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Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report for Dexdomitor extension (EMEA/V/C/000070/X/019)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

An application for an extension of the Community marketing authorisation of Dexdomitor has been submitted to the European Medicines Agency on 26 October 2011 by Orion Corporation in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I 2.(b) change or addition of a new strength/potency.

Dexdomitor contains dexmedetomidine hydrochloride and the currently approved strength of 0.5 mg/ml is presented in packs/containers of 10 ml vials. It is indicated for:

- Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.
- Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.
- Premedication in dogs and cats before induction and maintenance of general anaesthesia.

The route of administration is intramuscular and intravenous use. The target species is cats and dogs.

The extension application is to add a new strength containing 0.1 mg/ml dexmedetomidine hydrochloride. This lower concentration presentation will have the same indication and use information as the currently approved Dexdomitor 0.5 mg/ml. The new presentation has been developed to facilitate accurate dosing of animals with lower weights. The new strength is presented in vials of 20 ml filled with 15 ml of solution for injection.

The CVMP adopted an opinion and CVMP assessment report on 14 June 2012.

On 30 August 2012 the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

The CVMP considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Inspections of the drug substance manufacturing site and/or the drug product manufacturing site and/or the batch release site are not considered necessary for finalisation of assessment of Part 2 (quality).

Overall conclusions on administrative particulars

Part 2 - Quality

Composition

Dexdomitor 1 mg/ml solution for injection (1 mg/ml of dexmedetomidine base) contains dexmedetomidine hydrochloride as the drug substance, water for injections as the solvent, methyl parahydroxybenzoate and propyl parahydroxybenzoate as preservatives and sodium chloride to produce an isotonic solution. With the exception of the amount of the active pharmaceutical ingredient, the only difference to the currently approved strength is the slightly higher concentration of methyl

parahydroxybenzoate in Dexdomitor 0.1 mg/ml solution for injection (2.0 mg/ml in Dexdomitor 0.1 mg/ml and 1.6 mg/ml in Dexdomitor 0.5 mg/ml).

Container

Dexdomitor 0.1 mg/ml solution for injection is packed in 20 ml (fill volume 15 ml) moulded clear glass vials, European Pharmacopoeia (Ph. Eur.) type I. The vials are closed with fluoropolymer coated bromobutyl rubber stoppers.

Development pharmaceutics

The development is based on the knowledge gained from the manufacture and development of Dexdomitor 5 mg/ml solution for injection.

Method of manufacture

The process for the manufacturing of the finished product follows conventional pharmaceutical practices, which utilise a solution compounding step, filtration, filling into ampoules/vials followed by terminal sterilisation. The manufacturing of the finished product will be at a maximum batch size of 180 l. The process is also similar to the process for the already approved higher strength. Based on batch analysis data and adequacy of in-process controls, it is considered that the manufacture is sufficiently robust to provide assurance that the process produces the finished product of consistent quality, complying with the designed specification.

Control of starting materials

Active substance

The active substance dexmedetomidine hydrochloride is a white to almost white powder with a melting point of about 157 °C. At room temperature, dexmedetomidine hydrochloride is soluble in water at about 0.9 g/ml. The pKa (logarithmic acid dissociation constant) of dexmedetomidine hydrochloride is 7.1. Dexmedetomidine molecule contains one asymmetric carbon atom, which can exist in two enantiomeric forms, i.e. in (S) and in (R) form. The absolute configuration of dexmedetomidine has been determined by a single crystal X-ray diffraction method which found to be (S)-enantiomeric form. (R)-enantiomer (levo-form) is routinely determined from dexmedetomidine hydrochloride by a validated HPLC method. The HPLC method is selective for the separation of the two different enantiomers.

Dexmedetomidine hydrochloride appears in two different crystalline forms, A and B, which represent the dry and the humid form, respectively. The crystal structure of dexmedetomidine hydrochloride converts from the dry form to the humid form when the water content is about 7.1%, which value equals to that of the monohydrate form of the drug substance. The transition was found to be reversible; the dry form of dexmedetomidine hydrochloride can be obtained by heating the humid form at 120 – 140 ºC for about 30 minutes. Dexmedetomidine hydrochloride for pharmaceutical use is in its dry form.

