swissmedic

Date: 7 December 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Spevigo

International non-proprietary name: spesolimab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 450 mg

Route(s) of administration: intravenous

Marketing authorisation holder: Boehringer Ingelheim (Schweiz) GmbH

Marketing authorisation no.: 68625

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 9 August 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Creatinine clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
Da	Dalton
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
GPP	Generalised pustular psoriasis
GPPGA	GPP Physician Global Assessment
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IL-1R	Interleukin-1 receptor
IL-36	Interleukin-36
IL-36R	Interleukin-36 receptor
INN	International non-proprietary name
IP	Investigational product
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
Nab	Neutralising antibody
NO(A)EL	No observed (adverse) effect level
OL	Open-label
PBMC	Peripheral blood mononuclear cells
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics

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PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SC	Subcutaneous
SNDS	Système National des Données de Santé
SOC	Standard of care
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for spesolimab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 10 January 2022.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Spevigo is indicated for the treatment of flares in adult patients with generalised pustular psoriasis.

2.2.2 Approved indication

Temporarily authorised indication
Spevigo is indicated for the treatment of flares in adult patients with generalised pustular psoriasis.
Spevigo is used as a monotherapy.
This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Spevigo is a single dose of 900 mg (2 vials of 450 mg/7.5 ml each) and is administered as an intravenous infusion.
If flare symptoms persist, an additional dose of 900 mg may be administered 1 week after the first dose.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	8 December 2021
Formal objection	6 January 2022
Response to formal objection	13 January 2022
Formal control completed	19 January 2022
List of Questions (LoQ)	23 May 2022
Response to LoQ	14 August 2022
Preliminary decision	4 November 2022
Response to preliminary decision	23 January 2023
Labelling corrections	18 April 2023
Response to labelling corrections	16 May 2023
Final decision	9 August 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical context

Generalised pustular psoriasis (GPP) is a rare and severe skin disorder characterised by recurrent and widespread eruptions of sterile, visible pustules, often accompanied by systemic inflammation. These flares can lead to substantial morbidity and, in some cases, even mortality. During a GPP flare, there is an acute onset of painful skin manifestations, including the formation of aseptic pustules. These skin lesions are often accompanied by systemic symptoms such as high fever, extreme fatigue, and an acute phase response marked by elevated C-reactive protein levels. Severe GPP flares can lead to multi-organ failure, affecting vital systems such as the lungs (ARDS), liver, kidneys, and the cardiovascular system, potentially resulting in sepsis.
The severity of GPP flares can vary, but they have the potential to progress rapidly to a life-threatening state, necessitating hospitalisation and intensive inpatient medical care and monitoring. Studies have shown that hospitalisation rates for GPP are higher compared to plaque psoriasis, and inpatient stays are significantly longer. The range of reported mortality rates in contemporary contexts is estimated to be between 2% and 7%. Additionally, research based on the French SNDS database indicates that all-cause mortality for patients hospitalised with a GPP flare is approximately 2.5% within 4 weeks following the flare.
Despite the significant impact of GPP flares on patients' health and well-being, there are currently no approved therapies specifically indicated for the treatment of GPP flares. Available evidence on the efficacy and safety of non-targeted immunomodulatory therapies, such as methotrexate, cyclosporine, retinoids, and systemic corticosteroids, is limited. Furthermore, most of these therapies used in clinical practice are associated with toxicities that make them unsuitable for long-term use. This limitation in efficacy and safety data also applies to biologic treatment options for GPP, including TNF inhibitors (adalimumab, infliximab, and certolizumab pegol), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab).
To date, in Switzerland, no medicinal product has been authorized specifically for the treatment of GPP.

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4 Quality aspects

4.1 Drug substance

Spesolimab is a humanised antagonistic monoclonal IgG1 antibody that is directed against human IL-36 receptor. Spesolimab is a glycoprotein (molecular weight approx. 146,000 Da) composed of 2 heavy chains of 449 amino acids and 2 kappa light chains of 215 amino acids, which are linked through inter-chain disulfide bonds.

Spesolimab is produced in CHO cells. A two-tiered cell banking system of master cell bank and working cell bank (WCB) is in place. After thawing of the WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The cell culture fluid is harvested, and purification is performed with a series of chromatography steps, ultra-/diafiltration steps, and viral inactivation and viral filtration steps.

The fermentation and purification processes for the spesolimab drug substance are both validated with several consecutive batches, and the data demonstrated a consistent production and an efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for the spesolimab drug substance, including changes to manufacturing site and production scale. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the spesolimab drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release and stability of the spesolimab drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data, and stability data, and conform with current compendial or regulatory guidelines.

