Public Assessment Report
Scientific discussion

Dexmedetomidine Altan concentrate for solution for infusion 100 µg/ml

(Dexmedetomidine Hydrochloride)

ES/H/0462/001/DC

Applicant: Altan Pharma Limited

This module reflects the scientific discussion for the approval of **Dexmedetomidine Altan Concentrate for Solution for Infusion 100 µg/ml**. The procedure was finalised on May 2019.

INTRODUCTION

This application via the Decentralised Procedure concerns an article 10(3) hybrid application for Dexmedetomidine concentrate for solution for infusion 100µg/ml.

With Spain as Reference Member State, Altan Pharma Limited is applying for Marketing Authorisations in AT, BE, DE, FI, FR, IT, NL, NO, PL, PT, SE & UK.

The proposed indications for the product are:

1. 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)
2. For sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation

The medicinal product which has been authorised in accordance with Union provisions for not less than 6/10 years in the EEA for this application is PRECEDEX concentrate for solution for infusion 100µg/ml (Orion Corporation) authorised first in the Czech Republic 19-12-2001.

The reference product is DEXDOR 100µg/ml concentrate for solution for infusion, which was approved in the EU via a centralised procedure on 16-09-2011. The application was renewed unconditionally on 30-05-2016.

As indicated above, two indications are sought for this product. The first ”For sedation of adult ICU (Intensive Care Unit) patients requiring sedation level not deeper than arousal in response to verbal stimulation (corresponding to Richmond Agitation-Sedation Scale (RASS) 0 to -3) is identical to that approved for Dexdor. However the remaining indication was not approved for Dexdor at the start of the procedure and constitute the basis for this article 10(3) hybrid application. After the beginning of this procedure, Dexdor obtained a positive opinion from CHMP for this last indication on 28 June 2018.

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine, which displays specific and selective α2- adrenoceptor agonism. Dexmedetomidine is 8 times more specific for α2- adrenoceptors than clonidine. The actions of dexmedetomidine are suggested to be mediated through postsynaptic α2-adrenoceptors which activate pertussis toxinsensitive G proteins, thereby increasing conductance through potassium ion channels. Dexmedetomidine exerts a broad range of pharmacological properties, reflecting the extensive distribution of α2-receptors throughout the body. It has sedative, anxiolytic, sympatholytic, and analgesic sparing effects, and minimal depression of respiratory function.

The mechanism of action differs from those of currently used sedative agents, including clonidine. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the receptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Dexmedetomidine Altan 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 active substance dexmedetomidine is a known drug substance not described in the European Pharmacopoeia but described in the USP. The application uses the ASMF procedure.

Description of the manufacturing process is adequate. Elucidation and characterization of the drug substance are sufficient. Potential impurities of dexmedetomidine along with their control have been adequately discussed.

The proposed limits for related substances are in line with ICH thresholds and are considered acceptable. The remaining specification is appropriate to guarantee a sufficient quality of the active ingredient and the limits are justified. 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.

The control of the active substance at the finished product manufacturing site is according to the current USP monograph and the specifications set by the ASMF holder.

Drug product

Description of the product
Dexmedetomidine 100 micrograms/ml Concentrate for solution for infusion is a clear, colourless solution, pH 4.5 – 7.0

The qualitative composition of the ampoules is as follows:
Dexmedetomidine (as hydrochloride)
Sodium chloride

Sodium hydroxide / hydrochloric acid
Water for injection

Pharmaceutical development
The formulation development has been described. The manufacturing process development is briefly described. Dissolution, filtration and terminal sterilization are the main aspects from the process that can influence the quality of the product. Compatibility studies of the drug product with solvents for infusion are demonstrated.

Manufacture of the product and process controls
The proposed batch sizes and batch formulas are adequately presented. The manufacturing process and in-process controls are described with enough detail. Process validation data are presented.

Excipients
Excipients are adequately described.

Drug product specification
The drug product release and shelf-life specification are satisfying. The description and validation of the analytical methods are adequate. Batch analysis data are provided.

Reference standards or materials
The information about the reference standards is adequate.

Container closure system
A light blue ring colourless anonymous type I glass ampoule of 2 ml capacity is used as primary packaging material. The proposed container closure system complies with regulatory requirements.

Stability
The stability studies have been performed following the ICH guidelines. The proposed shelf-life of 24 months with no special storage conditions can be authorised based on the stability data presented.

II-2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of Dexmedetomidine hydrochloride are well known. As Dexmedetomidine hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)

Since *Dexmedetomidine Altan 100 micrograms/ml Concentrate for solution for infusion* is intended for generic substitution, this will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not deemed necessary.

Summary of main study results

Substance (INN/Invented Name): Dexmedetomidine Altan 100 micrograms/ml Concentrate for solution for infusion			
CAS-number (if available): CAS-145108-58-3 (hydrochloride salt**)**			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.89	Potential PBT (**N**)
PBT-assessment			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)	0.00012738	µg/L	> 0.01 threshold (**N**)
Other concerns (e.g. chemical class)			(**N**)

II.3 Clinical aspects

Introduction

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

Biowaiver

According to the Guideline on the investigation of bioequivalence, if the test product is an aqueous intravenous solution at time of administration and contains an active substance (dexmedetomidine hydrochloride) in the same concentration as an approved intravenous solution, bioequivalence studies may be waived.

As the qualitative composition of excipients is similar (i.e. both test and reference products contain sodium chloride and water for injection, and hydrochloric acid and sodium hydroxide (pH adjusters) in the applied product), and the quantitative composition of the excipients is also similar to those of the reference product, no bioequivalence study is required.

Bioequivalence

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 concentration that contain similar and well-known excipients.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.
No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

The applicant has submitted bibliographic data to support the second indication. The information provided is considered appropriate to authorize this indication for the medicinal product. The approval of this indication for Dexdor during the procedure and the fact that other similar medicinal product has been previously authorized for the same indication at european level (DK/H/2619/001/DC: Dexmedetomidine Ever Pharma concentrate for solution for infusion 100 µg/ml) has also be taken into account for the positive assessment on the benefit/risk profile of Dexmedetomidine Altan concentrate for solution for infusion 100 µg/ml regarding the second indication.

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.

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 concentration that contain similar and well-known excipients.

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.