The potential impurities of dexmedetomidine hydrochloride arising from the starting materials, intermediates and the chemical reactions have been discussed. The applicant had in the initial application presented justification for not considering two starting materials and impurities in these starting materials as potential impurities in the drug substance. The justification was based on knowledge of the reactions involved, in-process impurity testing and carry-over studies. The carry-over

studies were described in some detail and allowed the CVMP to conclude that the approach and results were acceptable.

The route of synthesis is sufficiently described, and the major phases in the synthesis of the drug substance are controlled during the reaction. Acceptable specifications on starting material, solvents and reagents, and isolated intermediate have been presented.

The specifications for the active substance are based on batch analyses of several batches of dexmedetomidine hydrochloride drug substance prepared by the commercial process and stability data. The methodology has been validated to meet the general requirements of the ICH guideline Q2B, Validation of Analytical Procedures; Methodology.

Dexmedetomidine hydrochloride is packed immediately after drying in tightly closed polyethylene containers, which are placed in tightly sealed, aluminium laminate bags. The stability data provided supports the proposed retest period of 5 years with "no storage precautions".

Excipients

All excipients comply with the relevant requirements and monographs in Ph. Eur.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

No excipients or starting materials of human or animal origin are used.

Control tests during production

Appearance, pH and final bulk weight of the solution is checked as in process controls. The solution filter is tested for integrity (bubble point value). pH of the filtrate is checked as in process control.

Sample for bioburden (filled vials) is taken before sterilisation.

After sterilisation the vials are 100% inspected for particles, rough over/low fill volume and packaging material defects.

Control tests on the finished product

The specification and control tests applied for the finished product at time of release and throughout the life of the product, are in compliance with general pharmacopoeial standards (Ph. Eur.) and ICH guidelines (Q3B and Q6A). The specifications for release and throughout shelf life are identical except for identification, optical purity and extractable volume. These parameters will only be tested at release. The degradation products are monitored only during shelf life in the stability studies.

The limits proposed have been justified and are in line with the limits approved for the higher strength.

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product. The results of the analysis of two production scale batches of the drug product are presented which comply with the required specification.

Stability

The stability data presented showed no significant changes in the results of tests for appearance, assay and degradation products for any of the batches for the reported duration of storage up to 6 months at

25 °C/65% and 6 months storage at 40 °C/75% RH. Stability results up to 36 months at long term conditions of commercial Dexdomitor 0.5 mg/ml solution for injection are presented as supportive data. Based on the stability data presented the proposed shelf-life of 3 years is considered acceptable. In use stability of the Dexdomitor 0.1 mg/ml solution for injection has been studied and the proposed in use shelf life of 28 days when stored below 25 ºC is considered acceptable. The solution for injection should be protected from freezing.

Overall conclusions on quality

Dexmedetomidine hydrochloride is chiral (one asymmetric carbon) and is isolated as a single enantiomer (dextro, +isomer) by separation from a racemic mixture. Dexdomitor is a simple water solution, which is produced by standard manufacturing methods for injection solutions including terminal sterilisation by moist heat in the final container.

The TSE risk is negligible due to the pure synthetic route. The manufacturing method of dexmedetomidine hydrochloride has been acceptably described.

The data provided demonstrate that the selected synthetic route is able to produce dexmedetomidine hydrochloride of required and consistent quality. Acceptable description of the synthesis of the active substance, relevant specifications with qualified impurity limits, validated methods and batch results complying with the specifications have been submitted.

With the exception of the amount of the active pharmaceutical ingredient, the only difference to the currently approved strength is the slightly higher concentration of methyl parahydroxybenzoate in Dexdomitor 0.1 mg/ml solution for injection (2.0 mg/ml in Dexdomitor 0.1 mg/ml and 1.6 mg/ml in Dexdomitor 0.5 mg/ml).

Based on the date provided the CVMP concluded that the change of the amount of the active pharmaceutical ingredient as well as the concentration of methyl parahydroxybenzoate have not led to a change in overall quality of the product. The quality part of the dossier for this extension was therefore considered to be acceptable.

Part 3 – Safety

The extension application is to add a new strength containing 0.1 mg/ml dexmedetomidine hydrochloride. This lower concentration presentation will have the same indication and use information as the currently approved Dexdomitor 0.5 mg/ml. The new presentation has been developed to facilitate accurate dosing of animals with lower weights. The new strength is presented in vials of 20 ml filled with 15 ml of solution for injection.