Batch analysis data for development, clinical, and process validation batches of the spesolimab drug substance were provided. All specific analytical methods are described and are fully validated.

The spesolimab drug substance is stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

4.2 Drug product

Spesolimab concentrate for solution for infusion 450 mg/vial (60 mg/mL) is a colourless to slightly brownish-yellow, clear to slightly opalescent solution. The 450-mg spesolimab concentrate is presented in 10 mL clear glass vials, with a rubber stopper and an aluminium crimp cap.

The concentrate for solution for infusion is a buffered, isotonic, preservative-free solution, which is diluted with 0.9% sodium chloride solution prior to administration to the target concentration.

The excipients, sodium acetate trihydrate, glacial acetic acid, sucrose, arginine hydrochloride, polysorbate 20, and water for injection, are of compendial grade and commonly used for the formulation of biopharmaceuticals.

Several drug product dosage strengths, formulations, presentations, and filling facilities were used during clinical development. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes.

The materials of the Type I glass vial and rubber stopper meet compendial requirements.

Compatibility studies were conducted to establish the in-use stability of the diluted drug product with the intended materials and conditions of use.

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The drug product manufacturing process consists of thawing the formulated drug substance, dilution and mixing, bioburden-reducing filtration, sterile filtration and aseptic filling, crimping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated a consistent production.

The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product including development batches, clinical batches, and process validation batches, were provided. All batch release data comply with the drug product specifications, which were valid at the time of testing. All specific analytical methods are validated.

The vials are stored at 2°C to 8°C protected from light. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product have been demonstrated. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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5 Nonclinical aspects

5.1 Pharmacology

Spesolimab demonstrated high affinity to human IL-36R (223 pM) in *in vitro* assays. It did not bind to IL-36R from rats, pigs, rhesus monkeys, marmosets, and hamsters, and showed only weak binding to cynomolgus monkey IL-36R. Therefore, a surrogate mouse antibody (BI 674304) was developed to study the pharmacology, pharmacokinetics, and toxicology of spesolimab. BI 674304 bound exclusively to mouse IL-36R (164 pM).

In cell-based assays, spesolimab inhibited IL-8 production and NFκB phosphorylation in a dose-dependent manner in human keratinocytes, dermal fibroblasts, and intestinal myofibroblasts stimulated with IL-36R ligands, with mean IC_{90} values of 1.6 nM and 3.3 nM, respectively. IL-8 inhibition was independent of IL-1R signalling. Spesolimab alone did not stimulate cytokine production in human PBMC, ruling out an agonistic activity.

BI 674304 inhibited the production of IL-2 and IFNγ (similar to PBMC in humans) with mean IC_{90} values of 5.5 and 3.8 nM, respectively, in mouse splenocytes stimulated with IL-36R ligands. IL-36 ligand-stimulated phosphorylation of NFκB in NIH3T3 and primary dermal fibroblasts cells were dose-dependently inhibited with IC_{90} values of 18 nM and 13 nM, respectively. No agonistic activity was observed in either the NIH3T3 or the dermal fibroblast NFκB assay in the absence of ligands.

These studies support the proposed mechanism of action of spesolimab. The *in vitro* binding affinity and functional activity data of BI 674304 support its use for the safety assessment in mice.

The *in vivo* effects of BI 674304 were studied in mouse models of skin inflammation (IL-36 or IL-36/TNFα and imiquimod ear swelling models). In both models ear swelling reduction was variable (43-84%) after single intraperitoneal doses of 250 and 500 µg. These *in vivo* studies indicate an anti-inflammatory effect of BI 674304.

No dedicated secondary pharmacology studies were conducted. The other members of the IL-1 family were investigated in the primary pharmacodynamics studies with no off-target effects. In addition, spesolimab is a specific antibody and the toxicology studies showed no adverse effects.

Spesolimab showed decreased binding to and a weaker affinity for the Fcγ receptors compared to IgG1 wild-type antibodies. Therefore, an antibody-dependent cell-mediated cytotoxicity is not expected.

Safety pharmacology parameters were evaluated in the repeat-dose toxicity studies with the surrogate in mice. There were no effects on cardiovascular, respiratory, and central nervous system function.

5.2 Pharmacokinetics

The pharmacokinetics of BI 674304 were investigated in mice following single intraperitoneal and repeated twice-weekly intravenous (IV) administration. BI 674304 clearance in mice was dose-dependent and comparable to the values in humans. Following IV administration, serum exposure increased dose-proportionally and was comparable in males and females. Drug accumulation ratios up to 3.0-fold were observed at 50 mg/kg/dose.

