Date: 22 February 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Solmucol Bronchoprotect

Active substance:

lysate of the following bacteria: *Staphylococcus aureus* (6 billion bacteria), *Streptococcus pyogenes* (6 billion bacteria), *Streptococcus oralis* (6 billion bacteria), *Klebsiella pneumonia* (6 billion bacteria), *Klebsiella ozaenae* (6 billion bacteria), *Haemophilus influenzae* type B (6 billion bacteria), *Neisseria catarrhalis* (6 billion bacteria), *Streptococcus pneumoniae* type 1 (1 billion bacteria), 2 (1 billion bacteria), 3 (1 billion bacteria), 5 (1 billion bacteria), 8 (1 billion bacteria) and 47 (1 billion bacteria)

Pharmaceutical form: sublingual tablet

Dosage strength: 50 mg

Route(s) of administration: oral

Marketing Authorisation Holder: IBSA Institut Biochimique SA

Marketing Authorisation No.: 67822

Decision and Decision date: approved on 6 January 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of the SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ELISA	Enzyme-linked immunosorbent assay
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
PVC	Polyvinyl chloride
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) 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 the status of a new active entity for the active substance "lysate of the following bacteria: *Staphylococcus aureus* (6 billion bacteria), *Streptococcus pyogenes* (6 billion bacteria*), Streptococcus oralis* (6 billion bacteria), *Klebsiella pneumonia* (6 billion bacteria), *Klebsiella ozaenae* (6 billion bacteria), *Haemophilus influenzae* type B (6 billion bacteria), *Neisseria catarrhalis* (6 billion bacteria), *Streptococcus pneumoniae* type 1 (1 billion bacteria), 2 (1 billion bacteria), 3 (1 billion bacteria), 5 (1 billion bacteria), 8 (1 billion bacteria) and 47 (1 billion bacteria)" of the medicinal product mentioned above.

Authorisation in accordance with Art. 14 para. 1 a^{bis} TPA
The applicant requested a simplified authorisation in accordance with Art. 14 para. 1 a^{bis} TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

Prophylaxis of recurrent respiratory tract infections in adults and children from the age of 3 years.

2.2.2 Approved Indication

Prophylaxis of recurrent respiratory tract infections in adults and children from the age of 3 years.

2.2.3 Requested Dosage

Adults and children from the age of 3 years:
One tablet daily for ten consecutive days in a month, for a period of three months.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	23 December 2019
Formal control completed	10 June 2020
List of Questions (LoQ)	7 October 2020
Answers to LoQ	23 December 2020
Predecision	18 March 2021
Answers to Predecision	17 May 2021 and 4 August 2021
2nd Predecision	1 September 2021
Answers to 2nd Predecision	31 October 2021
Final Decision	6 January 2022
Decision	approval

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3 Quality Aspects

3.1 Drug Substance

INN: not applicable.
The common name of the active ingredient is lyophilised bacterial lysate and is not described in the European Pharmacopoeia

The active ingredient is a complex blend of products coming from the lysis of specific microorganisms (listed below), including proteins, glycoproteins, polysaccharides, lipids, and nucleic acids. Therefore, the traditional chemical structure and molecular formula are not applicable.

Staphylococcus aureus,
Streptococcus pyogenes,
Klebsiella pneumoniae,
Klebsiella ozaenae,
Neisseria (Branhamella = Moraxella) catarrhalis.
Haemophilus influenzae,
Streptococcus (viridans) oralis,
Streptococcus (Diplococcus) pneumoniae Ty 1,
Streptococcus (Diplococcus) pneumoniae Ty 2,
Streptococcus (Diplococcus) pneumoniae Ty 3,
Streptococcus (Diplococcus) pneumoniae Ty 5,
Streptococcus (Diplococcus) pneumoniae Ty 8,
Streptococcus (Diplococcus) pneumoniae Ty 47.

Among these 13 strains, six belong to the same species: *Streptococcus (Diplococcus) pneumoniae*.
The lyophilised bacterial lysate is obtained by blending the 13 different lyophilised lysates.
The final composition of the active powder is 14% bacterial lysate and 86% glycine used as support for lyophilisation.

The manufacturing process is adequately described, including fermentation, inactivation by heat, mechanical lysis, freeze-drying on glycine and grinding. Each strain is separately cultivated. Then, the final lysate is obtained by blending 13 single lysates.

Specification: Appearance, identity, loss on drying, immunostimulating activity, and microbiological quality are specified. The identification of each strain is performed using enzyme-linked immunosorbent assay (ELISA), a widely used method in immunology. The method does not allow for discrimination between sub-species. The proposed specifications and analytical methods were considered appropriate.

