mL.

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

Solution for injection (injection)

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Spevigo is indicated for the prevention of generalised pustular psoriasis (GPP) flares in adults and adolescents from 12 years of age.

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 or with an intravenous dose of spesolimab to treat a GPP flare (see Spevigo 450 mg concentrate for solution for infusion Summary of Product Characteristics).

Posology

The recommended dose for GPP flare prevention in adults and adolescents from 12 years of age and weighing at least 40 kg is a subcutaneous loading dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered subcutaneously every 4 weeks.

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 subcutaneous loading dose of 300 mg (two 150 mg injections), followed by 150 mg (one 150 mg injection) administered subcutaneously every 4 weeks (see section 5.2).

Clinical data on concomitant use of other GPP treatments with spesolimab is limited. Spesolimab is not recommended for use in combination with other GPP treatments, and tapering of previous GPP treatments should be considered at initiation of therapy (see sections 4.4 and 4.5).

GPP flare treatment during subcutaneous GPP prevention treatment
If a patient experiences a GPP flare while receiving subcutaneous Spevigo, the GPP flare may be treated with intravenous Spevigo (see Spevigo 450 mg concentrate for solution for infusion Summary of Product Characteristics).

Initiating or reinitiating subcutaneous GPP prevention treatment after intravenous GPP flare treatment
Four weeks after treatment with intravenous Spevigo, subcutaneous Spevigo can be initiated or reinitiated. A subcutaneous loading dose is not required.

Missed dose

If a dose is missed, the dose should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special populations

Elderly
No dose adjustment is required.

Renal or hepatic impairment
Spesolimab 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.

Method of administration

The injection should be administered subcutaneously in the upper thighs or abdomen. The pre-filled syringe should not be injected into areas where the skin is tender, bruised, erythematous, indurated, or scarred.

Adults and adolescents from 12 years of age and weighing at least 40 kg
The 600 mg subcutaneous loading dose (see section Posology) should be administered by a healthcare professional. A different injection site should be chosen for each injection, at least 2 cm away from the other injection sites.

For subsequent subcutaneous 300 mg doses, if the healthcare professional determines that it is appropriate, patients may self-inject or caregivers may administer the pre-filled syringe after proper training in subcutaneous injection technique.

For a complete 300 mg dose, two 150 mg pre-filled syringes are required to be injected, one right after the other. A different injection site should be chosen for each of the two injections, at least 2 cm away from the other injection site.

Detailed instructions for use are provided in the package leaflet.

Adolescents from 12 years of age weighing ≥ 30 and <40 kg:
Spevigo should be administered by a healthcare professional.
For the 300 mg subcutaneous loading dose (see section Posology) two 150 mg pre-filled syringes are required to be injected, one right after the other. A different injection site should be chosen for each injection, at least 2 cm away from the other injection sites.
For a subsequent 150 mg dose, one 150 mg pre-filled syringe is required to be injected.

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 during or after treatment with spesolimab.

If a patient is on treatment with Spevigo subcutaneous injection for GPP flare prevention, and develops a clinically important active infection, treatment with Spevigo should be stopped. Re-initiation can be considered once the infection resolves or is adequately treated.

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. During and after spesolimab treatment, patients should be monitored for signs and symptoms of active TB.

Hypersensitivity reactions

Hypersensitivity 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).

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

For the treatment of GPP flares, see Spevigo 450 mg concentrate for solution for infusion Summary of Product Characteristics.
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 or immunosuppressants

The safety and efficacy of spesolimab in combination with immunosuppressants, including biologics, have not been evaluated systematically. In the GPP flare prevention clinical study, other GPP treatments had to be stopped before initiation of spesolimab treatment, with a washout period for most other treatments (biologics, other systemic immunomodulating treatments), or a stop at the day of randomisation (the day of starting the spesolimab prevention treatment) (see section 5.1).

Spesolimab is not recommended for use in combination with other GPP treatments. To prevent the risk of GPP flares, tapering of previous treatments should be considered at initiation of spesolimab GPP prevention therapy. If needed, other GPP treatments may be used occasionally during treatment (e.g. in case of worsening or after a flare) at the discretion of the treating physician.

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 during and for at least 16 weeks after treatment with spesolimab.

Prior to initiating spesolimab for GPP flare prevention, completion of all appropriate immunisations should be considered according to current immunisation guidelines.

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

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 (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 (33.3%) with serious infections in 3 patients (3.2%) (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 (≥ 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 disorders	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 (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. Eight 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 national reporting system listed in Appendix V.

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 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 2).

Table 2: Treatment arms in Effisayil 2

	Loading dose	*Subsequent doses*
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 3).

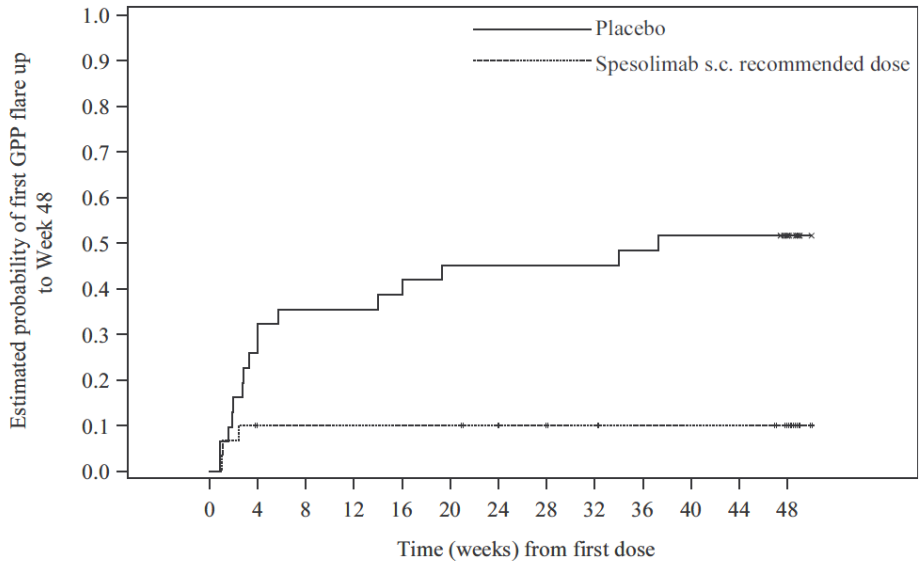
Table 3: Time to the first GPP flare and occurrence of at least one GPP flare up to week 48 (Effisayil 2)

	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 European Medicines Agency 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).

