12 December 2019
EMA/29822/2020
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Dexmedetomidine Accord

International non-proprietary name: dexmedetomidine

Procedure No. EMEA/H/C/005152/0000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Administrative information

Name of the medicinal product:	Dexmedetomidine Accord
Applicant:	Accord Healthcare S.L.U. World Trade Center Moll de Barcelona S/N Edifici Est, 6a Planta 08039 Barcelona SPAIN
Active substance:	Dexmedetomidine hydrochloride
International non-proprietary name/Common name:	dexmedetomidine
Pharmaco-therapeutic group (ATC Code):	Psycholeptics, hypnotics and sedatives, other hypnotics and sedatives (N05CM18)
Therapeutic indication(s):	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.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	100 µg/ml

Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial, 25 vials, 4 vials and 5 vials

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List of abbreviations

AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the Ph.Eur.
MS	Member State
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
DMF	Drug Master File = Active Substance Master File
DP	Decentralised (Application) Procedure
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
IPC	In-process control test
IR	Infrared
LOA	Letter of Access
LOD	Limit of Detection
LOQ	Limit of Quantification / Quantitation
LoQ	List of Questions
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
ND	Not detected
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OOS	Out of Specifications
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
TGA	Thermo-Gravimetric Analysis
UV	Ultraviolet
XRD	X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 23 November 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Dexmedetomidine Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'.

The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 September 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which, taking into account the accession of Czech Republic to the EU on 1st May 2004, it is considered that a marketing authorisation has been granted in a Member State in accordance with the *Acquis Communautaire* and on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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..

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and literature references instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Precedex, 100 micrograms/ml, concentrate for solution for infusion
- Marketing authorisation holder: Orion Corporation
- Date of authorisation: 21-11-2002[1]
- Marketing authorisation granted by:
  - Member State (EEA): Czech Republic
    - National procedure
- Marketing authorisation number: 57/270/02-C

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Dexdor, 100 micrograms/ml, concentrate for solution for infusion
- Marketing authorisation holder: Orion Corporation

[1] For the purpose of counting the data exclusivity period, said period starts from the date of accession of Czech Republic to the EU i.e. 1st May 2004

- Date of authorisation: 16-09-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EMEA/H/C/002268

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

The application was received by the EMA on	23 November 2018
The procedure started on	28 December 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 March 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	1 April 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 April 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 July 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	27 August 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 September 2019

The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	19 September 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	27 November 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dexmedetomidine Accord on	12 December 2019

2. Scientific discussion

2.1. Introduction

This application is for the marketing authorization of Dexmedetomidine Accord 100 micrograms/ml concentrate for solution for infusion and is based on Directive 2001/83/EC Article 10 (1): a generic application, referring to Precedex for the purpose of calculating the expiry of the data exclusivity period and Dexdor as the European Reference Medicinal Product.

The active substance dexmedetomidine has been in medical use for more than 10 years in the Community.

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 Accord 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.

Dexmedetomidine Accord 100 micrograms/ml concentrate for solution for infusion contains the same active ingredient in the same concentration as the reference product and for use in the same indication, strength and route of administration as the reference medicinal product Dexdor. Therefore, in accordance with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), no bioequivalence study was submitted to support the application.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as concentrate for solution for infusion 1 ml of concentrate contains 118.0μg of dexmedetomidine hydrochloride equivalent to 100.0μg dexmedetomidine.

Other ingredients are: Sodium chloride and water for injection. Nitrogen is used in sparging of bulk solution and headspace flushing during vial filling.

The product is available in a clear glass vial type I (in sizes of 2 mL, 6 mL or 10 mL) stoppered with rubber stopper and sealed with aluminium flip-off seal and then packed in an outer carton.

The pack sizes (number of vials in the carton) are greater than that for the reference product.

2.2.2. Active substance

General information

The chemical name of Dexmedetomidine is 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole corresponding to the molecular formula $C_{13}H_{16}N_2 \cdot HCl$. It has a relative molecular mass of 236.7 g/mol and the following structure:

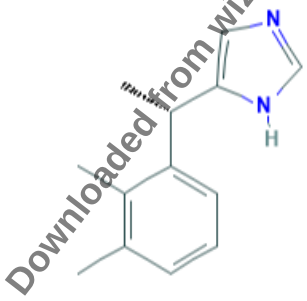

Figure 1: active substance structure

The chemical structure of Dexmedetomidine was elucidated by a combination of NMR ^{1}H and ^{13}C, FTIR, elemental analysis, UV-Vis, Mass Spectroscopy and Chiral HPLC. The solid-state properties of the active substance were measured by X-ray powder diffractometry (XRD), differential scanning calorimetry (DSC), thermogravimetry (TG) and the gravimetric method for hygroscopicity determinations.