Stability: The proposed shelf-life and storage conditions are supported by the stability data.

3.2 Drug Product

Description and composition: The drug product is an immediate release, non-coated, round scored tablet for oromucosal use. Each sublingual tablet contains 50 mg lyophilised bacterial lysate (composed of 7 mg lyophilised bacterial lysate and 43 mg glycine) and excipients: microcrystalline cellulose, calcium hydrogen phosphate dihydrate, colloidal hydrated silica, magnesium stearate, ammonium glycyrrhizate and a flavouring in compliance with the EC food regulation, mint powder essence (with E220).

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The lyophilised bacterial lysate contains 7 mg of:
Staphylococcus aureus, 6 billion,
Streptococcus pyogenes, 6 billion,
Streptococcus (viridans) oralis, 6 billion,
Klebsiella pneumoniae, 6 billion,
Klebsiella ozaenae, 6 billion,
Haemophilus influenza serotype B, 6 billion,
Neisseria catarrhalis, 6 billion,
Streptococcus (Diplococcus) pneumoniae, 6 billion (of which type TY1, 1 billion; Type TY2, 1 billion; Type TY3, 1 billion; Type TY5, 1 billion; Type TY8, 1 billion; Type TY47 1 billion)
and 43 mg glycine (support for freeze-drying process)

Pharmaceutical development: Considering that the submitted drug product has been manufactured for more than 15 years, sufficient information has been provided, which includes, for example, the selection of the lyophilised form of the bacterial lysate and the choice of manufacturing process. The hardness of the tablets should allow rapid disintegration in the mouth.

Manufacture: The drug product manufacturing is a direct compression process. Adequate revalidation data on three recent consecutive batches, including holding times, has been provided.

Specification: Adequate specifications at release and at shelf-life have been described including the following parameters: appearance (whitish tablets presenting brownish spots and a light characteristic odour), average weight, disintegration, uniformity of mass of single-dose preparations, humidity, hardness, identity (ELISA), immunostimulating activity and microbiological quality (compliant with Ph Eur 5.1.4 for oromucosal use).
The presence of each lyophilised bacterial lysate is controlled with ELISA up to the strain, not the sub-species. The quantitative composition of each strain is not controlled in the drug product, but the immunostimulating activity is tested, which is non-specific. The drug product composition is ensured through GMP compliance.

Container-Closure System: The primary packaging is a PVC/aluminium blister.

Stability: Sufficient stability data have been provided. Based on these results, a satisfactory shelf-life of 36 months has been established when stored in a PVC/aluminium blister at no more than 25°C.

3.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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4 Nonclinical Aspects

Swissmedic has not assessed the primary data relating to preclinical aspects of this application and is taking over the results of the assessment of the foreign reference authority of Poland. The current SwissPAR relating to preclinical aspects refers to the publicly available Assessment Report regarding Bacterial lysates-containing medicinal products for respiratory conditions (Procedure number: EMEA/H/A-31/1465; date of issue 27 June 2019) issued by the EMA.

5 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical aspects of this application and is taking over the results of the assessment of the foreign reference authority of Poland. The current SwissPAR relating to clinical aspects refers to the publicly available Assessment Report regarding Bacterial lysates-containing medicinal products for respiratory conditions (Procedure number: EMEA/H/A-31/1465; date of issue 27 June 2019) issued by the EMA.

6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Solmucol Bronchoprotect 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Solmucol® Bronchoprotect®

The efficacy and safety of Solmucol Bronchoprotect have only been summarily checked by Swissmedic. The authorisation of Solmucol Bronchoprotect is based on that of Ismigen, which contains the same active substances, is authorised in Poland and for which the information was updated in June 2020.

Composition

Active substances

Lyophilised bacterial lysate of *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus (viridans) oralis*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Haemophilus influenzae*, *Neisseria catarrhalis*, *Streptococcus pneumoniae.*

Excipients

Glycine (support for lyophilisation of the bacterial lysate, hydrated colloidal silica, microcrystalline cellulose, calcium hydrogenphosphate dihydrate, magnesium stearate, ammonium glycyrrhizate, mint aroma (contains E220).