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) µg·day/mL and 238 (218, 256) µg/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 µg/mL (37.6%) to 42.3 µg/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

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

6.4 Special precautions for storage

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

Do not freeze. Do not use the Spevigo pre-filled syringe if it has been frozen, even if it has been thawed.

Store in the original package in order to protect from light.

Prior to use, the pre-filled syringe may be kept at temperatures up to 25 °C for up to 14 days, if stored in the original package in order to protect from light. Spevigo pre-filled syringe must be discarded if it has been kept at temperatures up to 25 °C for more than 14 days.

6.5 Nature and contents of container

Pre-filled glass syringe assembled with an automatic needle guard, extended finger flange, plunger rod, and plunger stopper (coated butyl rubber, siliconised).

Pack size of 2 pre-filled syringes.

6.6 Special precautions for disposal and other handling

The pre-filled syringes should be taken out of the refrigerator and removed from the carton 15 to 30 minutes before injecting to allow to reach room temperature (up to 25 °C). Do not place the pre-filled syringes in direct sunlight.

General special precautions

Prior to use, a visual inspection of each pre-filled syringe is recommended. The solution should be clear to slightly opalescent, colourless to slightly brownish-yellow. The solution may contain a few translucent to white product-related particles. Spevigo should not be used if the solution is cloudy or discoloured, or contains large particles.

Do not use if the pre-filled syringes have been dropped or look damaged.
Do not remove the cap until you are ready to inject.

Each pre-filled syringe is for single use only.

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

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER

EU/1/22/1688/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 December 2022

Date of latest renewal: 14 November 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach an der Riss
GERMANY

Name and address of the manufacturer(s) responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach an der Riss
GERMANY

Boehringer Ingelheim France
100-104 Avenue de France
75013 Paris
FRANCE

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a(4) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of spesolimab in the treatment of flares in adult and adolescent patients from 12 years of age with generalised pustular psoriasis (GPP), the MAH should conduct and submit the final results of study 1368-0120, an open-label trial in the treatment of recurrent flares in adult patients with generalised pustular psoriasis, conducted according to an agreed protocol.	January 2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Spevigo 450 mg concentrate for solution for infusion
spesolimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 450 mg spesolimab in 7.5 mL.

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

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate (E262), glacial acetic acid (E260), sucrose, arginine hydrochloride, polysorbate 20 (E432), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
2 vials of 450 mg/7.5 mL each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Prior to use, the unopened vial may be kept at temperatures up to 30 °C for up to 24 hours.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1688/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Spevigo 450 mg sterile concentrate
spesolimab
IV infusion after dilution

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7.5 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Spevigo 150 mg solution for injection in pre-filled syringe
spesolimab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 150 mg spesolimab in 1 mL.

3. LIST OF EXCIPIENTS

Excipients: sodium acetate trihydrate (E262), glacial acetic acid (E260), sucrose, arginine hydrochloride, polysorbate 20 (E432), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Prior to use, Spevigo may be kept at temperatures up to 25 °C for up to 14 days.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim International GmbH
55216 Ingelheim am Rhein
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1688/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Spevigo 150 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TRAY

1. NAME OF THE MEDICINAL PRODUCT

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE(S) OF ADMINISTRATION

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

19. OTHER – PRINTING ON TRAY

Injection 1
Injection 2

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Spevigo 150 mg injection
spesolimab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Spevigo 450 mg concentrate for solution for infusion
spesolimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully, because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spevigo is and what it is used for

What Spevigo is
Spevigo contains the active substance spesolimab. Spesolimab belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by blocking the activity of a protein called IL36R, which is involved in inflammation.

What Spevigo is used for
Spevigo is used alone in adults and adolescents from 12 years of age to treat flares of a rare inflammatory skin disease called generalised pustular psoriasis (GPP). During a flare, patients may experience painful skin blisters that develop suddenly over large areas of the skin. These blisters, also called pustules, are filled with pus. The skin may become red, itchy, dry, cracked or scaly. Patients may also experience more general signs and symptoms, such as fever, headache, extreme tiredness, or a burning sensation of the skin.
Spevigo improves skin clearance and reduces symptoms of GPP during a flare.

2. What you need to know before you are given Spevigo

A doctor experienced in treating patients with inflammatory skin diseases will start and supervise your treatment.

You must not receive Spevigo if you:
- are allergic to spesolimab or any of the other ingredients of this medicine (listed in section 6).
- have active tuberculosis or other severe infections (see “Warnings and precautions”).

Warnings and precautions
Talk to your doctor or nurse before you are given Spevigo if you:
- currently have an infection or have an infection that keeps coming back. Fever, flu-like symptoms, tiredness or shortness of breath, a cough which will not go away, warm, red and painful skin, or a painful rash with blisters can be signs and symptoms of an infection.
- have, have had tuberculosis, or have been in close contact with someone with tuberculosis.
- have recently had a vaccination or plan to have a vaccination. You should not be given certain

types of vaccines (live vaccines) for at least 16 weeks after being given Spevigo.
- experience symptoms like weakness in your arms or legs that was not there before or numbness (loss of sensation), tingling or a burning sensation in any part of your body. These might be signs of peripheral neuropathy (damage of the peripheral nerves).

