COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Penicilline G Kabi 1.000.000 IU, 2.000.000 IU, 5.000.000 IU and 10.000.000 IU powder for solution for injection/infusion (benzylpenicillin sodium)

NL/H/5681/001-004/DC

Date: 14 July 2025

This module reflects the scientific discussion for the approval of Penicilline G Kabi 1.000.000 IU, 2.000.000 IU, 5.000.000 IU and 10.000.000 IU powder for solution for injection/infusion. The procedure was finalised on 23 January 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IM	Intramuscular
IU	International Units
IV	Intravenous
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Penicilline G Kabi 1.000.000 IU, 2.000.000 IU, 5.000.000 IU and 10.000.000 IU powder for solution for injection/infusion, from Fresenius Kabi Deutschland GmbH.

The product is indicated for the treatment of the following infections in adults, adolescents, children, newborn infants and pre-term infants, (see section 5.1 of the SmPC):

- acute bacterial skin and skin structure infections (ABSSSI)
- diphtheria (in addition to antitoxin)
- community acquired pneumonia
- empyema
- bacterial endocarditis
- peritonitis
- meningitis
- brain abscesses
- osteomyelitis
- infections of the genital tract caused by fusobacteria
- complicated gonorrhoea (gonorrhoeal endocarditis or arthritis)
- syphilis (congenital syphilis)
- lyme borreliosis (meningopolyneuritis Garin-Bujadoux-Bannwarth, acrodermatitis chronica atrophicans, Lyme arthritis, Lyme carditis).

The product is also used for the treatment of the following specific infections:

- anthrax
- tetanus
- gas gangrene
- listeriosis
- pasteurellosis
- rat bite fever
- fusospirochaetosis
- actinomycosis

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

NL/H/5681/001/DC, NL/H/5681/003/DC and NL/H/5681/004/DC
The marketing authorisation for the strengths 1.000.000 IU, 5.000.000 IU and 10.000.000 IU has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application. For this application reference is made to the originator product Penicillin G-

Natrium "Sandoz", 1.000.000 IU, 5.000.000 IU and 10.000.000 IU Trockenstechampulle, which has been registered in Austria via the decentralised 8(3) full application procedure AT/H/0659/002-004 since 16 February 1965. In the Netherlands, Penicillin G Sodium have been registered by the mutual recognition procedure AT/H/0659/002-004/MR (NL RVG 120400, 120401 and 120402) by Sandoz B.V. since 21 March 2017.

NL/H/5681/002/DC
The application for the 2.000.000 IU strength is submitted under Article 10(1) (generic application) in Estonia and Germany and under 10(3) of Directive 2001/83/EC (hybrid application) for the other CMSs, as this strength has not been registered for the reference medicinal product Penicillin G-Natrium "Sandoz" 1.000.000 IU (AT/H/0659/002).

The concerned member states (CMS) involved in this procedure were:

NL/H/5681/001/DC:
Austria, Belgium, Czechia, Denmark, Estonia, Finland, Germany, Ireland, Latvia, Lithuania, Luxembourg, Norway, Romania, Slovakia, Slovenia, Sweden and United Kingdom (Northern Ireland).

NL/H/5681/002/DC:
Austria, Belgium, Denmark, Estonia, Finland, Germany, Ireland, Latvia, Lithuania, Luxembourg, Norway, Slovenia, Sweden and United Kingdom (Northern Ireland).

NL/H/5681/003/DC:
Austria, Belgium, Bulgaria, Czechia, Denmark, Estonia, Finland, Germany, Latvia, Lithuania, Luxembourg, Norway, Slovakia, Slovenia and Sweden.

NL/H/5681/004/DC:
Austria, Belgium, Czechia, Denmark, Estonia, Finland, Germany, Latvia, Lithuania, Luxembourg, Norway, Slovakia, Slovenia and Sweden.

Similarity assessment
According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. The MAH has provided a similarity assessment between Obiltoxaximab SFL, SFL Pharmaceuticals Deutschland GmbHand, the current orphan product authorised in the EU for the treatment of anthrax.