As exposure in offspring was confirmed in mice, use during lactation should be avoided, even though no adverse effects were observed in the enhanced pre-/postnatal development (ePPND) study. The text in the information for healthcare professionals is adequate.

Studies on distribution, metabolism, and excretion were not conducted and are not required since spesolimab is a monoclonal antibody.

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5.3 Toxicology

Spesolimab did not show pharmacological activity in preclinical species. Therefore, the toxicology assessment was conducted in mice with surrogate antibody BI 674304. In all studies, the administration route was IV, consistent with the clinical route of administration. The dosing frequency was twice weekly, i.e. more often than proposed for clinical use to ensure adequate exposure.

The maximum duration of the repeated-dose studies (6 months) supports the proposed chronic clinical use. Safety margins were not calculated, as according to ICH S6(R1), toxicity studies conducted with homologous monoclonal antibodies are useful for hazard identification, but are not useful for quantitative risk assessment.

No single-dose toxicity studies were conducted. In the repeated-dose studies with up to 50 mg/kg/dose, there were no local or systemic adverse effects related to BI 674304 treatment. No toxicological effects were identified on the immune system.

Genotoxicity and carcinogenicity studies were not conducted for spesolimab according to ICH S6(R1). An adequate risk assessment of the carcinogenic potential of spesolimab based on the literature was submitted. The weight of evidence indicates a low risk for carcinogenicity.

A fertility and early embryonic development study was conducted in male and female mice. No BI 674304-related findings were observed in fertility indices, oestrus cycles, implantations, and in reproductive organs of females and males.

In the embryofetal development study, pregnant mice were administered BI 674304 up to 50 mg/kg/dose on gestation days (GD) 6, 9, 12 and 15. There were no BI 674304-related effects on maternal parameters or on fetal growth and dysmorphogenesis at any dose.

In the ePPND study, female mice were treated with BI 674304 up to 50 mg/kg/dose on GD 6, 9, 12, 15, and 17, and on lactation days 3, 6, 9, 12, 15, and 18. There was no BI 674304-related effect on maternal performance or on body weight, reproductive maturation, neurobehaviour, and reproductive competency of the adult offspring.

No local effects were observed following subcutaneous administration of spesolimab in rabbits.

In a human tissue cross-reactivity study, spesolimab-specific staining was detected in many organs/tissues including skin, which is known to have a high IL-36 gene expression and is the target organ for the therapeutic use of spesolimab. Toxicological findings were not observed in any of these organs in mice treated with the surrogate antibody.

There were no effects in the cytokine release assay *in vitro*.

There are no concerns related to excipients or impurities.

The summary of the key findings from the nonclinical studies in the RMP is acceptable. Overall, no safety risks were identified in the nonclinical studies that would require specific post-authorisation monitoring.

Since spesolimab is a protein, there is no risk for the environment by its therapeutic use.

5.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of the surrogate antibody BI 674304 was well characterised and the studies are considered adequate to evaluate the safety of spesolimab. The application is approvable from the nonclinical view.

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6 Clinical aspects

6.1 Clinical pharmacology

Absorption
Spesolimab is administered by IV infusion.

Distribution
The steady state volume of distribution of spesolimab was 6.39 L in a typical ADA-negative GPP patient.

Metabolism and elimination
No studies regarding the metabolism of spesolimab have been conducted considering the biological nature of the molecule.
Spesolimab is eliminated by parallel target-mediated drug disposition (TMDD) and linear clearance. TMDD is saturated at doses > 0.3 mg/kg in healthy subjects. Due to a lack of PK data in GPP patients in the low dose range, the extent of TMDD versus linear clearance in GPP patients has not been assessed. However, in the therapeutically relevant dose range, the PK of spesolimab is linear in GPP patients.
The terminal elimination half-life of spesolimab in a typical ADA-negative GPP patients was 25.5 days.

Special populations / Intrinsic factors

Body weight
As is to be expected for an antibody drug, body weight had an influence on the PK and was included as a covariate with fixed allometric scaling factors on the clearance and volume terms in the PopPK model. Simulations indicated that lighter subjects (54.5 kg) may have a higher AUC (1.25-fold), while heavier subjects (97 kg) may have a lower AUC (0.75-fold) compared to a typical GPP patient weighing 70 kg. Similar effects were observed on C_{max}.