Infections
Tell your doctor as soon as possible if you notice any signs or symptoms of an infection after you have been given Spevigo, see section 4 "Possible side effects".

Allergic reactions
Seek medical help immediately if you notice any signs or symptoms of an allergic reaction while or after you are given this medicine. You can also have allergic reactions some days or weeks after receiving Spevigo. For signs and symptoms see section 4 "Possible side effects".

Children and adolescents
Spevigo is not recommended for children under 12 years of age because it has not been studied in this age group.

Other medicines and Spevigo
Tell your doctor if you are:
- taking, have recently taken or might take any other medicines, including any other medicines to treat GPP.
- going to have or have recently had a vaccination. You should not be given certain types of vaccines (live vaccines) for at least 16 weeks after receiving Spevigo.

Pregnancy and breast-feeding
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because it is not known how this medicine will affect the baby.

It is therefore preferable to avoid the use of Spevigo during pregnancy.
If you are pregnant, you should only receive this medicine if your doctor has clearly recommended it.

Breast-feeding
It is not known whether Spevigo passes into breast milk. Spevigo may pass into breast milk in the first days after birth. You should therefore tell your doctor if you are breast-feeding or plan to breast-feed, so you and your doctor can decide if you can be given Spevigo.

Driving and using machines
Spevigo is not expected to affect your ability to drive and use machines.

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

3. How Spevigo will be given

The recommended dose for adults and adolescents from 12 years of age and weighing at least 40 kg is 900 mg (two vials of 450 mg).

The recommended dose for adolescents from 12 years of age weighing 30 to less than 40 kg is 450 mg (one vial of 450 mg).

Your doctor or nurse will give you this medicine by infusion (drip) into a vein. It will be given over a period of 90 minutes, up to a maximum of 180 minutes if the infusion is slowed down or stopped

temporarily.

If you still experience flare symptoms your doctor can decide to give you a second dose of Spevigo one week after the first.

If you have any further questions on the use of this medicine, ask your doctor.

If you are given more Spevigo than you should
This medicine will be given to you by your doctor or nurse. If you think you have been given too much Spevigo, tell your doctor or nurse straight away.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek medical help immediately if you notice any signs or symptoms of an allergic reaction while or after you are given this medicine. These may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps, that is different from your GPP symptoms
- feeling faint.

You can also have allergic reactions some days or weeks after receiving Spevigo.
Seek medical help immediately if you develop any widespread skin rash that was not there before, fever, and/or facial swelling 2-8 weeks after receiving the medicine. These might be signs of a delayed allergic reaction (hypersensitivity).

Tell your doctor as soon as possible if you notice any signs or symptoms of an infection.
Very common (may affect more than 1 in 10 people). These may include:
- fever, cough
- frequent urination, pain or burning while urinating or bloody urine, which may be symptoms of urinary tract infections

Tell your doctor or nurse if you get any of the following other side effects:

Very common (may affect more than 1 in 10 people)
- redness, swelling, hardening, warmth, pain, peeling of the skin, small, solid raised bumps on the skin, itching, skin rash, or hives at the injection site

Common (may affect up to 1 in 10 people)
- itching
- feeling tired

Not known (frequency cannot be estimated from the available data)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spevigo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C) (see information for Healthcare Professionals at the end of this Package leaflet).
Do not freeze.
Store in the original package in order to protect from light.

6. Contents of the pack and other information

What Spevigo contains
- The active substance is spesolimab. Each vial contains 450 mg spesolimab in 7.5 mL of concentrate for solution for infusion.
- The other ingredients are sodium acetate trihydrate (E262), glacial acetic acid (E260) (for pH adjustment), sucrose, arginine hydrochloride, polysorbate 20 (E432) and water for injections.

What Spevigo looks like and contents of the pack
Spevigo concentrate for solution for infusion is a clear to slightly opalescent, colourless to slightly brownish-yellow solution supplied in a 10 mL colourless glass vial (type I glass), with a coated rubber stopper and aluminium crimp cap with blue plastic button.

Each pack contains two vials.

Marketing Authorisation Holder

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

Boehringer Ingelheim France
100-104 Avenue de France
75013 Paris
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Boehringer Ingelheim SComm
Tél/Tel: +32 2 773 33 11

България
Бьорингер Ингелхайм РЦВ ГмбХ и Ко. КГ – клон България
Тел: +359 2 958 79 98

Česká republika
Boehringer Ingelheim spol. s r.o.
Tel: +420 234 655 111

Danmark
Boehringer Ingelheim Danmark A/S
Tlf: +45 39 15 88 88

Deutschland
Boehringer Ingelheim Pharma GmbH & Co. KG
Tel: +49 (0) 800 77 90 900

Eesti
Boehringer Ingelheim RCV GmbH & Co KG
Eesti filiaal
Tel: +372 612 8000

Ελλάδα
Boehringer Ingelheim Ελλάς Μονοπρόσωπη Α.Ε.
Τηλ: +30 2 10 89 06 300

España
Boehringer Ingelheim España, S.A.
Tel: +34 93 404 51 00

France
Boehringer Ingelheim France S.A.S.
Tél: +33 3 26 50 45 33

Hrvatska
Boehringer Ingelheim Zagreb d.o.o.
Tel: +385 1 2444 600

Ireland
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Ísland
Vistor ehf.
Sími: +354 535 7000

Lietuva
Boehringer Ingelheim RCV GmbH & Co KG
Lietuvos filialas
Tel: +370 5 2595942

