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 flares in adult patients with generalised pustular psoriasis (GPP) as monotherapy.

4.2 Posology and method of administration

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

Posology

The recommended dose is a single dose of 900 mg (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.

Clinical data for treatment of subsequent flares is very limited (see section 4.4).

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

Elderly
No dose adjustment is required.

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

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

Method of administration

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

Following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, it is administered as a continuous intravenous infusion through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micron) over 90 minutes. No other infusion should be administered in parallel via the same intravenous access.

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

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Traceability

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

Infections

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

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

Pre-treatment evaluation for tuberculosis

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

Anti-TB therapy should be considered prior to initiating spesolimab treatment in patients with latent TB, a history of TB or possible previous exposure to people with active tuberculosis in whom an

adequate course of treatment cannot be confirmed. After spesolimab treatment, patients should be monitored for signs and symptoms of active TB.

Hypersensitivity and infusion-related reactions

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

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

If a patient develops mild or moderate hypersensitivity during the infusion, treatment should be stopped and appropriate medical therapy should be considered (e.g., systemic anti-histamines and/or corticosteroids). Upon resolution of the reaction, the infusion may be restarted at a slower infusion rate with gradual increase to complete the infusion (see section 4.2).

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

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

Concomitant use with other GPP treatments

The safety and efficacy of spesolimab in combination with immunosuppressants, including biologics, have not been evaluated systematically (see section 4.5). In the GPP flare treatment clinical study, there was a washout period for most other treatments (biologics, other systemic immunomodulating treatments), while some treatments were discontinued before initiation of spesolimab treatment with no washout period required (methotrexate, cyclosporine, retinoids, topical treatments) (see section 5.1).
Concomitant use of other immunosuppressants and spesolimab is not recommended. At initiation of spesolimab treatment, other GPP treatments should be stopped and other treatments (e.g. with systemic immunosuppressants) should not be used concomitantly to treat the flare.

Re-treatment

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

Immunisations

It is unknown whether spesolimab affects the efficacy of vaccines.

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

Peripheral neuropathy

The potential for peripheral neuropathy with 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. For the treatment of GPP flares, spesolimab is not expected to cause cytokine mediated CYP interaction as a perpetrator.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data from the use of spesolimab in pregnant women. Non-clinical studies using a surrogate, mouse specific anti-IL36R monoclonal antibody do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Human immunoglobulin (IgG) is known to cross the placental barrier. As a precautionary measure, it is preferable to avoid the use of spesolimab during pregnancy.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

Table 1 provides a list of the adverse reactions reported from clinical trials. The adverse reactions are listed by MedDRA System Organ Class (SOC) 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
Skin and subcutaneous tissue disorders	Pruritus	Common
General disorders and administration site conditions	Injection site reactions	Very common[b)]
	Fatigue	Common

[a)] The most commonly reported infections were Urinary tract infection (Common) and Upper respiratory tract infection (Common)
[b)] Not reported in Effisayil 1

Description of selected adverse reactions

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

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

Immunogenicity
In patients with GPP treated with spesolimab in Effisayil 1, anti-drug antibodies (ADA) formed with a median onset of 2.3 weeks. Following intravenous administration of spesolimab 900 mg, 24% of patients had a maximum ADA titer greater than 4 000 and were Neutralising antibody-positive by end of the trial (weeks 12 to 17). Females appeared to have higher immunogenicity response; the percentage of patients with ADA titer greater than 4 000 was 30% in females, and 12% in males, respectively.
In some patients with ADA titer values > 4 000, plasma spesolimab concentrations were reduced, with no apparent impact on pharmacokinetics at ADA titers below 4 000.
As the majority of patients did not experience a subsequent new flare in Effisayil 1, the data on re-treatment of patients with ADA (n = 4) is limited. It is currently unknown if there is a correlation between the presence of ADA to spesolimab and maintenance of efficacy or hypersensitivity reactions upon re-treatment.

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. Adverse reactions observed in subjects receiving single or repeated doses up to 1 200 mg were consistent with the known safety profile of spesolimab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, interleukin inhibitors, ATC code: L04AC22

Mechanism of action

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

Pharmacodynamic effects

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

Clinical efficacy and safety

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

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

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

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

The primary endpoint of the study was the proportion of patients with a GPPGA pustulation sub score

of 0 (indicating no visible pustules) at week 1 after treatment. The key secondary endpoint of the study was the proportion of patients with a GPPGA total score of 0 or 1 (clear or almost clear skin) at week 1. For the GPPGA pustulation sub score of 0, the GPPGA total score of 0/1 and the GPPASI 75, non-responder imputation was used to handle the occurrence of escape (treatment at the investigator's choice if the disease worsened) and rescue (single 900 mg dose of intravenous spesolimab) medication use and missing data.

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

The study population consisted of 32% men and 68% women. The mean age was 43 (range: 21 to 69) years; 55% of patients were 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

	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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Spevigo in one or more subsets of the paediatric population 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. In some patients with ADA titer values > 4 000, plasma spesolimab concentrations were reduced, with no apparent impact on pharmacokinetics at ADA titers below 4 000 (see section 4.8).

Distribution

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

Biotransformation

The metabolic pathway of spesolimab has not been 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 (0.3-20 mg/kg), based on the population PK model, spesolimab clearance (95% CI) in a typical ADA-negative patient with GPP, weighing 70 kg was 0.184 L/day. The terminal-half-life was 25.5 days. Clearance of spesolimab was increased in some patients with ADA titer values > 4 000.

Linearity/non-linearity

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

Body weight

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

Elderly / gender / race

Based on population pharmacokinetic analyses, age, gender and race do not have an effect on the pharmacokinetics of spesolimab.

Hepatic and renal impairment

As a monoclonal antibody, spesolimab is not expected to undergo hepatic or renal elimination. No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of spesolimab was conducted.
Population PK analysis did not identify mild hepatic impairment or mild or moderate renal impairment as having an influence on the systemic exposure of spesolimab.

Paediatric population

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

5.3 Preclinical safety data

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

Developmental and reproductive toxicity

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

Genotoxicity

Genotoxicity studies have not been conducted with spesolimab.

Carcinogenicity

Carcinogenicity and mutagenicity studies have not been conducted with spesolimab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

3 years.

After opening

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

After preparation of infusion

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

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

6.4 Special precautions for storage

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. 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 (complete content from two vials of 450 mg/7.5 mL). Mix gently before use. The diluted spesolimab infusion solution should be used immediately.
- Spevigo must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of diluted spesolimab infusion solution, if the compatibility information above is considered. The line must be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

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

7. 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:

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 patients 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

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 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 and adolescents under 18 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 is 900 mg (2 vials of 450 mg/7.5 mL).

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 or pain at the injection site

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

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.

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This leaflet was last revised in

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 is a single dose of 900 mg (2 vials of 450 mg) administered as an intravenous infusion. Spevigo must be diluted before use. It should not be administered as an intravenous push or bolus.

If flare symptoms persist, an additional 900 mg dose may be administered 1 week after the initial dose.

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. 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 (complete content from two vials of 450 mg/7.5 mL). Mix gently before use. The diluted spesolimab infusion solution should be used immediately.

- Spevigo must not be mixed with other medicinal products. A pre-existing intravenous line may be used for administration of 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.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.