ADAs
ADA/NAb development was assessed, in 2 studies in GPP patients. In one study, 23 (46%) of the spesolimab-treated patients were ADA-positive after treatment, and the majority (87%) of the ADA-positive patients (40% of total treated) were also NAb positive. In the other study 50% (n=3 of 6) of spesolimab-treated patients were ADA-positive.

Evaluation of PK by ADA status indicated a significant influence of ADAs on the PK:
The mean AUC was lower in ADA-positive patients than in ADA-negative patients, with a high variability in the ADA-positive patients. In addition, the terminal half-life for ADA-positive patients was shorter than for ADA-negative patients, with high variability.
A quantitative analysis of ADA effects on the PK was conducted in the PopPK analyses. ADA titres, as a continuous time-varying covariate, were modelled to have a Michaelis-Menten type of effect on CL. However due to the large heterogeneity in ADA response between individuals, the respective parameters were estimated with high uncertainty. Nevertheless, a large ADA titre tended to be associated with a decrease in AUC while C_{max} was unaffected.

Renal or hepatic function
No dedicated studies in subjects with impaired renal or hepatic function have been submitted. However, considering the biological nature of the molecule and the mechanism of action, no effects of renal or hepatic function on the PK of spesolimab are expected. The lack of specific PK studies in these subpopulations is acceptable.

Ethnicity, age, gender
Based on the PopPK analysis, age, gender, and ethnicity had no significant effects on the PK of spesolimab and no dose adjustments are required based on these factors.

Interactions

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Considering the biological nature of the molecule and the mechanism of action of spesolimab, the interaction potential for a direct interaction with enzymes involved in xenobiotic metabolism or with drug transporters is generally considered to be low.
The DDI potential due to modulation of inflammatory cytokines was considered to be low, as an increase in pro-inflammatory biomarkers in GPP is transient, primarily associated with flares, and tends to be quickly normalised (within 48h) by spesolimab treatment before significant changes in enzyme expression may take place.

Pharmacodynamics

Mechanism of action and primary pharmacology
Spesolimab is a humanised antagonistic monoclonal IgG1 antibody that binds to IL-36R and blocks human IL-36α-, IL-36β-, and IL-36γ-induced IL-36R activation and downstream inflammatory signalling cascades.

Secondary pharmacology (safety)
Considering the biological nature of the molecule and the mechanism of action of spesolimab, no effects on the QT interval are expected.

6.2 Dose finding and dose recommendation

No specific dose finding was performed in this indication.

The dose used in the phase 1 proof-of-concept study 1368-0011 was used to determine the dosing scheme for the pivotal study 1368-0013. In study 1368-0011 a dose of 10 mg/kg was shown to be safe and well tolerated in GPP patients with moderate flares (n=7), with no severe or serious adverse events. In study 1368-0013, an approximately 25% higher fixed dose of 900 mg was selected, mainly to maintain the PK exposures observed and to allow flexibility to recruit patients with a body weight >70 kg.

6.3 Efficacy

Efficacy in patients with GPP was investigated in study 1368-0013, which was a double-blind, randomised, placebo-controlled, multicentre study of a single intravenous dose of spesolimab.

Patients aged 18-75 years with GPP presenting with a flare of moderate to severe intensity were randomised to receive 900 mg IV spesolimab or placebo (2:1). In total, n=53 patients were enrolled: n=18 into the placebo and n=35 into the investigational product (IP) group.

GPP flare of moderate-to-severe intensity was defined as a GPP Physician Global Assessment (GPPGA) total score of ≥3, new appearance or worsening of existing pustules, a GPPGA pustulation subscore of ≥2, and erythema covering ≥5% body surface area (BSA).

Patients received either 900 mg spesolimab or placebo according to their treatment assignment on Day 1 in a double-blind manner. The investigator could treat the patient with a standard of care (SOC) treatment of his/her choice in case disease worsened within the first week, independent of the prior treatment administered in the study. The SOC was not predefined and included all available therapeutic options for psoriasis. Patients in both arms who had not received SOC as rescue treatment and had persistent symptoms based on a predefined threshold were eligible to receive treatment with an open-label dose of spesolimab 900 mg IV on Day 8. This allowed patients randomised to spesolimab for exploration of a higher total dose (second dose) in this trial.

After Day 8, only 1 rescue treatment with a single IV dose of 900 mg spesolimab could be further administered in case of a reoccurrence of a flare.

The primary endpoint was defined as a GPPGA pustulation subscore of 0, indicating no visible pustules, at Week 1. The key secondary endpoint was defined as a GPPGA total score of 0 or 1 at Week 1.