Luxembourg/Luxemburg
Boehringer Ingelheim SComm
Tél/Tel: +32 2 773 33 11

Magyarország
Boehringer Ingelheim RCV GmbH & Co KG
Magyarországi Fióktelepe
Tel: +36 1 299 89 00

Malta
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Nederland
Boehringer Ingelheim B.V.
Tel: +31 (0) 800 22 55 889

Norge
Boehringer Ingelheim Danmark
Norwegian branch
Tlf: +47 66 76 13 00

Österreich
Boehringer Ingelheim RCV GmbH & Co KG
Tel: +43 1 80 105-7870

Polska
Boehringer Ingelheim Sp. z o.o.
Tel: +48 22 699 0 699

Portugal
Boehringer Ingelheim Portugal, Lda.
Tel: +351 21 313 53 00

România
Boehringer Ingelheim RCV GmbH & Co KG Viena – Sucursala Bucureşti
Tel: +40 21 302 28 00

Slovenija
Boehringer Ingelheim RCV GmbH & Co KG
Podružnica Ljubljana
Tel: +386 1 586 40 00

Slovenská republika
Boehringer Ingelheim RCV GmbH & Co KG
organizačná zložka
Tel: +421 2 5810 1211

Italia
Boehringer Ingelheim Italia S.p.A.
Tel: +39 02 5355 1

Κύπρος
Boehringer Ingelheim Ελλάς Μονοπρόσωπη Α.Ε.
Τηλ: +30 2 10 89 06 300

Latvija
Boehringer Ingelheim RCV GmbH & Co KG
Latvijas filiāle
Tel: +371 67 240 011

Suomi/Finland
Boehringer Ingelheim Finland Ky
Puh/Tel: +358 10 3102 800

Sverige
Boehringer Ingelheim AB
Tel: +46 8 721 21 00

United Kingdom (Northern Ireland)
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

This leaflet was last revised in {MM/YYYY}.

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

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.

Posology and method of administration
The recommended dose for adults and adolescents from 12 years of age and weighing at least 40 kg is a single dose of 900 mg (2 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.

The recommended dose for adolescents from 12 years of age weighing ≥ 30 and < 40 kg is a single dose of 450 mg (1 vial of 450 mg) administered as an intravenous infusion. If flare symptoms persist, an additional 450 mg dose may be administered 1 week after the initial dose.

Spevigo must be diluted before use. It should not be administered as an intravenous push or bolus.

Following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, Spevigo 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.

Handling instructions
- The vial should be visually inspected before use.
  - Spevigo is a colourless to slightly brownish-yellow, clear to slightly opalescent solution.

- If the solution is cloudy, discoloured, or contains large or coloured particulates, the vial should be discarded.

- Spesolimab sterile concentrate 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 the diluted spesolimab infusion solution. 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.

- Spevigo 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).

Storage conditions

Unopened vial

- 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.

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 – 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 – 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.

Package leaflet: Information for the patient

Spevigo 150 mg solution for injection in pre-filled syringe
spesolimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully, because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spevigo is and what it is used for

What Spevigo is
Spevigo contains the active substance spesolimab. Spesolimab belongs to a group of medicines called interleukin (IL) inhibitors. This medicine works by blocking the activity of a protein called IL36R, which is involved in inflammation.

What Spevigo is used for
Spevigo is used in adults and adolescents to treat and prevent flares of a rare inflammatory skin disease called generalised pustular psoriasis (GPP). During a flare, patients may experience painful skin blisters that develop suddenly over large areas of the skin. These blisters, also called pustules, are filled with pus. The skin may become red, itchy, dry, cracked or scaly. Patients may also experience more general signs and symptoms, such as fever, headache, extreme tiredness, or a burning sensation of the skin.
Spevigo clears pustules and other skin manifestations and can therefore help to reduce the signs and symptoms of your disease.

2. What you need to know before you use Spevigo

A doctor experienced in treating patients with inflammatory skin diseases will start and supervise your treatment.

Do not use Spevigo if you:
- are allergic to spesolimab or any of the other ingredients of this medicine (listed in section 6).
- have active tuberculosis or other severe infections (see “Warnings and precautions”).

Warnings and precautions
Talk to your doctor or nurse before and during the use of Spevigo if you:
- currently have an infection or have an infection that keeps coming back. Fever, flu-like symptoms, tiredness or shortness of breath, a cough which will not go away, warm, red and painful skin, or a painful rash with blisters can be signs and symptoms of an infection.
- have, have had tuberculosis, or have been in close contact with someone with tuberculosis.

- have recently had a vaccination or plan to have a vaccination. You should not be given certain types of vaccines (live vaccines) for at least 16 weeks after being given Spevigo. Your doctor will check if you need any vaccines before you start using Spevigo.
- experience symptoms like weakness in your arms or legs that was not there before or numbness (loss of sensation), tingling or a burning sensation in any part of your body. These might be signs of peripheral neuropathy (damage of the peripheral nerves).

It is important to keep a record of the batch number of your Spevigo.
Every time you get a new pack of Spevigo, note down the date and the batch number (which is on the packaging after "Lot") and keep this information in a safe place.

Infections
Tell your doctor as soon as possible if you notice any signs or symptoms of an infection while you are using Spevigo, see section 4 "Possible side effects".

Allergic reactions
Seek medical help immediately if you notice any signs or symptoms of an allergic reaction while you are using or after you have used this medicine. You can also have allergic reactions some days or weeks after starting the use of Spevigo. For signs and symptoms see section 4 "Possible side effects".

Children and adolescents
Spevigo is not recommended for children under 12 years of age because it has not been studied in this age group.

Other medicines and Spevigo
Tell your doctor if you are:
- taking, have recently taken or might take any other medicines.
- going to have or have recently had a vaccination. You should not be given certain types of vaccines (live vaccines) for at least 16 weeks after receiving Spevigo.