The assessment included the comparison of the therapeutic indication, active substance, mechanism of action and principal (molecular) structure. After consideration of the MAH arguments, Penicilline G Kabi is not considered similar to the orphan product with regard to the therapeutic indication (as defined in Article 3 of Commission Regulation (EC) No. 847/2000). Therefore, the existence of any market exclusivity for Obiltoxaximab SFL, in the treatment of gastro-entero-pancreatic neuroendocrine tumours and Ayvakyt in the treatment of anthrax, does not prevent the granting of the marketing authorisation for Penicilline G Kabi, powder for solution for injection/infusion.

II. QUALITY ASPECTS

II.1 Introduction

Penicilline G Kabi is a white or almost white crystalline powder for solution for injection/ infusion and contains as active substance benzylpenicillin sodium.

1.000.000 IU
Each vial contains 1.000.000 IU equivalent to approximately 600 mg benzylpenicillin sodium. Each vial contains 39 mg of sodium.

2.000.000 IU
Each vial contains 2000000 IU equivalent to approximately 1200 mg benzylpenicillin sodium. Each vial contains 77 mg of sodium.

5.000.000 IU
Each vial contains 5.000.000 IU equivalent to approximately 3000 mg benzylpenicillin sodium. Each vial contains 194 mg of sodium.

10.000.000 IU
Each vial contains 10.000.000 IU equivalent to approximately 6000 mg benzylpenicillin sodium. Each vial contains 387 mg of sodium.

The product contains no excipients.

The different strengths are fully dose proportional.

The powder for solution for injection/ infusion is packed in type-II glass vial with bromobutyl rubber stopper and sealed with centre tear-off caps in aluminium with plastic top.

II.2 Drug Substance

The active substance is benzylpenicillin sodium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white, crystalline powder and is very soluble in water. Benzylpenicillin sodium sterile shows isomerism due to the presence of three asymmetric carbon atoms. The configuration of these is established during the fermentation process at the beginning of the manufacturing process. Polymorphism is not relevant as the drug substance will be used as solution for injection/infusion.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent

Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

The manufacturing process consists of a conversion step of an intermediate product (crude), and sterilisation. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for sterility, bacterial endotoxins, residual solvents, particulate contamination, nickel content and impurities. The specification is acceptable. Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for three commercial scale batches of the drug substance analysed by the drug substance and drug product manufacturers.

Stability of drug substance

Stability data on the active substance have been provided for three batches of each strength in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Since the product, like the reference product, consists only of the drug substance without any excipients, pharmaceutical development was mainly aimed at obtaining a product with properties similar to the reference product. The formulation was developed in view of the CPMP guidance on “Note for guidance on the investigation of bioavailability and bioequivalence”, section 5.1.6 - parenteral solutions. Therefore, no bioequivalence study is required as the drug product is for intravenous (IV) and intramuscular (IM) administration as an aqueous solution containing the same active substance in the same concentration as the reference medicinal product. The pharmaceutical development of the product has been adequately performed, including studies on the selection of the sterilisation method, solubility, photostability, vial filling process and the effect of headspace in the vial. Compatibility with the container closure system is

demonstrated. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process is a non-standard process and consists of filling the powder drug substance directly into the vials followed by stoppering and capping of the filled vials. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches of each product size.

Control of excipients

Not applicable, there are no excipients used in the formulation of this product.

Compatibility

As stated in the SmPC, the drug product is reconstituted and if necessary diluted before use in water for injection, 5% (50 mg/mL) glucose solution or 0.9% (9 mg/mL) sodium chloride. Adequate compatibility and chemical and physical in-use stability data have been demonstrated for the reconstituted and diluted product in these solvents.