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A total of n=27 patients (spesolimab: n=12 patients, 34.3%; placebo: n=15 patients, 83.3%) received OL treatment with spesolimab on Day 8, and n=6 patients (spesolimab: n=4 patients, 11.4%; placebo: n=2 patients, 11.1%) received rescue treatment with spesolimab after Day 8.

For the primary endpoint, there was a statistically significant improvement in the rate of patients with a GPPGA pustulation subscore of 0 at week 1 in the spesolimab arm, with a risk difference of 48.7% (95% CI: 21.5, 67.2) and a one-sided p-value of 0.0004. N=19 patients (54.3%) in the IP group and n=1 patient in the comparator arm (5.6%) achieved a GPPGA postulation subscore of 0 at Week 1.

As for the key secondary endpoint, the proportion of patients who achieved a GPPGA total score of 0 or 1 was significantly higher in the spesolimab group (n=15, 42.9%) compared with the placebo group (n=2, 11.1%), leading to a risk difference of 31.7% (one-sided p-value=0.0118).

All other secondary endpoints included in the hierarchical testing strategy were statistically significant.

Analyses regarding open label application of spesolimab are of exploratory value only; however, spesolimab appeared to be effective even when applied 1 week “too late” and not directly at the time point of flare.

Analysis of the treatment effect in the predefined subgroups for the primary and key secondary endpoints showed overall consistent results across subgroups. However, the interpretability of the results is limited due to the small sample sizes.

6.4 Safety

The assessment of the safety profile of spesolimab for the current application is based on the pivotal study 1368-0013 and supportive data from other GPP trials. The overall number of patients exposed to spesolimab was n=401.The total number of patients who received at least 1 dose of ≥ 900 mg spesolimab IV across all trials in patients was 172. The long-term safety data are therefore very limited.

Safety was difficult to assess, given that the comparison to placebo could only be made throughout Week 1, which corresponds to the double-blind period. In the early phase of treatment, there was a higher incidence of adverse events (AEs) of any grade in the spesolimab arm (77.1% vs. 66.7%), also with regard to grade (G) 3-4 (17.1% vs. 11.1%). The rate of serious adverse events (SAEs) was similar between both treatment arms: n=5 (14.3%) in the IP group vs. n=3 (16.7%) in the placebo group.

In the later study period, almost all patients received at least 1 dose of spesolimab (n=51), irrespective of initial randomisation. Up to Week 12, any AEs were reported in almost all patients (92.2%) and G3-4 AEs in about one-fifth of patients (21.6%). The rate of SAEs increased to 25.5%.

The following AEs by system organ class (SOC) were reported more frequently in the spesolimab arm compared to placebo:

Up to Week 1:
- Infections and infestations 17.1% vs. 5.6%
- Urinary tract infection 5.7% vs. 0%

Up to Week12:
- Infections and infestations 34.3% vs. 5.6%
- Urinary tract infection 5.7% vs. 0%
- Bacteraemia 2.9% vs. 0%
- Headache 11.4% vs. 5.6%
- Gastrointestinal disorders 17.1% vs. 5.6%
- Nausea 8.6% vs. 0%
- Vomiting 5.7% vs. 5.6%

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The immunogenicity of spesolimab was tested through sampling and analysis for anti-drug antibodies (ADAs) in the healthy volunteer trials.

The influence of ADA development on safety in the clinical trials was mainly assessed based on hypersensitivity adverse events. In trial 13-0013 and most other trials, the frequency and incidence rate of such events was comparable before and after ADA development.

6.5 Final clinical benefit risk assessment

GPP is a rare skin disease with potentially life-threatening systemic sequelae. To date, in Switzerland, no medicinal product has been authorized for the treatment of GPP specifically.

Efficacy of spesolimab was established in study 1368-0013.

For the primary endpoint, there was a statistically significant improvement in the rate of patients with GPPGA pustulation subscore of 0 at week 1 in the spesolimab arm.

The secondary endpoints included in the hierarchical testing strategy were statistically significant.

The analysis of the treatment effect in the predefined subgroups for the primary and key secondary endpoints showed overall consistent results across subgroups.

Overall, efficacy of spesolimab in the proposed indication was sufficiently demonstrated.

The assessment of the safety profile is hampered by the short time interval of double-blind treatment and the limited size of the trial. From the data so far available, no prohibitive safety signal emerged.

The applicant is committed to gather more longer-term safety data as a post-marketing requirement.

In addition, immunogenicity will be further studied given that a very fast ADA development was observed and its impact on efficacy and safety is not known in case of a longer-term therapy with repetitive doses.

Concerning repetitive doses, there were almost no data or clinical experience in patients receiving more than 3 doses of spesolimab 900 mg IV subsequently. This issue was reflected accordingly in the information for healthcare professionals.