If you are not sure, talk to your doctor, pharmacist or nurse before and during the use of Spevigo.

Pregnancy and breast-feeding
Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. This is because it is not known how this medicine will affect the baby.

It is therefore preferable to avoid the use of Spevigo during pregnancy.
If you are pregnant, you should only receive this medicine if your doctor has clearly recommended it.

Breast-feeding
It is not known whether Spevigo passes into breast milk. Spevigo may pass into breast milk in the first days after birth. You should therefore tell your doctor if you are breast-feeding or plan to breast-feed, so you and your doctor can decide if you can use Spevigo.

Driving and using machines
Spevigo is not expected to affect your ability to drive and use machines.

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

3. How to use Spevigo

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor

or pharmacist if you are not sure.

How much Spevigo to use

Adults and adolescents from 12 years of age and weighing at least 40 kg:		
	How much?	**When?**
1st dose	600 mg (**four** 150 mg injections)	When your doctor tells you
Further doses	300 mg (**two** 150 mg injections)	Every 4 weeks starting after the 1st dose

The first dose should be given by your doctor or nurse.

You and your doctor or nurse will decide if you should inject this medicine yourself. Do not inject yourself with this medicine unless you have been trained by your doctor or nurse. A caregiver may also give your injections after they have been trained.

Read the 'Instructions for use' at the end of this leaflet before injecting Spevigo yourself.

Adolescents from 12 years of age weighing 30 to less than 40 kg:		
	How much?	**When?**
1st dose	300 mg (**two** 150 mg injections)	When your doctor tells you
Further doses	150 mg (**one** 150 mg injection)	Every 4 weeks starting after the 1st dose

Spevigo should be given by your doctor or nurse.

If you use more Spevigo than you should
If you have used more Spevigo than you should or the dose has been given sooner than prescribed, talk to your doctor.

If you forget to use Spevigo
If you forget to use Spevigo, inject a dose as soon as you realise. Talk to your doctor if you are not sure what to do.

If you stop using Spevigo
Do not stop using Spevigo without talking to your doctor first. If you stop treatment, your symptoms may come back or you may experience a flare.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Seek medical help immediately if you notice any signs or symptoms of an allergic reaction while using or after you have used this medicine. These may include:
- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps, that is different from your GPP symptoms
- feeling faint.

You can also have allergic reactions some days or weeks after you have used Spevigo.
Seek medical help immediately if you develop any widespread skin rash that was not there before, fever, and/or facial swelling 2-8 weeks after you have used the medicine. These might be signs of a delayed allergic reaction (hypersensitivity).

Tell your doctor as soon as possible if you notice any signs or symptoms of an infection. These may include:

Very common (may affect more than 1 in 10 people)
- fever, cough
- frequent urination, pain or burning while urinating or bloody urine, which may be symptoms of urinary tract infections

Tell your doctor or nurse if you get any of the following other side effects:

Very common (may affect more than 1 in 10 people)
- redness, swelling, hardening, warmth, pain, peeling of the skin, small, solid raised bumps on the skin, itching, skin rash, or hives at the injection site

Common (may affect up to 1 in 10 people)
- itching
- feeling tired

Not known (frequency cannot be estimated from the available data)
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Spevigo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled syringe and the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). **Do not** freeze. **Do not** use Spevigo if frozen, even if it has been thawed.

If needed, Spevigo can be stored at room temperature (up to 25 °C) for up to 14 days. Throw away Spevigo if it has been kept at room temperature for more than 14 days.

Store in the original package in order to protect from light.

Do not use this medicine if the liquid is cloudy or contains flakes or large particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Spevigo contains
- The active substance is spesolimab. Each pre-filled syringe contains 150 mg spesolimab in 1 mL solution.
- The other ingredients are sodium acetate trihydrate (E262), glacial acetic acid (E260) (for pH adjustment), sucrose, arginine hydrochloride, polysorbate 20 (E432) and water for injections.

What Spevigo looks like and contents of the pack
Spevigo solution for injection is a clear to slightly opalescent, colourless to slightly brownish-yellow solution in a pre-filled syringe with safety cover. The liquid may contain tiny white or clear particles. Each pre-filled syringe contains 150 mg in 1 mL solution for injection.

Each pack contains 2 pre-filled syringes.

Marketing Authorisation Holder

Boehringer Ingelheim International GmbH
Binger Str. 173
55216 Ingelheim am Rhein
Germany

Manufacturer

Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65
88397 Biberach an der Riss
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Boehringer Ingelheim SComm
Tél/Tel: +32 2 773 33 11

Lietuva
Boehringer Ingelheim RCV GmbH & Co KG
Lietuvos filialas
Tel: +370 5 2595942

България
Бьорингер Ингелхайм РЦВ ГмбХ и Ко. КГ – клон България
Тел: +359 2 958 79 98

Luxembourg/Luxemburg
Boehringer Ingelheim SComm
Tél/Tel: +32 2 773 33 11

Česká republika
Boehringer Ingelheim spol. s r.o.
Tel: +420 234 655 111

Magyarország
Boehringer Ingelheim RCV GmbH & Co KG
Magyarországi Fióktelepe
Tel: +36 1 299 89 00

Danmark
Boehringer Ingelheim Danmark A/S
Tlf: +45 39 15 88 88

Malta
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Deutschland
Boehringer Ingelheim Pharma GmbH & Co. KG
Tel: +49 (0) 800 77 90 900

