COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dexmedetomidine Baxter 100 micrograms/ml, concentrate for solution for infusion

(dexmedetomidine hydrochloride)

NL/H/5020/001/DC

Date: 11 March 2021

This module reflects the scientific discussion for the approval of Dexmedetomidine Baxter 100 micrograms/ml. The procedure was finalised on 7 January 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
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 Dexmedetomidine Baxter 100 micrograms/ml, concentrate for solution for infusion from Baxter B.V.

The product is indicated for

- sedation of adult ICU (Intensive Care Unit) patients requiring a sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3).
- sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

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 product Dexdor 100 micrograms/ml, concentrate for solution for infusion (EMEA/H/C/002268) which has been registered in the EEA by Orion Corporation via the centralised procedure since 16 September 2011.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Norway, Portugal, Spain, Sweden and the UK.

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

II. QUALITY ASPECTS

II.1 Introduction

Dexmedetomidine Baxter 100 micrograms/ml is a clear, colourless solution with pH 4.5 – 7.0. Each ml of concentrate contains dexmedetomidine hydrochloride equivalent to 100 micrograms dexmedetomidine. Each 2 ml vial contains 200 micrograms of dexmedetomidine.

The concentration of the final solution after dilution should be either 4 micrograms/ml or 8 micrograms/ml.

The concentrate is packed in a 2 ml type I glass vial (with filling volume of 2 ml), with grey bromobutyl rubber closure with fluoropolymer coating.

The excipients are: sodium chloride, water for injections.

II.2 Drug Substance

The active substance is dexmedetomidine hydrochloride, an established active substance described in the United States Pharmacopoeia (USP). The active substance is a white or almost white powder, is freely soluble in water and alcohols and slightly soluble in methylene chloride and acetone. The drug substance is not known to show polymorphism. The drug substance has one chiral asymmetric centre. The final obtained active substance corresponds to the optically active form (S-enantiomer) with a characteristic specific optical rotation.

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

Dexmedetomidine hydrochloride is synthesised in six reaction steps. The manufacturing process has been adequately described. The starting material is in line with ICH Q11 and the level of impurities originating from the synthesis of the starting material has been proven to not have a significant effect on the impurity profile of the final drug substance. The last stage of the manufacturing process includes salt formation.
The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials.

Quality control of drug substance

The active substance specification is in line with the USP monograph, with additional requirements for identification, residue on ignition, residual solvents (including skip testing for Class 1 solvents), palladium and microbial contamination.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for four commercial scaled batches.

Stability of drug substance

The active substance is stable for five years based on the analysis of three commercial scaled batches stored at 25°C± 2%/ 60% ± 5 %RH (48 months) and 40°C ± 2%/75% ± 5 % RH (6 months). No special storage conditions are required.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are justified in relation to the innovator, including the sterilisation process. A two-step filtration of the bulk solution followed by a sterilisation of solution filled in the glass vials under compendial conditions has been proposed and adequately discussed. Compatibility studies between the drug product and the container materials and the tubing system as well as studies for the suitability of the selected filters have been performed and adequately described. The general structure of the pharmaceutical development section is in line with the Notice to Applicants - Medicinal Products for human use (Volume 2B). The pharmaceutical development of the product has been adequately performed, including information regarding the microbiological attributes and the compatibility between the drug product and the diluents. An appropriate discussion regarding the submission of test reports addressed to a previous drug substance supplier has been included.

Manufacturing process

The product is manufactured using conventional manufacturing techniques, and the MAH has provided detailed process description. A commitment to validate the first three full scale batches has been presented and the validation protocol presented is fully in line with the requirements set in Appendix I of the EMA Guideline on Process validation for finished products.

Control of excipients

The specification of all excipients complies with the Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, pH, extractable volume, particulate contamination for subvisible particles, assay of drug substance, assay of sodium chloride, chromatographic purity, enantiomeric impurity, bacterial endotoxin and sterility. The requirements are identical at release and shelf-life except for the assay of sodium chloride. The MAH has justified this divergence based on stability data and additional discussion. The MAH has adequately justified the absence of osmolality as test parameter in the specification of the drug product. A risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided in line with the Notice EMA/409815/2020.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial-scaled batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three commercial-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 2 ml Type-I glass vial, stoppered with teflon coated rubber closure and sealed with aluminium flip-off seal. In view of the stability results, the proposed shelf life of 24 months under no specific temperature storage conditions is acceptable.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

The MAH has provided in-use stability data after dilution in line with ICH Q1A. This has been substantiated with in-use specifications after dilution as well as with studies including all proposed diluents. Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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 Dexmedetomidine Baxter 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 Dexmedetomidine Baxter 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

This product is a generic formulation of Dexdor, which is available on the European market. 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

Dexmedetomidine hydrochloride 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

Dexmedetomidine Baxter 100 micrograms/ml, concentrate for solution for infusion 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Dexmedetomidine Baxter 100 micrograms/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

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 Dexmedetomidine Baxter.

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

Important identified risks	Bradycardia
	Hypotension
	Hypertension
	Hyperglycaemia
	Withdrawal syndrome
Important potential risks	Atrioventricular block
	Ischaemic heart disease
	Cortisol suppression
	Convulsions
	Hypothermia
	Respiratory depression
	Cardiac arrest
	Torsade de pointes/QT prolongation
	Overdose
	Off-label use
Missing information	Pregnancy

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 Dexdor. No new clinical studies were conducted. The MAH demonstrated that the product is similar to the reference product based on chemical-pharmaceutical properties. Risk management is adequately addressed. This generic medicinal product 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, 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

Dexmedetomidine Baxter 100 micrograms/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Dexdor 100 micrograms/ml, concentrate for solution for infusion. Dexdor is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. 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 Dexmedetomidine Baxter with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 7 January 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