In summary, while from the data at hand, a positive benefit-risk ratio could be assessed, uncertainties especially with regard to (longer-term) safety, dose selection and immunogenicity, remain. Swissmedic therefore decided to grant a *conditional* approval for Spevigo in the treatment of GPP.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Spevigo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.
Spevigo is temporarily authorised – see "Indications/Uses" section.

Spevigo®

Composition

Active substances

Spesolimab (manufactured from genetically modified CHO [Chinese Hamster Ovary] cells)

Excipients

Each vial contains: sodium acetate trihydrate (corresp. 6.8 mg sodium), glacial acetic acid, saccharose, arginine hydrochloride, polysorbate 20, water for injection ad solutionem pro 7.5 mL.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion: one vial with 7.5 mL contains 450 mg spesolimab

Indications/Uses

Temporarily authorised indication
Spevigo is indicated for the treatment of flares in adult patients with generalized pustular psoriasis.
Spevigo is used as a monotherapy.
This indication has been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Dosage/Administration

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

Traceability

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

Dosage

The recommended dose of Spevigo is a single dose of 900 mg (2 x 450 mg/7.5 ml vials) 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 “Warnings and precautions”).

Special dosage instructions

Patients with impaired hepatic or renal function

Spevigo has not been studied in these patient populations. However, these conditions are not expected to have any clinically relevant impact on the pharmacokinetics of Spevigo and no dose adjustments are considered necessary.

Elderly patients

No dose adjustment is required.
There is limited information in patients aged 65 years and older.

Children and adolescents

The safety and efficacy of Spevigo in children below the age of 18 years have not been established. No data are available.

Mode of administration

Spevigo must be diluted before use (see section “Instructions for handling”).

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 µm) over 90 minutes.

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 “Warnings and Precautions”).

Contraindications

Severe or life-threatening hypersensitivity to the active substance or to any of the excipients (see section “Composition” and “Warnings and Precautions”)

Warnings and precautions

Infections
Spevigo may increase the risk of infections. During the 1-week placebo-controlled period in the Effisayil-1 trial, infections were reported in 17.1% of patients treated with Spevigo compared with 5.6% of patients treated with placebo (see section “Undesirable effects”).

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 Spevigo. Treatment with Spevigo 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 Spevigo.

Pre-treatment evaluation for tuberculosis
Patients should be evaluated for tuberculosis (TB) infection prior to initiating treatment with Spevigo. Spevigo should not be administered to patients with active TB infection.

Anti-TB therapy should be considered prior to initiating Spevigo in patients with latent TB or a history of TB in whom an adequate course of treatment cannot be confirmed. After Spevigo 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 Spevigo. 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, Spevigo should be discontinued immediately and appropriate treatment should be initiated (see section “Contraindications”).

If a patient develops mild or moderate infusion-related reaction, Spevigo should be stopped and appropriate medical therapy should be considered (e.g., systemic antihistamines and/or corticosteroids). Upon resolution of the reaction, the infusion may be restarted at a slower infusion rate with gradual increase to complete the infusion (see “Dosage/Administration”).

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.

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 were followed up for a minimum of 8 weeks.

Immunisations

No specific studies have been conducted in patients who have recently received live viral or live bacterial vaccines. The interval between live vaccinations and initiation of Spevigo therapy should be at least 4 weeks. Live vaccines should not be administered for at least 16 weeks after treatment with Spevigo.

Peripheral neuropathy

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 900 mg dose, that is to say essentially ‘sodium free’.

Interactions

No interaction studies have been performed.

Live vaccines should not be given concurrently with Spevigo (see section “Warnings and Precaution”).

Pharmacokinetic interactions

Population PK analyses indicated that concomitant use of immunosuppressants or oral corticosteroids did not have a direct impact on the pharmacokinetics of spesolimab.

Pregnancy, lactation

Pregnancy

There are limited data from the use of spesolimab in pregnant women. Pre-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 “Preclinical data”). As a precautionary measure, the use of Spevigo should be avoided during pregnancy.

Lactation

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. Pre-clinical 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.

Effects on ability to drive and use machines

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

Undesirable effects

Summary of the safety profile

The safety data provided in the following are based on Effisayil 1, a double-blind, randomised trial comparing a single intravenous 900 mg dose of Spevigo (n=35) with placebo (n=18) in patients with generalized pustular psoriasis for up to 12 weeks after treatment and four double-blind, placebo-controlled trials of 254 spesolimab-treated patients who received doses up to 1200 mg intravenous or subcutaneous spesolimab for other diseases.