Nederland
Boehringer Ingelheim B.V.
Tel: +31 (0) 800 22 55 889

Eesti
Boehringer Ingelheim RCV GmbH & Co KG
Eesti filiaal
Tel: +372 612 8000

Norge
Boehringer Ingelheim Danmark
Norwegian branch
Tlf: +47 66 76 13 00

Ελλάδα
Boehringer Ingelheim Ελλάς Μονοπρόσωπη Α.Ε.
Τηλ: +30 2 10 89 06 300

Österreich
Boehringer Ingelheim RCV GmbH & Co KG
Tel: +43 1 80 105-7870

España
Boehringer Ingelheim España, S.A.
Tel: +34 93 404 51 00

France
Boehringer Ingelheim France S.A.S.
Tél: +33 3 26 50 45 33

Hrvatska
Boehringer Ingelheim Zagreb d.o.o.
Tel: +385 1 2444 600

Ireland
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

Ísland
Vistor ehf.
Sími: +354 535 7000

Italia
Boehringer Ingelheim Italia S.p.A.
Tel: +39 02 5355 1

Κύπρος
Boehringer Ingelheim Ελλάς Μονοπρόσωπη Α.Ε.
Τηλ: +30 2 10 89 06 300

Latvija
Boehringer Ingelheim RCV GmbH & Co KG
Latvijas filiāle
Tel: +371 67 240 011

Polska
Boehringer Ingelheim Sp. z o.o.
Tel: +48 22 699 0 699

Portugal
Boehringer Ingelheim Portugal, Lda.
Tel: +351 21 313 53 00

România
Boehringer Ingelheim RCV GmbH & Co KG Viena – Sucursala Bucureşti
Tel: +40 21 302 28 00

Slovenija
Boehringer Ingelheim RCV GmbH & Co KG
Podružnica Ljubljana
Tel: +386 1 586 40 00

Slovenská republika
Boehringer Ingelheim RCV GmbH & Co KG
organizačná zložka
Tel: +421 2 5810 1211

Suomi/Finland
Boehringer Ingelheim Finland Ky
Puh/Tel: +358 10 3102 800

Sverige
Boehringer Ingelheim AB
Tel: +46 8 721 21 00

United Kingdom (Northern Ireland)
Boehringer Ingelheim Ireland Ltd.
Tel: +353 1 295 9620

This leaflet was last revised in {MM/YYYY}.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for use

Spevigo 150 mg solution for injection in pre-filled syringe

Getting to know Spevigo
The pre-filled syringe contains the active substance spesolimab in a solution for subcutaneous injection that helps to deliver a fixed dose of spesolimab.

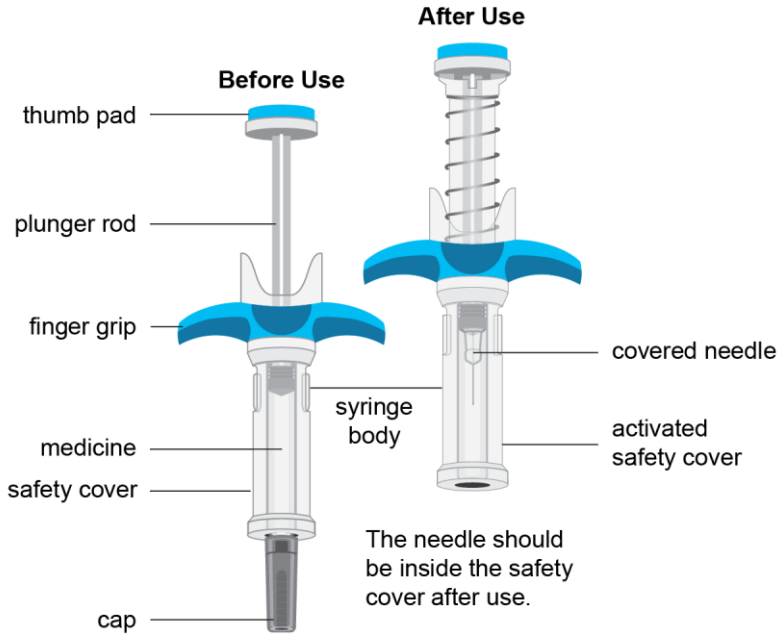
Before you start using this medicine on your own or your child, first make sure that you get trained by your doctor or nurse. Then read the package leaflet and these instructions for use to make sure you get the correct dose. If you are visually impaired and cannot see well, you must be assisted by a trained caregiver.

If you have further questions, ask your doctor, pharmacist or nurse.

Spevigo is for single use. **Do not** reuse the pre-filled syringe.

<u>This is what Spevigo pre-filled syringe looks like</u>
Spevigo is a pre-filled syringe with a safety cover. The needle is pulled back into the safety cover after injection.

The following picture shows Spevigo before use and after use with the activated safety cover.



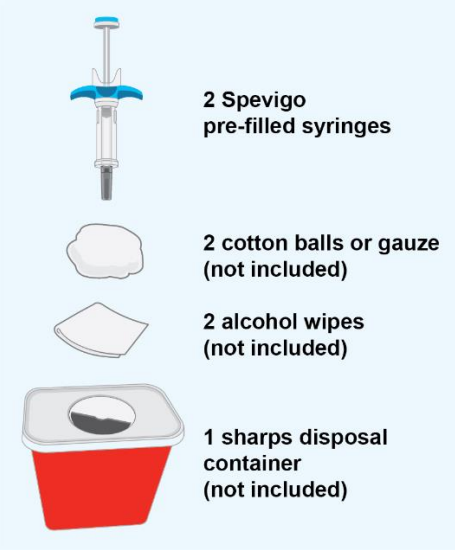
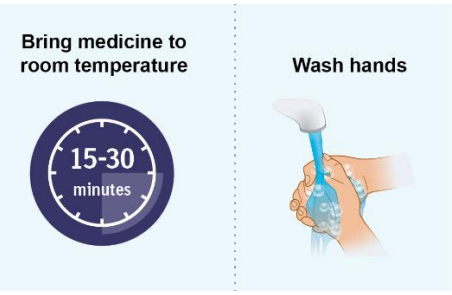
Your healthcare professional has prescribed a dose of Spevigo for you or your child that requires two injections to deliver a complete dose. You must inject the contents of both pre-filled syringes that come in the carton to deliver the complete dose.