The Dexmedetomidine hydrochloride is a white to off-white, fine powder, hygroscopic at high temperature, freely soluble in water, chloroform, methanol and ethanol.

Dexmedetomidine exhibits stereoisomerism due to the presence of one chiral centre. Dexmedetomidine hydrochloride is the (+)-(S)- enantiomer. Enantiomeric purity is controlled in the final active substance.

Polymorphism has been observed for Dexmedetomidine. There are two recognized polymorphic forms of Dexmedetomidine Hydrochloride: anhydrous (form A) and monohydrate (form B). Form A is consistently obtained during synthesis and is used in the manufacture of the finished product.

Manufacture, characterisation and process controls

The active substance information was provided through the ASMF procedure. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The specifications for starting materials were not acceptable and a major objection was raised and resolved when the information was provided.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. A risk assessment is presented according ICH Q3D.

The active substance is packaged in materials which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: appearance (visual), identity (IR, HPLC, UV-Vis, chlorides), appearance of solution (Ph. Eur.), melting point (Ph. Eur.), solubility (Ph. Eur.), loss on drying (Ph. Eur.), water content (KF), pH of solution (Ph. Eur.), total halogen (in-house Method), Heavy metal (Ph. Eur.), residue on ignition (Ph. Eur.), related substances (I HPLC), assay (HPLC) and microbial examination (Ph. Eur.), and bacterial endotoxins (Ph. Eur.)

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of 3 commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 4 commercial batches of active substance from the proposed manufacturer stored in a similar commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

Results on stress conditions performed under acid, base, oxidation, heat and light conditions, were also provided.

All tested parameters were within the specifications.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Dexmedetomidine 100 µg/mL concentrate for solution for infusion is a clear, colourless solution in a clear glass vial. This medicinal product is supplied in vials as a sterile, concentrate for solution for infusion containing 200 µg/2 mL, 400 µg/4 mL and 1000 µg/10 mL of Dexmedetomidine.

No overages of excipients are present in the formulation, no overfill is claimed. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The vials are of different sizes (the smaller vial size (2ml) can be distinguished from the 6ml and 10ml vial sizes, while the 6ml and 10ml are closer in size). The mock-ups of the labels and the cartons contain different colours for each vial size to differentiate between the vial sizes. This is sufficient to allow for distinction between the vial size.

The applicant has developed Dexmedetomidine Injection 100 µg/mL, 2 mL, 4 mL and 10 mL to match the pharmaceutical properties of the European reference product Dexdor® [Dexmedetomidine (as hydrochloride)], 100 micrograms/mL concentrate for solution for infusion (MAH: Orion Corporation, Finland). The qualitative composition of Dexmedetomidine Accord is the same as the reference product.

The information provided on the active substance includes the description, structure, molecular formula and weight, some information on the solubility in aqueous and organic solvents, melting point, isomerism, and chemical name has been provided. The applicant discusses and presents data to show the effect of heat, light, moisture, oxidation and pH on the active substance and its influence of these on the active substance in the finished product. The chemical stability of the active substance in the finished product in solution is demonstrated.

Pre-formulation and formulation development studies were carried out. Analytical methods for the test of related compounds and assay were developed and validated. The microbiological test methods of sterility & bacterial endotoxins showed satisfactory results. The development batches were tested for stability and showed satisfactory results.

The similarity of the applicant‘s formulation with reference formulation was demonstrated by comparison of composition, impurity profile and other parameters as description, clarity and colour of solution and pH.

The manufacturing process development was adequately described. Dilution study was also carried out. On the basis of dilution stability data of the product, it is concluded that the Dexmedetomidine Injection 100 µg/mL is stable for 72 hours when diluted with recommended diluents to produce 4 µg/mL and 8 µg/mL concentration and remains well within acceptance criteria.

Based on characterisation of the reference product Dexdor® concentrate for solution for infusion, 100 µg/mL, 2 mL, 4 mL and 10 mL, clear glass vial (type-I) of 2 mL, 6 mL and 10 mL are selected as containers for 2 mL, 4 mL and 10 mL packs respectively. The glass container for the product complies with the requirements as mentioned in European Pharmacopoeia under Glass containers for Pharmaceutical use (Ph. Eur. <3.2.1>. Type I glass containers offer maximum protection against pH drift.

For the glass vials: the container compatibility data have been provided(lab batch and scale up batch stability data). Based on this, the applicant concluded that selected clear glass vial (type- I) is compatible with the

formulation. Photostability studies ensured the suitability of the vials. For the rubber stoppers: Compatibility studies with the stopper have been carried out by the applicant. Container closure integrity study has been included by the applicant and it complies.

Manufacture of the product and process controls

The manufacturing process and process controls are adequately described in the dossier.