The following adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows:

"very common" (≥1/10)
"common" (≥1/100, <1/10),
"uncommon" (≥1/1,000, <1/100)
"rare" (≥1/10,000, <1/ 1,000)
"very rare" (<1/10,000)
"not known" (frequency cannot be estimated from the available data)

Infections and infestations

Very Common	infection (17.1%)[a)]

Skin and subcutaneous tissue disorders

Common	pruritus

General disorders and administration site conditions

Common:	fatigue
Not known	injection site reactions[b)]

[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 specific adverse reactions and additional information

Infections
The most frequent adverse reactions that occurred in subjects treated with Spevigo were infections. During the 1-week placebo-controlled period in Effisayil 1, infections were reported in 17.1% of patients treated with Spevigo compared with 5.6% of patients treated with placebo. Serious infection (urinary tract infection) was reported in 1 patient (2.9%) treated with Spevigo and no patients treated with placebo. 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
During clinical development, injection site reactions (including injection site erythema, injection site swelling, injection site pain, injection site induration, and injection site warmth) occurred with spesolimab. Injection site reactions were typically mild-to-moderate in severity.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.
In patients with GPP treated with Spesolimab in Effisayil-1, anti-drug antibodies (ADA) formed with a median onset of 2.3 weeks. Following administration of i.v. spesolimab 900 mg, 46% of patients were ADA-positive and 24% of patients had a maximum ADA titer greater than 4000. A total of 40% of patients developed Neutralising antibodies (Nab) by end of the trial (Weeks 12 to 17).
Females appeared to have higher immunogenicity response; the percentage of patients with positive ADAs were 58% in females compared with 24% in males. Maximum ADA titer was greater than 4000 in 30% of females and 12% of males, respectively.
In some ADA-positive patients, plasma spesolimab concentrations were reduced with larger effect seen at higher titers. In the presence of ADA, efficacy was observed upon re-treatment of recurring flares with Spevigo in open label extension trial. There was no apparent correlation between the presence of ADA to spesolimab and hypersensitivity reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no clinical experience with overdoses of Spevigo.
The highest dose of Spevigo administered in clinical trials was 1200 mg. Adverse events observed in subjects receiving single or repeated doses up to 1200 mg were consistent with the known safety profile of Spevigo.
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.

Properties/Effects

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 and pro-fibrotic pathways. IL-36R signalling is differentiated from TNF-α, integrin and IL-23 inhibitory pathways by directly and simultaneously blocking both inflammatory and pro-fibrotic pathways. Genetic human studies have established a strong link between IL36R signalling and skin inflammation.

Pharmacodynamics

Following treatment with Spevigo in patients with GPP, reduced levels of C-reactive protein (CRP), interleukin (IL)-6, 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

A randomised, double-blind, placebo-controlled study (Effisayil-1) was conducted to evaluate the clinical efficacy and safety of Spevigo in adult patients with flares of Generalized 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 Generalized 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 (BSA) covered with erythema and the presence of pustules. Patients were required to discontinue systemic and topical therapy for GPP prior to receiving study drug. Patients with an immediate life-threatening flare of GPP or requiring intensive care treatment were excluded from the study.

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.

A total of 53 patients were randomised (2:1) to receive a single intravenous dose of 900 mg Spevigo (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 Spevigo, resulting in 12 patients (34%) in the Spevigo arm receiving a second dose of Spevigo and 15 patients (83%) in

the placebo arm receiving one dose of Spevigo on Day 8. In addition, 6 patients (4 Spevigo arm; 2 placebo arm) received rescue treatment with a single 900 mg dose of intravenous Spevigo for reoccurrence of a flare after Day 8.

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

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 Spevigo arm compared with placebo (see Table 1).

Table 1 GPPGA Pustulation Sub Score and GPPGA Total Score at Week 1

	Placebo	Spevigo 900mg iv
Number of Patients analysed	18	35
Patients achieving a GPPGA pustulation sub score of 0, n (%)	1 (5.6)	19 (54.3)
Risk difference versus placebo, % (95% CI)	48.7 (21.5, 67.2)	
p-value*	0.0004	
Patients achieving a GPPGA total score of 0 or 1, n (%)	2 (11.1)	15 (42.9)
Risk difference versus placebo, % (95% CI)	31.7 (2.2, 52.7)	
p-value*	0.0118	

GPPGA = Generalized Pustular Psoriasis Physician Global Assessment; iv = intravenous

*One-sided p-value

In patients randomized to Spevigo, pustular clearance (GPPGA pustulation sub score of 0) was achieved as early as one day after treatment in 11.4% (4/35) of patients. The effect of up to two doses of Spevigo on GPPGA pustulation sub score and GPPGA total score was sustained until Week 12 .