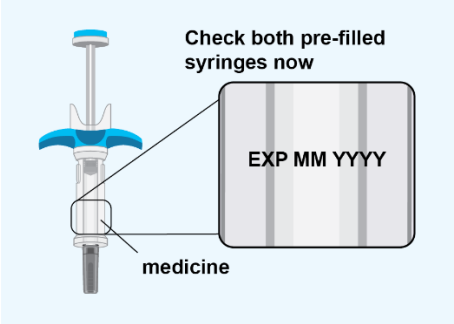
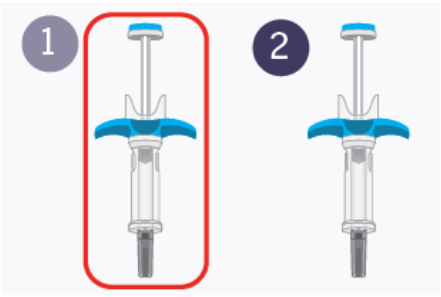
<u>Important</u> <u>information you need to know before injecting Spevigo</u>
- **Do not** use the pre-filled syringe until you have been shown the right way to give the injection and have read and understood these handling instructions.
- Inspect the carton that the product comes in to be sure that you have the correct medicine, the correct number of pre-filled syringes for your or your child's prescribed dose, for any damage, and the expiry date.
- **Do not** remove the cap until you are ready to inject.
- **Do not** use Spevigo:

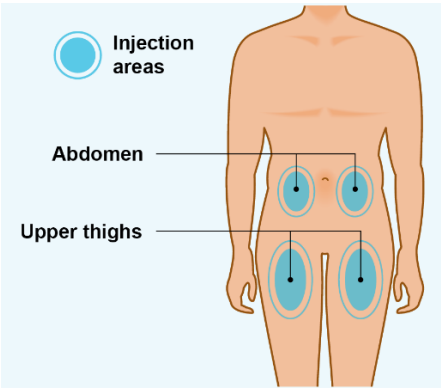
- if the liquid is cloudy or contains flakes or large particles.
- if the **expiry date (EXP)** has passed.
- if the pre-filled syringes have been dropped or look damaged.

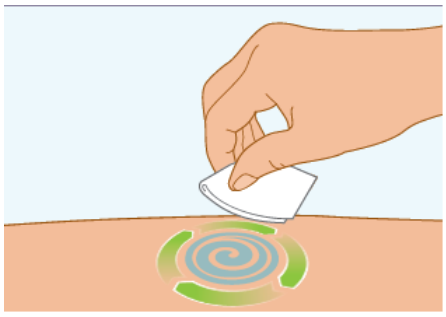
- It is important to keep a record of the batch number of your Spevigo. Every time you get a new pack of Spevigo, note down the date and the batch number (which is on the packaging after "Lot") and keep this information in a safe place.
- Inject Spevigo under the skin (subcutaneous injection) in either the upper thighs or stomach area (abdomen). **Do not** inject Spevigo into any other area of the body.
- If you have any problems with your injection, **do not** repeat the injection steps with Spevigo pre-filled syringe. Call your doctor for help.
- If you have further questions, ask your doctor or pharmacist.

<u>Follow the steps below when you use Spevigo</u>

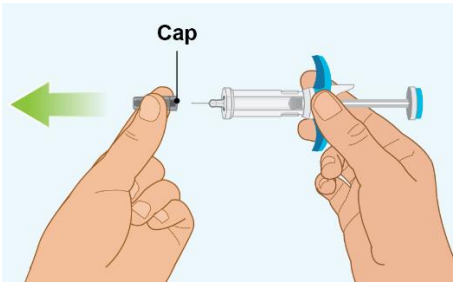
STEP 1	**Gathering supplies**
	• Take the Spevigo carton out of the refrigerator and remove the pre-filled syringes from the carton. • Gather supplies listed on the left side and place them on a clean, flat work surface in a well-lit area. • If you do not have all the supplies listed, contact your pharmacist. • For disposal, see step 10: **"Disposing of the used pre-filled syringes and caps."**
STEP 2	**Preparing to inject Spevigo**
	• Wait 15 to 30 minutes to allow the medicine to reach room temperature to avoid discomfort during injection. **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water. • **Do not** leave the pre-filled syringes in direct sunlight. • Wash your hands well with soap and water and dry them.

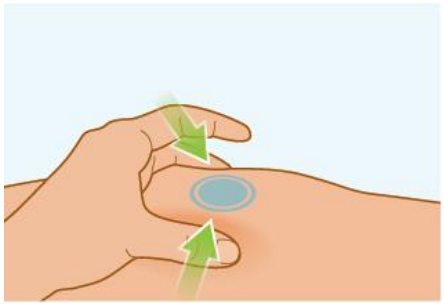
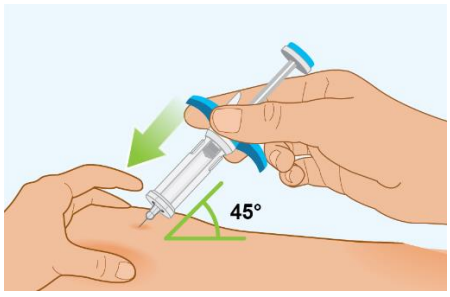
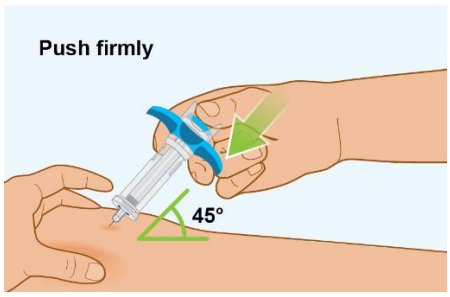
STEP 3	**Inspecting the pre-filled syringes**
	**Check both pre-filled syringes now:** • Check to make sure the medicine name and dose on the pre-filled syringes match your or your child's prescription. • Check the expiry date (EXP) on both pre-filled syringes. **Do not** use if the expiry date has passed. • Check both pre-filled syringes for damage, cracks, and leakage. **Do not** use if any part of the pre-filled syringes appears cracked, broken, or is leaking. • Make sure the medicine in both pre-filled syringes is colourless to slightly yellow. It may contain tiny white or clear particles. **Do not** use if the medicine is cloudy or has flakes or large particles in it. • It is normal to see air bubbles, they do not need to be removed. • **Do not** use if the Spevigo pre-filled syringes have been dropped.
Preparing for your first injection	
	**Prepare for the first of two injections.** **Remember, you will repeat the following steps with the second pre-filled syringe right away after your first injection.** **Two injections are needed for a complete dose.**
STEP 4	**Choosing the injection site**