Major steps of the manufacturing process have been validated by a number of studies in 3 commercial scale batches of the 2 mL, 4 mL and 10 mL vials. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products (https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-information-nitrosamines-marketing-authorisation-holders_en.pdf, https://www.ema.europa.eu/en/documents/referral/nitrosamines-emea-h-a53-1490-questions-answers-information-nitrosamines-marketing-authorisation_en.pdf), MAHs of products containing chemically-synthesized active substances are being asked to review their products for potential presence of nitrosamine impurities and to conduct risk evaluations/risk assessments as appropriate.

No risk evaluation has been submitted for dexmedetomidine Accord within the current procedure. Therefore, it is recommended that a risk evaluation on the potential risk of presence of nitrosamine in dexmedetomidine Accord is conducted after the marketing authorisation, within six months of the publication of the call for review (19th September 2019). In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within 3 years of the publication of the call for review (19th September 2019), or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (UV, HPLC), pH (Ph. Eur.), clarity and colour of solution (Ph. Eur.), extractable volume (Ph. Eur.), sodium chloride content (Titration), impurities (HPLC), assay (HPLC), subvisible particles (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.) and osmolality (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial batches of each presentation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches of finished product of each presentation stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. No significant changes have been observed on the data provided.

Photostability studies for one batch were performed according to ICH Q1B. The testing was conducted on the final marketable product using the marketable pack.

In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

[2]6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Based on available stability data, the proposed shelf-life of 24 months and "This medicinal product does not require any special temperature storage conditions. Keep the vials in the outer carton in order to protect from light." as stated in the SmPC (section 6.3) are acceptable.

For storage conditions after dilution of the medicinal product:

After dilution: chemical and physical in-use stability has been demonstrated for 72 hours at 25°C and 2° to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2° to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress and to investigate the risk of presence of nitrosamine in their medicinal products, the CHMP recommends the following points for investigation:

- It is recommended that a risk evaluation on the potential presence of nitrosamine impurities in dexmedetomidine Accord is conducted after the marketing authorisation, within six months of the publication of the call for review (19th September 2019). In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within 3 years of the publication of the call for review (19th September 2019), or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Dexmedetomidine Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all dexmedetomidine containing products and the exposure of the environment to the active substance. The CHMP agrees with the applicant that the ERA is expected to remain similar.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. The pharmacology, pharmacokinetics and toxicology data of dexmedetomidine are well known and thus new non-clinical data are not required. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical aspects adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a concentrate for solution for infusion containing 100 micrograms/ml of dexmedetomidine. Dexmedetomidine Accord contains the same active substance as Dexdor and is intended for parenteral administration.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of dexmedetomidine based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) is of particular relevance.

GCP

No new clinical data have been presented.

Exemption

For the clinical assessment the EMA Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 is of relevance.

Dexmedetomidine Accord 100 micrograms/ml concentrate for solution for infusion contains the same active ingredient in the same concentration as the reference product and for use in the same indication, strength and route of administration as the reference medicinal product Dexdor. Therefore, according to the EMA guideline, a bioequivalence study is not considered necessary for the above-mentioned product.

2.4.2. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

In accordance with the Guideline on the Investigation of Bioequivalence, no bioequivalence study was submitted to support the application.

Dexmedetomidine Accord is considered essentially similar to Dexdor 100 micrograms/ml concentrate for solution for infusion.

2.4.4. Conclusions on clinical aspects

Based on scientific literature, a clinical overview has been provided. The overview justifies why there is no need to generate additional clinical data. The clinical aspects of the SmPC are in line with the SmPC of the reference product.

Therefore, the CHMP agreed that no further clinical studies are required.

2.5. Risk management plan

Safety concerns

Summary table of the safety concerns

Important identified risks	• Bradycardia • Hypotension • Hypertension • Hyperglycemia • 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

Pharmacovigilance plan

The PRAC and CHMP agreed that routine pharmacovigilance activities, including collection and reporting of adverse reactions, and signal detection are considered sufficient to monitor the safety of the medicinal product in the licensed indication. No additional pharmacovigilance activities are deemed necessary.

Risk minimisation measures

The PRAC and CHMP agreed that routine risk minimisation measures are considered sufficient. The safety information in the PI is aligned to the originator product.

Conclusion

The CHMP and PRAC considered that the RMP version 1.1 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Dexdor (for key safety message) and Zoledronic Acid Accord (for design and layout). The bridging report submitted by the applicant is acceptable.

3. Benefit-risk balance

This application concerns a generic version of dexmedetomidine concentrate for solution for infusion. The reference product Dexdor 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) and for sedation of non-intubated adult patients prior to and/or during diagnostic or surgical procedures requiring sedation, i.e. procedural/awake sedation.

No non-clinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Bioequivalence studies were not required as the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dexmedetomidine Accord is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.