The results of the primary and key secondary endpoints were consistent across subgroups including sex, age, race, GPPGA pustulation sub score at baseline, GPPGA total score at baseline, mutation status in IL36RN, and irrespective of any GPP treatment prior to randomization acknowledging the small sample sizes.

Pharmacokinetics

Absorption

A population pharmacokinetic model was developed based on data collected from healthy subjects, patients with GPP and patients with other diseases. After a single i.v. dose of 900 mg, the population PK model-estimated AUC0-∞ (95% CI) and Cmax (95% CI) in a typical ADA-negative patient with GPP were 4750 (4510, 4970) µg·day/mL and 238 (218, 256) µg/mL, respectively.

Distribution

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

Metabolism

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

Elimination

In the linear dose range (0.3-20 mg/kg), based on the population PK model, spesolimab clearance (95% CI) in a typical GPP patient without ADA, weighing 70 kg was 0.184 (0.175, 0.194) L/day. The terminal-half-life was 25.5 (24.4, 26.3) days. In patients with ADA titers greater than 4000 the geometric mean clearance of spesolimab was nearly doubled (see *Immunogenicity).*

Linearity/non-linearity

At low doses, spesolimab exhibited target-mediated drug disposition (TMDD) kinetics after single i.v. 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.

Kinetics in specific patient groups

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 renal impairment as having an influence on the systemic exposure of spesolimab.

Body weight
Spesolimab clearance increased with body weight in a less-than-proportional manner, such that a -/+50% change in body weight resulted in a -45% to 41% change in clearance. The impact of body weight on spesolimab clearance is not expected to be clinically meaningful.

Geriatric patients/Sex/Ethnicity

Based on population pharmacokinetic analyses, age (range: 18 to 76 years), gender (47% male, 53% female) and race (71% White, 24% Asian) do not have an effect on the pharmacokinetics of spesolimab.

Children and adolescents

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

Preclinical data

Pre-clinical data reveal no special hazard for humans.

Repeat dose toxicology studies were conducted in mice using a surrogate, mouse specific anti-IL36R monoclonal antibody by twice weekly intravenous injection for 26 weeks at a dose (50 mg/kg) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. No adverse changes in body weight, food consumption or clinical observations were noted at this dose. No adverse effects on clinical pathology parameters including haematology, immunophenotyping, clinical chemistry and histopathology, including lymphoid tissues, have been observed.

The binding specificity of spesolimab to human tissues was evaluated in a tissue cross-reactivity study. No unexpected tissue binding was observed.

Genotoxicity
Genotoxicity studies have not been conducted with spesolimab.

Carcinogenicity
Carcinogenicity studies have not been conducted with spesolimab.

Reproductive Toxicity

Pre-clinical studies conducted in mice using a surrogate antibody directed towards murine IL-36R do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development or fertility, at intravenous doses up to 50 mg/kg twice weekly.

Other information

Incompatibilities

Spevigo must not be mixed with other medicinal products.

Shelf life

This medicinal product may only be used until the date marked with “EXP” on the container.

Shelf life after opening

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

Shelf life after preparation of infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2-30°C followed by 3 hours infusion time.

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 2-8°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

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.

Keep medicines out of the reach of children.

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

Instructions for handling

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.

Spevigo is for single-use only and does not contain preservatives. Aseptic technique must be used to prepare the solution for infusion. Draw and discard 15 ml from a 100 ml container of sterile 0.9% sodium chloride solution and replace slowly with 15 ml Spevigo (complete content from two vials of 450 mg/7.5 ml). Mix gently before use. The diluted Spevigo 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 Spevigo. The line must be flushed with sterile 0.9% sodium chloride solution prior to and at the end of infusion. No other infusion should be administered in parallel via the same intravenous access.

No incompatibilities have been observed between Spevigo and infusion sets composed of polyvinylchloride (PVC), polyethylene (PE), polypropylene (PP). polybutadiene and polyurethane (PUR), and in-line filter membranes composed of polyethersulfone (PES, neutral and positively charged) and positively charged polyamide (PA).

Authorisation number

68625 (Swissmedic)

Packs

Packs of 2 vials (each with 450 mg spesolimab in 7.5 mL) [A].

Marketing authorisation holder

Boehringer Ingelheim (Schweiz) GmbH, Basel, Switzerland.

Date of revision of the text

November 2022