	Choose an injection site.
	• You may use an area on your:
	  ○ **upper thighs** or
	  ○ **stomach area (abdomen)**, except for an area 5 cm around your navel (belly button).
	• **Choose a different injection site** each time you inject, at least 2 cm away from the last injection site.
	• **Do not** inject into an area near your waistline or belly button.
	• **Do not** inject into areas that are tender, bruised, red, hard, or scarred.
	• **Do not** inject through clothes.

STEP 5	**Cleaning the injection site**
	• Clean the injection site with an alcohol wipe and let air dry. • **Do not** touch this area again before injecting. • **Do not** fan or blow on the clean area.

STEP 6	**Removing the cap**

	• Hold the pre-filled syringe by the finger grip with one hand. With the other hand, pull the cap straight off.
	  ○ **Do not** pull on or hold the plunger rod.
	  ○ **Do not** twist the cap. Twisting the cap could damage the needle.
	  ○ **Do not** use the prefilled syringe if the needle is bent or damaged. If you accidentally bend the needle **Do not** attempt to straighten it.
	• Put the cap aside.
	• Use right away after removing the cap.
	  ○ **Do not** try to recap the needle. Re-capping can lead to needle-stick injury.
	  ○ **Do not** touch the needle or let the needle touch anything before injecting.

STEP 7	**Pinch the skin**
	• Gently pinch the area of cleaned skin around your injection site and hold it firmly. • Keep the skin pinched during the entire injection. You will inject into the pinched skin. • **Do not** let go until you have removed the needle from your skin at the end of the injection.
STEP 8	**Before injecting, review steps A, B, and C to learn the correct way to inject**
Important: Do not move the pre-filled syringe when inserting the needle into your skin, while injecting, or when removing the needle from your skin.	
	• Hold the pre-filled syringe by the blue finger grip. Avoid touching the blue thumb pad. • Using a quick, “dart-like” motion, insert the needle into the pinched skin at about a **45-degree angle**. • **Do not** move the needle while inserting or during the injection.
A Inserting the needle	
	**To inject Spevigo:** • Use your thumb to slowly press down on the blue thumb pad to push the plunger rod down inside the syringe body. • Continue pressing on the blue thumb pad until the plunger rod has moved all the way down. • Make sure that the blue thumb pad cannot be pressed any further so that **the built-in safety cover can be activated**.
B Injecting the medicine	

<table>
<tr><td> 
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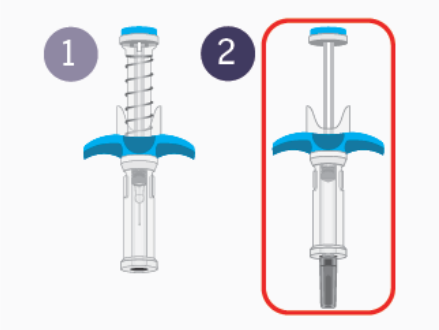
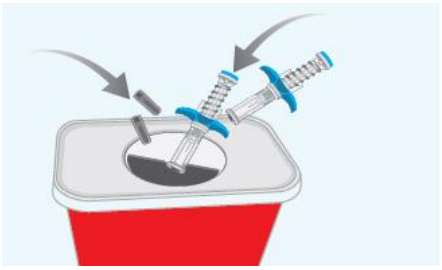
Slowly remove your thumb from the blue thumb pad, to move the needle out of your skin and up into the safety cover.

Check that the thumb pad springs back and that the needle is inside the safety cover.
If the needle is not inside the safety cover call your doctor. You may not have received a full dose.

If there is bleeding, press a cotton ball or gauze on the site for a few seconds.
Do not rub the injection site.
Apply a plaster if needed.

</td></tr>
<tr><td>C Checking injection is complete</td><td></td></tr>
<tr><td>STEP 9</td><td>Second injection</td></tr>
<tr><td> 
</td><td>

Choose a different injection site.
The new injection site should be at least 2 cm away from last injection site.
Take the second pre-filled syringe.
Repeat steps 4 through 8 right away.
Then continue to step 10.

Important: You must inject the contents of both Spevigo pre-filled syringes to give a complete dose.
</td></tr>
<tr><td>STEP 10</td><td>Disposing of the used pre-filled syringes and caps</td></tr>
<tr><td>  </td><td>

Put the used pre-filled syringes and caps in a sharps disposal container right away after use.
Do not throw away the pre-filled syringes in the household waste.
Your doctor, pharmacist, or nurse will tell you how to return the full sharps disposal container.
Do not reuse the pre-filled syringes.

Important: Always keep the sharps disposal container out of the reach of children.
</td></tr>
</table>