COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Teicoplanine SUN 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution (teicoplanin)

NL/H/5171/001-002/DC

Date: 13 October 2021

This module reflects the scientific discussion for the approval of Teicoplanine SUN 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution. The procedure was finalised on 11 August 2021. 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
CAPD	Continuous ambulatory peritoneal dialysis
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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
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 Teicoplanine SUN 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution, from Sun Pharmaceutical Industries Europe B.V.

Teicoplanine SUN are indicated in adults and in children from birth for the parenteral treatment of the following infections (see sections 4.2, 4.4 and 5.1 of the SmPC):

- complicated skin and soft tissue infections
- bone and joint infections
- hospital acquired pneumonia
- community acquired pneumonia
- complicated urinary tract infections
- infective endocarditis
- peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD)
- bacteraemia that occurs in association with any of the indications listed above.

Teicoplanine SUN are also indicated as an alternative oral treatment for *Clostridium difficile* infection-associated diarrhoea and colitis.

Where appropriate, teicoplanin should be administered in combination with other antibacterial agents.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Targocid 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution (NL RVG 13473 (200 mg) and 15374 (400 mg)) which have been registered in the Netherlands by Genzyme Europe B.V. since 14 November 1990 and 22 July 1991 through mutual recognition procedure DE/H/3916/002-003.

The concerned member states (CMS) involved in this procedure were Italy and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Teicoplanine SUN consist of a powder and solvent. The powder for solution for injection/infusion or oral solution is a white-ivory spongy lyophilised powder. The solvent is a clear, colourless and odourless liquid.

Each powder vial of the 200 mg product contains 200 mg teicoplanin equivalent to not less than 200,000 IU. After reconstitution, the solution will contain 200 mg teicoplanin in 3.0 ml.

Each powder vial of the 400 mg product contains 400 mg teicoplanin equivalent to not less than 400,000 IU. After reconstitution, the solution will contain 400 mg teicoplanin in 3.0 ml.

Teicoplanine SUN 200 mg powder is packed in a 10 ml colourless Type I glass vial closed with a bromobutyl rubber stopper and an aluminium flip-off seal. Each vial contains 200 mg teicoplanin.

Teicoplanine SUN 400 mg powder is packed in a 20 ml colourless Type I glass vial closed with a bromobutyl rubber stopper and an aluminium flip-off seal. Each vial contains 400 mg teicoplanin.

The solvent water for injection is packed in a colourless Type I glass ampoule. Each ampoule contains 3 ml solvent.

The excipients are:
Powder - sodium chloride (E551) and sodium hydroxide (E524) (for pH adjustment).
Solvent - water for injections.

II.2 Drug Substance

The active substance is teicoplanin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Teicoplanin is a mixture of glycopeptides produced by certain strains of *Actinoplanes teichomyceticus sp*. Teicoplanin is a white or yellowish, amorphous powder freely soluble in water, sparingly soluble in dimethylformamide and practically insoluble in ethanol.

The active substance is supplied by two manufacturers, for which the Active Substance Master File (ASMF) procedure (manufacturer I) and the Certification Procedures of the EDQM of the Council of Europe (CEP procedure; manufacturer II) are used.

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.

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 used by manufacturer I consists of a fermentation process, and no chemical transformation occurs. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised, in line with the Ph. Eur. monograph and the EMA recommendation.

A CEP has been submitted for manufacturer II; therefore no details on this manufacturing process have been included.

Quality control of drug substance

The active substance specifications are considered adequate to control the quality and meet the requirements of the monograph in the Ph. Eur and additional in-house criteria. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches per manufacturer.

Stability of drug substance

Stability data on the active substance manufactured by the ASMF-holder have been provided for six batches stored at 25°C/60% RH (up to six months) and 5°C (up to 36 months). Out of specifications were observed under accelerated conditions at three and six months. Based on the data submitted, a retest period could be granted of 24 months. Since no photostability studies have been performed, and since the storage bags do not provide protection from light, the storage claim ‘store protected from light’ has been included. This is in line with the Ph. Eur. storage claim.

The active substance supplied by the CEP-holder is stable for two years when stored at 2°C to 8°C in double polyethylene bags placed in an aluminium drum. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Products

II.3.1 Finished products

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients has been justified and their functions are explained. The choices of the manufacturing process and packaging are sufficiently justified.

The development focused mainly on obtaining stable drug products equivalent to the innovator products Targocid. The following aspects have been taken into consideration: stability of the active substance, physico-chemical and microbiological properties and sterility of the drug product. The stability of the drug products reconstituted in water, and its compatibility with several diluents has been investigated.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the products have been presented for three batches per strength in accordance with the relevant European guidelines. The manufacturing process consists of aseptic filtration of a bulk solution of drug products, which is then aseptically filled in vials and lyophilised. The sterile filtration method was selected due to the instability of the drug substance at high temperatures. The principle of the filter integrity tests, the solution used in the test and the acceptance criteria before and after filtration are described and are acceptable.