Microbiological attributes

Adequate information on the microbiological attributes was submitted by the MAH including relevant precautionary measures during production, sterilisation process, controls on the microbiological quality and integrity of the container. The sterility of the drug product is assured by aseptic processing. The sterility and bacterial endotoxins tests are included in the quality control of the product. The limits for these tests are in accordance with the relevant European guidelines.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, loss on drying, uniformity of dosage units, pH, reconstitution time, appearance of reconstituted solution, clarity and opalescence of reconstituted solution, particulate matter, related substances, assay, nickel content, bacterial endotoxins and sterility. The release and shelf-life limits in the specification are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate risk evaluation report has been provided for elemental impurities and nitrosamines. Low risk for the presence of nitrosamines in the drug product was identified. Appropriate tests and limits have been set for elemental impurities (nickel content) and are part of the quality control of the final product which is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) have been provided on three batches per strength at the proposed commercial scale, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches per strength stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. All results stay well within the limits. Under long term conditions little change is seen up to 18 months. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. Based on the 18 months long term data submitted, a shelf life was granted of 2 years. No specific storage conditions needed to be included in the SmPC or on the label.

Depending on the dosage and the route of administration, the drug product is reconstituted and if necessary diluted before use. For this, water for injections, 5% (50 mg/mL) glucose solution or 0.9% (9 mg/mL) sodium chloride may be used. Chemical and physical in-use stability data have been provided on the reconstituted and the diluted product. The results show that the in-use stability of the reconstituted and diluted product depends on its concentration and temperature. Based on the data submitted the following in-use shelf life was granted:

- For the reconstituted solution in a concentration range of 500.000 – 910.000 IU/mL 0.3- 0.546 g/mL 300-546 mg/mL) (for IM injection):
  6 hours when stored at 2°C – 8°C and 1 hour when stored below 25°C.
- For the diluted solution in a concentration range of 100.000 IU/mL 0.06 g/mL 60 mg/mL (for IV injection):
  8 hours when stored at 2°C – 8°C and 1 hour when stored below 25°C.

To study the impact of extreme low temperature conditions outside the labelled storage conditions, which may occur during drug product shipment, a thermal excursion study was performed on Penicillin G sodium powder for solution for injection/infusion. From the results it can be concluded that exposure of the product to 60°C ± 2°C and -20°C ± 5°C for 7 days does not have any deleterious effect on product stability. In addition, a thermal cycling study was performed (three cycles of -20°C ± 5°C for 2 days followed by 60°C ± 2°C for 2 days), the results show that short exposure of product to fluctuating temperatures from -20ºC ± 5°C to 60°C ± 2°C does not have any significant deleterious effect on the product stability.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Penicilline G Kabi has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Penicilline G Kabi is intended for generic or hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

As benzylpenicillin sodium is a widely used, well-known active substance with known pharmacodynamic, pharmacokinetic and toxicological properties, the MAH has not provided additional studies. Instead, an adequate non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Benzylpenicillin sodium is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 pharmacology, efficacy and safety

Penicillin G Sodium is the sodium salt form of benzylpenicillin, a semi-synthetic, broad-spectrum penicillin antibiotic with bactericidal activity. Benzylpenicillin sodium binds to and inactivates penicillin-binding proteins (PBP) located on the inner membrane of the bacterial cell wall. Inactivation of PBPs interferes with the cross-linkage of peptidoglycan chains necessary for bacterial cell wall strength and rigidity. This results in the weakening of the bacterial cell wall and causes cell lysis. Penicillin G Sodium is indicated for the treatment of infections caused by penicillin-sensitive pathogens as described in section 5.1 of the product SmPC in adults, adolescents, children, newborn infants and pre-term infants.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Penicilline G Kabi. At the time of approval, the most recent version of the RMP was version 0.1 dated 1 July 2022; date of final sign off 17 August 2022.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Penicillin G-Natrium "Sandoz". No new clinical studies were conducted, instead the MAH submitted an adequate review of published clinical data. Overall, this medicinal product can be used for the specified indications. The clinical aspects of this product are approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Penicilline G Kabi 1.000.000 IU, 2.000.000 IU, 5.000.000 IU and 10.000.000 IU powder for solution for injection/infusion have a proven chemical-pharmaceutical quality. The chemical-pharmaceutical documentation in relation to the proposed products is of sufficient high quality in view of the present European regulatory requirements.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that there are no non-clinical or clinical concerns for Penicilline G Kabi. The benefit/risk relation is considered positive. The decentralised procedure was finalised with a positive outcome on 23 January 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.