Public Assessment Report
Scientific discussion v.2

Dexmedetomidine B. Braun 100 mcg/mL concentrate for solution for infusion

Dexmedetomidine Hydrochloride

ES/H/0754/001/DC

Applicant: B Braun Melsungen AC

This module reflects the scientific discussion for the approval of **Dexmedetomidine B. Braun Concentrate for Solution for Infusion 100 µg/ml**. The procedure was finalisedin August 2020.

CHANGE CONTROL

Version	Date	Change	Replaced by
1	20/11/2020	n/a	Version 2
2	17/03/2021	Text for clarification inserted in the introduction that does not modify the content of the report.	n/a

INTRODUCTION

This application via the Decentralised Procedure concerns an article 10(1) generic application for Dexmedetomidine concentrate for solution for infusion 100µg/ml.

Dexdor® is the medicinal product chosen by the Applicant as the reference medicinal product in this application, both as the medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA as well as the medicinal product authorised in the Union/Member State where the application is made or European reference medicinal product.

The originator product is Precedex® 100 micrograms/ml concentrate for solution for infusion, which was authorised in CZ on the basis of a full national application on November 21st 2002 (MAH: Abbott Lab.). Accordingly, the authorisation of the originator product dates back at least 10 years.

On September 09th 2011 the dexmedetomidine hydrochloride containing product Dexdor® (MA number EU/1/11/718/001-007) received an approval via a centralised procedure, (EMEA/H/C/002268). Marketing Authorisation Holder of this product is Orion Corporation, Orionintie 1, 02200 Espoo, Finland.

Dexdor® and Precedex® are considered identical products, solely authorised under different trade names. According to the guideline 98/C 229/03 "Commission communication on the Community marketing authorisation procedures for medicinal products", the company Abbott Laboratories is considered as licensee of the Orion Corporation. Thus, the concept of the global marketing authorisation (GMA) as detailed in article 6(1) second subparagraph of directive 2001/83/EC is applicable here.

Additionally, in June 2015 it was confirmed by CMDh that the medicinal products Precedex® and Dexdor® belong to one Global Marketing Authorisation.

Hence, Dexdor® is chosen by the Applicant to be the reference medicinal product for this application.

With Spain as the Reference Member State in this Decentralized Procedure, B Braun Melsungen AC, is applying for the Marketing Authorisations of Dexmedetomidine B. Braun 100 mcg/mL concentrate for solution for infusion in: AT, BE, CZ, DE, DK, FI, FR, HU, IE, IT, LT, NL, NO, PL, PT, SE, SI, SK

Dexmedetomidine is a selective alpha-2 receptor agonist with a broad range of pharmacological properties. It has a sympatholytic effect through decrease of the release of noradrenaline in sympathetic nerve endings. The sedative effects are mediated through decreased firing of locus coeruleus, the predominant noradrenergic nucleus in the brainstem. Dexmedetomidine has analgesic and anaesthetic/analgesic-sparing effects.

The proposed indications for Dexmedetomidine are the same as for the reference product Dexdor®: 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) and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Dexmedetomidine B. Braun 100 micrograms/ml concentrate for solution for infusion, in the treatment of:

- 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)

- For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation

is approvable.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance
The drug substance is dexmedetomidine (as hydrochloride). There is no Ph. Eur. monograph for this drug substance.
The applicant has used the ASMF procedure.
Description of the manufacturing process is adequate. Elucidation and characterization of the drug substance are sufficient, including an acceptable proposal on impurities to control.
Specification for drug substance is considered adequate. Analytical methods are correctly described and their validation is performed according to ICH.
The proposed container for storage is similar than the one used in the stability studies.
Stability studies have been performed according to ICH/CPMP guidelines and guarantee the proposed retest period and storage conditions.

Drug Product
The drug product is presented as a sterile solution in water for injection.
The name, address and responsibilities of the finished product manufacturers have been provided. An adequate description of the manufacturing process, indicating critical steps and in-process controls, is included. Industrial batch sizes are stated.
The excipients used in the formulation are compedial.
The specification proposed is acceptable. Analytical methods are adequately described and their validation is performed according to ICH.
Proposed packages are Ph. Eur. type I colourless glass ampoules of 2 ml, 5 ml or 10 ml.
Stability studies have been performed according to ICH. The proposed shelf-life and storage conditions can be accepted.

II-2 Non-clinical aspects

Environmental Risk Assessment (ERA)

II.3 Clinical aspects

Introduction

Dexmedetomidine hydrochloride is a well-known drug with established efficacy and safety.

The Applicant did not conduct any clinical study to support this application (please refer to biowaiver section).

Biowaiver

The Applicant claims that a bioequivalence study is not required since Dexmedetomidine B Braun contains the same active substance in the same quantity and concentration as the reference product and has the same indications, route of administration, dosage form and posology. The applied product also contains qualitatively the same excipients in similar amounts as thereferenceproduct.The quantitative differences are not expected to affect the bioavailability.

According to the ”Guideline on the Investigation of Bioequivalence” a bioequivalence study is not required for an aqueous parenteral solution with similar excipients in similar amounts.

Risk Management Plan

Discussion on the clinical aspects

According to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) no bioequivalence study is required to demonstrate therapeutic equivalence, since the bioequivalence is self-evident for intravenous aqueous solutions with the same active substance strength that contain similar and well-known excipients.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

From a clinical standpoint, the use of Dexmedetomidine concentrate for solution for infusion 100 µg/ml is justified 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) and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

The application contains an adequate review of published clinical data and the clinical bioequivalence studies are not necessary in view that the reference product and the proposed products are aqueous intravenous solution containing the same amount of the active substance as the currenly approved product. Moreover, the qualitative composition in excipients is the same and the quantitative composition in excipients is similar between the innovator and proposed product.

The SmPC, PIL and labelling are considered satisfactory. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.