COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dobutamine SUN 5 mg/ml solution for infusion in pre-filled syringe (dobutamine hydrochloride)

NL/H/5074/001/DC

Date: 27 October 2021

This module reflects the scientific discussion for the approval of Dobutamine SUN 5 mg/ml solution for infusion in pre-filled syringe. The procedure was finalised at 23 June 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
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
COP	Cyclic olefin copolymer
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ERP	European Reference Product
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 Dobutamine SUN 5 mg/ml solution for infusion in pre-filled syringe, from Sun Pharmaceutical Industries Europe B.V.

The product is indicated for adults who require a positive inotropic support in the treatment of cardiac decompensation due to depressed contractility, caused by an organic heart disease or by cardiac surgery.

Note: In cardiogenic shock characterised by heart failure with severe hypotension and in case of septic shock dobutamine may be useful if added to vasoconstrictors such as noradrenaline preferentially or dopamine in case of disturbed ventricular function, raised filling pressure of the ventricles and raised systemic resistance.

Dobutamine may also be used for detection of myocardial ischaemia and of viable myocardium within the scope of an echocardiographic examination (dobutamine stress echocardiography), if patients cannot undergo a period of exercise or if the exercise yields no information of value.

Paediatric population
Dobutamine is indicated in all paediatric age groups (from neonates to 18 years of age) as inotropic support in low cardiac output hypoperfusion states resulting from decompensated heart failure, following cardiac surgery, cardiomyopathies and in cardiogenic or septic shock.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the European Reference Product (ERP) Dobutrex Liquid, 12.5 mg/ml, concentrate for solution for infusion, first marketed by Germany by Lilly Germany Limited Liability Company on 17 October 1980. The ERP is currently discontinued and is physically not available on the market.

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

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, due to the following differences with the ERP:

- Change in pharmaceutical form
- Change in strength

<u>Scientific advice</u>
Scientific advice concerning Dobutamine SUN was given by the Medical Evaluation Board (MEB) in the Netherlands and by the German Federal Institute for Drugs and Medical Devices (BfArM) in August 2018. Both agencies provided three answers on the chemical,

pharmaceutical and biological development, the toxico-pharmacological development and on the clinical development of the proposed drug product.

II. QUALITY ASPECTS

II.1 Introduction

Dobutamine SUN is a clear, colourless to slightly yellow solution for infusion in a pre-filled syringe, with pH between 3.4 and 3.8, and osmolality between 270 and 330 mOsm/kg.

The product contains as active substance dobutamine (as hydrochloride). One ml of the solution for infusion contains dobutamine (as hydrochloride) corresponding to 5 mg dobutamine. Each pre-filled syringe of 50 ml contains dobutamine (as hydrochloride) corresponding to 250 mg dobutamine.

The pre-filled syringe is made of cyclic olefin copolymer (COP) fitted with a chlorobutyl elastomeric screw on tip cap with a bromobutyl plunger stopper, and contains 50 ml of solution for infusion. One plunger rod and one oxygen scavenger is included in the aluminium pouch along with a pre-filled syringe, which are further packed in cartons.

The excipients are: disodium edetate (E386), cysteine hydrochloride monohydrate, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water (for injection).

II.2 Drug Substance

The active substance is dobutamine, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a crystalline powder and is sparingly soluble in water. The manufacturing process consistently gives the crystalline form. Dobutamine hydrochloride contains one asymmetric carbon atom, therefore, it exhibits optical isomerism. The dobutamine hydrochloride manufactured is a racemate, in accordance with the Ph. Eur.

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.

Manufacturing process

In the manufacturing process, starting materials are transformed in key intermediates via several chemical transformation steps. The synthesis route for the final dobutamine hydrochloride consists of two chemical steps, comprising an isolation step and subsequently one final purification step. No class-1 solvents or heavy metal catalysts are used during the manufacture of the active substance. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality, and is in line with the Ph. Eur., with additional requirements for residual solvents, bacterial endotoxins and microbial quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production batches of dobutamine hydrochloride.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches in accordance with applicable European guidelines. The batches were stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months) in double polyethylene bags in a fibreboard drum. No significant changes nor trends have been observed in any of the parameters studied. Based on the data submitted, a retest period could be granted of two years when stored in line with the following storage conditions: “Preserve in tight containers and store at controlled room temperature at 20°C to 25°C, excursions are permitted between 15°C and 30°C.”

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. The MAH provided a description of the full development of the formulation. The drug product differs in composition from the reference product as follows:

- The medicinal product is a prefilled syringe of 5 mg/ml in a 50 ml syringe and is ready-to-use, whereas the ERP product is a concentrate solution of 12.5 mg/ml and needs to be diluted to a concentration of 0.5-5 mg/ml. Thus, at the time of administration, patients are exposed to similar dilution concentrations.
- The medicinal product contains cysteine hydrochloride monohydrate and disodium edetate, whereas the ERP contains sodium metabisulfite. The choice to avoid the use of sodium metabisulfite (because of potential adverse effects) and using a combination of cysteine hydrochloride monohydrate (reducing agent) and disodium edetate (chelating agent) in the formulation to prevent oxidation of the active substance is considered acceptable. Disodium edetate is widely used in parenteral

products, and cysteine is present in another authorised product that is indicated for use in children from birth.