Control of excipients

The excipients comply with the specifications as stated in the Ph. Eur. These specifications are acceptable.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage forms. The specification includes tests for appearance, identification pH, reconstitution time, colour and clarity of solution, water content, content ratio, microbiological assay, leak test, uniformity of dosage units, particulate matter, sterility and bacterial endotoxins. The release and shelf life limits are not identical; a wider limit is applied at shelf-life for two teicoplanin glycopeptides, which is acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the products. In line with EMA/409815/2020, the MAH evaluated the risk of the formation/presence of nitrosamines in the final drug product. This risk is considered as low, which is acceptable.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the products have been provided for three batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The batches were stored in type 1 amber glass bottles closed with bromobutyl rubber stopper, and sealed with aluminium overseals with a flip off cap. The conditions used in the stability studies are according to the ICH guideline. Under accelerated conditions, an increase of two types of teicoplanin glycopeptides were observed. This was due to a known hydrolysis reaction. Additionally, a slight increase in water content, and some variability for total and any non-teicoplanin like impurity were observed. Nevertheless, all values remained below the reporting thresholds. Additionally, photostability studies have been conducted, and the lyophilised powder is stable when stored in the glass bottle.

On basis of the data submitted, a shelf life of the lyophilised powder was granted of 36 months. The labelled storage conditions are: 'This medicinal product does not require any special temperature storage conditions' and 'Store in the original package.'

The stability of teicoplanin reconstituted in water and further diluted in several media has been sufficiently investigated. Comparability with the reference products has also been investigated. All results comply with the specification. The proposed shelf life of 24 hours at 2 to 8°C could be granted.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.3.2 Reconstitution solution

Pharmaceutical development

The reconstitution solution is identical to the solution of the innovator products. No additional components beside water for injection are present in the formulation. The formulation is sterilised. No manufacturing or further development studies were performed.

Manufacturing process

Water for injection is manufactured by filtration of distilled water through a 0.22 µm filter prior to filling into the ampoules. All materials in contact with the bulk solution are sterilised and the ampoules are depyrogenated. Integrity of the filters is performed before sterilisation and after filtration. After filling, the ampoules are sealed and terminally sterilised.

The manufacturing process is a non-standard process, which been validated on three batches. The manufacturing process has been adequately validated.

Excipients
The only inactive ingredient used in the preparation of the solvent complies with the Ph. Eur. monograph and is tested according to pharmacopeial procedures.

Quality control of drug product
Water for injection is tested according to the Ph. Eur. monograph. Additionally, a test for extractable volume is included. All tests are performed in accordance with the Ph. Eur.

Stability of drug product
Stability data on the reconstitution solution have been provided for three commercial scale batches stored at 25°C/60% RH (24 months). Additionally, 60 months stability data of two pilot batches under long term conditions have also been provided. No studies at accelerated storage conditions have been performed. The proposed shelf life of 60 months is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Teicoplanine SUN have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance, finished products and reconstitution solution.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Teicoplanine SUN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

These products is are generic formulations of Targocid which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. A 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

Teicoplanin 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 Pharmacokinetics

Teicoplanine SUN 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution are parenteral formulations and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Teicoplanine SUN are entirely the same as the originator products. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal products. The current products can be used instead of its reference products.

IV.3 Clinical efficacy and safety

The efficacy of teicoplanin was discussed extensively for the innovator product in the Article 30 referral; EMEA/H/A-30/1301; Targocid; Teicoplanin. Later on, the safety was discussed as well in a PSUR Worksharing procedure (teicoplanin; EL/H/PSUR/0001/002). For these generic products, the product information is harmonised with that of the innovator products.

IV.4 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 Teicoplanine SUN.

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

Important identified risks	• None
Important potential risks	• None
Missing information	• Safety of 24 mg/kg/day loading dose regimen.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient to identify, characterise, prevent or minimise risks.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Targocid. No new clinical studies were conducted. Considering that both the test and reference formulations are to be administered as an aqueous intravenous solution containing the same active substance, a bioequivalence study was not necessary. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference product.

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 test consisted of a pilot test with three 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

Teicoplanine SUN 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution have a proven chemical-pharmaceutical quality and are generic forms of Targocid 200 mg and 400 mg, powder and solvent for solution for injection/infusion or oral solution. Targocid are well-known medicinal products with established favourable efficacy and safety profiles. Since both the reference and current products are intended for parenteral use, no bioequivalence study was deemed necessary. A biowaiver has been granted.

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 essential similarity has been demonstrated for Teicoplanine SUN with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome at 11 August 2021.

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