Pharmaceutical form and active substance quantity per unit

Sublingual tablets 7 mg of lyophilised bacterial lysate of *Staphylococcus aureus* 6 billion, *Streptococcus pyogenes* 6 billion, *Streptococcus (viridans) oralis* 6 billion, *Klebsiella pneumoniae* 6 billion, *Klebsiella ozaenae* 6 billion, *Haemophilus influenzae* 6 billion, *Neisseria catarrhalis* 6 billion, *Streptococcus pneumoniae* 6 billion (of which, Type 1 - 1 billion, Type 2 - 1 billion, Type 3 -1 billion, Type 5 - 1 billion, Type 8 - 1 billion, Type 47 - 1 billion), obtained by mechanical lysis.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Indications/Uses

Prophylaxis of recurrent respiratory tract infections in adults and children from the age of 3 years.

Dosage/Administration

Adults and children from the age of 3 years

1 tablet of Solmucol Bronchoprotect per day for 10 consecutive days per month, for 3 months.

Method of administration

Sublingual administration: hold the tablet under the tongue until it dissolves completely.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special warnings and precautions for use

Solmucol Bronchoprotect may cause hypersensitivity reactions. If allergic reactions or signs of intolerance occur, the treatment must be stopped immediately.

No clinical trial has been able to demonstrate that the use of Solmucol Bronchoprotect can prevent the development of pneumonia. Administration of Solmucol Bronchoprotect for this purpose is therefore not recommended.

Interactions

No interaction with medicinal products has been reported with this medicinal product.

Pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Solmucol Bronchoprotect in pregnant women. If the patient is, suspects she is or plans to become pregnant, she should consult her doctor or pharmacist before using Solmucol Bronchoprotect.

Lactation

If the patient is breast-feeding, she should consult her doctor or pharmacist before using Solmucol Bronchoprotect.

Fertility

No data are available concerning the effect on male and female fertility.

Effects on ability to drive and use machines

No corresponding studies have been performed.

Undesirable effects

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies.

The frequencies are listed in descending order 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).

Gastrointestinal disorders

Frequency not known: vomiting, stomatitis, abdominal pain and nausea.

Skin and subcutaneous tissue disorders

Frequency not known: allergic reactions (urticaria, rash, pruritus and oedema).

Infections and infestations

Frequency not known: rhinitis

General and administration site conditions
Frequency not known: fever, headache
Respiratory, thoracic and mediastinal disorders
Frequency not known: cough, oropharyngeal pain
Treatment should be discontinued in the event of persistent problems.
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
No cases of overdose have been reported.

Properties/Effects
ATC code
R07AX
Mechanism of action
Solmucol Bronchoprotect contains a lysate of bacteria that cause respiratory tract infections. The mechanism of action consists of increasing immunity to microorganisms that are responsible for infections of the upper and lower respiratory tract. Solmucol Bronchoprotect has a protective effect in recurrent respiratory tract infections. This action is made possible by a decreased number of recurrences, reduced duration of fever and decreased use of antibiotics. No depressant or stimulatory effect on the cardiovascular or respiratory system has been observed.
The immunomodulatory properties of Solmucol Bronchoprotect depend on:

- maturation of dendritic cells that are capable of specifically stimulating B and T lymphocytes;
- secretion of salivary IgA that is specific for surface antigens of pathogenic bacteria;
- stimulation of the mechanism of opsonisation of the bacteria by granulocytes;
- stimulation of innate (via dendritic cells and granulocytes) and acquired (secretion of IgA specific for bacterial surface structures) immunity.

Pharmacokinetics
In view of the mechanism of action and method of administration of the medicinal product, no pharmacokinetic studies are possible.

Preclinical data
Toxicity studies following a single exposure have been conducted in mice and rats. Solmucol Bronchoprotect was administered by the oral and intraperitoneal route. No fatal cases were confirmed

after the use of maximum doses. Toxicity studies after multiple exposures (110-150 days), conducted in rats and dogs, did not show Solmucol Bronchoprotect to have any clinically significant toxic effects. No macroscopic or microscopic haematological, haemochemical or pathological lesions were demonstrated.
Controlled studies showed that the product has no adverse effects on reproduction in rats, no foetotoxic effects in mice and rabbits, and no adverse reproductive effects in the perinatal and postnatal period in rats.

Other information

Incompatibilities

No incompatibility with other substances has been reported.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store in the original packaging. Do not store above 25°C. Keep out of the reach of children.

Authorisation number

67822 (Swissmedic)

Packs

Packs of 30 sublingual tablets.

Marketing authorisation holder

IBSA Institut Biochimique SA, Lugano

Date of revision of the text

Foreign comparator medicinal product: June 2020
No addition of safety-relevant information by Swissmedic March 2021.