Formulation and manufacturing process development studies have been performed covering the need for an overage, stability of the formulation at different pH levels, temperature cycling studies, compatibility of the product with process equipment, choice of the sterilisation method and antioxidant effectiveness. Compatibility of the drug product with the primary packaging materials was demonstrated and the integrity of the container closure system was confirmed. The active substance is sensitive to light and oxidation. No novel excipients are used and all excipients are known for their use in parenteral preparations. The effectiveness of the antioxidants at their chosen level has been demonstrated as part of the development studies. During the manufacturing process measures are taken to reduce light and oxygen exposure. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The product is manufactured using conventional manufacturing techniques. The main steps of the manufacturing process are the preparation of the bulk solution, filtration, filling and stoppering, terminal sterilisation and packaging. Process validation data on the product have been presented for two full scaled batches and one pilot scaled batch in accordance with the relevant European guidelines.

Control of excipients

All excipients in the formulation comply and are tested in accordance with their respective Ph. Eur. Monographs.

Microbiological attributes

Microbiological attributes were evaluated to assure manufacturing controls, finished product quality and container closure integrity. The manufacturing process is an aseptic process. The product is terminally sterilised. During the manufacturing process bioburden is reduced by pre-filtration and sterile filtration. The integrity of the container closure system was adequately demonstrated and sterility was further confirmed as part of the formal stability studies. This is sufficient to ensure the sterility of the product throughout its shelf-life.

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 description, identity, pH, osmolality, extractable volume, uniformity of dosage units, break-loose force, glide force, particulate contamination, weight loss, related substances, sterility, bacterial endotoxins, assay of dobutamine, assay of cysteine hydrochloride monohydrate, assay of disodium edetate and assay of sodium chloride. Except for weight loss (only tested at shelf-life), related substances and assay of cysteine hydrochloride monohydrate, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate

for adequate quality control of the product. An adequate risk evaluation concerning the presence of impurities has been provided, and no risks were identified.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data on two full scaled batches and one pilot scaled batch from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for two production scaled batches and one pilot scaled batch stored at 25°C/40% RH (12 months) and 40°C/25% RH (six months) in the commercial primary packaging. The conditions used in the stability studies are according to the ICH stability guideline. The stability data showed a clear decrease in assay of cysteine hydrochloride monohydrate at both storage conditions. No clear trends or changes were seen in any of the other tested parameters. Results were consistent between batches and in compliance with the specification limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of two years. No specific storage conditions need to be included in the SmPC or on the label.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless preparation has taken place in controlled and validated aseptic conditions.

Stability data have been provided demonstrating that the product remains stable for 24 hours at 25°C and at 37°C after admixture with 5% glucose solution and 0.9% sodium chloride in 5% glucose solution in PVC and non-PVC infusion bags, and in PVC and non-PVC intravenous infusion sets. Furthermore, chemical and physical compatibility of the undiluted product with a syringe pump intravenous extension set of PVC and non-PVC was demonstrated for seven days at 25°C and at 37°C.

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 Dobutamine SUN 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 Dobutamine SUN is intended for substitution of similar dobutamine containing products, 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

This product is a hybrid medicine and has essential similarity with the ERP Dobutrex Liquid. Reference is made to the preclinical data obtained with the innovator product. 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

Dobutamine 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. However, since this procedure concerns a hybrid application in which the drug product differs in three clinically relevant aspects from the ERP, the MAH specifically addressed the clinical efficacy and clinical safety of the drug product (IV.3).

IV.2 Pharmacokinetics

No new pharmacokinetic studies were considered needed for this hybrid application. The MAH presented bibliographical data to describe the absorption, bioavailability, distribution, elimination, excretion and metabolism of dobutamine. Sufficient references were provided to support the presented data on pharmacokinetics.

Biowaiver

Dobutamine SUN 5 mg/ml solution for infusion in pre-filled syringe is a parenteral formulation and therefore fulfils 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).

IV.3 Clinical efficacy and clinical safety

Dobutamine SUN differs from the reference product in two clinically relevant aspects, namely:

- Pharmaceutical form. The drug product is a prefilled syringe and is ready-to-use, whereas the European reference product is a solution to be further diluted.
- Strength. The drug product has a higher concentration of the active substance than the European reference product has after the necessary dilution.

The changes in pharmaceutical form and strength have been justified. The ERP product is a concentrate solution of 12.5 mg/ml and needs to be diluted to a concentration of 0.5-5 mg/ml. Thus, at the time of administration, patients are exposed to similar dilution concentrations. Furthermore, the difference in strength is considered not to affect the bioavailability since both products are aqueous solutions.

Overall, the clinical efficacy and safety of Dobutamine SUN have been appropriately addressed in this hybrid application. Changes in the pharmaceutical form and strength are acceptable.

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 Dobutamine SUN.

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 clinical safety.

IV.5 Discussion on the clinical aspects

For this hybrid authorisation, reference is made to the clinical studies and experience with the innovator product Dobutrex Liquid. 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 is not necessary. Furthermore, the difference in strength is considered not to affect the bioavailability and in line with a hybrid application,

and is considered acceptable. A clinical overview with relevant references was provided and no new clinical studies were required. Risk management is adequately addressed. Changes in pharmaceutical form and strength have been adequately discussed and are acceptable.

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 three participants, followed by two rounds with ten 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

Dobutamine SUN 5 mg/ml solution for infusion in pre-filled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Dobutrex Liquid, 12.5 mg/ml, concentrate for solution for infusion. Dobutrex Liquid is a has an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted. Clinically relevant changes that were made compared to the reference product have been adequately addressed and the clinical efficacy and clinical safety profiles were considered acceptable.

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 Dobutamine SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 June 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