Reference is therefore made to the safety assessment for the currently approved Dexdomitor 0.5 mg/ml.

The active ingredient of Dexdomitor is dexmedetomidine hydrochloride, which is the pure dextro-enantiomer of medetomidine. The levo-enantiomer is devoid of pharmacodynamic activity, thus justifying the development of the single enatiomer. Dexmedetomidine is a potent and selective α2-adrenoceptor agonist with sedative and analgesic properties. Receptor binding studies in vitro, and in vivo models of α2-agonist activity, demonstrate that dexmedotomidine is two times more potent than medetomidine.

The toxicity of dexmedetomidine was high in all species (mouse, rat and dog) investigated. Dose-related clinical signs, similar in mice, rats and dogs, were sedation, piloerection, exophtalmus,

salivation (rat) and convulsions (rat and dog). Target organs of toxicity were eyes and liver. Cloudiness of corneas was noted in rats and central opacities in dogs. At histological examination of rat eyes, keratitis of the eyes was observed which demonstrated dose-dependent incidence and severity. In dogs superficial keratitis was noted in 5/6 HD animals after i.v. administration. This should be reflected in the SPC. An increased liver weight was seen in HD male animals after i.v. administration and in one HD male after i.m. administration, while no change was observed in females. Histopathological finding with dose-dependent severity, in both male and female animals, were eosinophilic intracytoplasmic inclusions in liver hepatocytes detected in MD and HD animals. Since the proposed indication for dexmedetomidine is single use, the liver finding is considered of no clinical relevance.

Dexmedetomidine is not genotoxic. No studies on carcinogenic potential of dexmedetomidine have been performed and are not requested for the intended short time use.

User Safety

Dexmedetomidine is a potent α2-adrenoceptor agonist. Small doses of dexmedetomidine, either administered parenterally, inhaled, applied to skin or swallowed may cause sedation, somnolence, decreased blood pressure and heart rate. High doses may cause bradycardia, first degree AV block and second degree heart block or sinus pause. Dexmedetomidine 0.2-0.7 μg/kg administered to man caused first degree AV block and second degree heart block.

Accidental splashing of dexmedetomidine on skin or mucosa may lead to some penetration and there is risk for sedation and haemodynamic changes. Local tolerance studies in animals indicate that there will be no significant skin or corneal damage after accidental splashing of dexmedetomidine.

Assuming a worst case scenario when the whole volume recommended to an 80 kg dog is injected accidentally by the user, serious haemodynamic changes might occur.

Dexmedetomidine should be handled with care by the veterinary medicinal staff. If dexmedetomidine has been inhaled, one should immediately get fresh air. In case of skin or eye contact, the exposed area should be rinsed with water and soap (skin) or large amounts of water (eyes). In case of parenteral or oral exposure to dexmedetomidine, a physician should immediately be contacted. Haemodynamic symptoms should be treated symptomatically. An antidote, the α2-adrenoceptor antagonist atipamezole, exists as a small animal antidote, but the human experience is yet limited.

The proposed wording of the SPC section 4.5 is accepted.

The CVMP concluded that the data provided in the initial application confirmed also for this extension that the risk to the user has been appropriately addressed and is acceptable.

Environmental risk assessment

A Phase I assessment provided during the intial application by the applicant demonstrated satisfactorily that the correct use of Dexdomitor in accordance with the SPC will not result in levels of drugs residues that are hazardous to the environment. In accordance with the CVMP VICH Topic GL6 (Ecotoxicity Phase I) Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-final) a Phase II environmental risk assessment is not required. The CVMP concluded that the data provided in the initial application confirmed also for this extension that there is no risk for the environment when Dexdomitor is used according to the labelling.

Residues documentation

Not applicable.

Overall conclusions on safety

The CVMP concluded that due to the fact that the dose in the target animal will remain the same with the added benefit of a more accurate dosing in animals with lower weight the safety profile of the product remains unchanged and the safety part of this extension application is therefore acceptable.

Part 4 – Efficacy

The extension application is to add a new strength containing 0.1 mg/ml dexmedetomidine hydrochloride. This lower concentration presentation will have the same indication and use information as the currently approved Dexdomitor 0.5 mg/ml. The new presentation has been developed to facilitate accurate dosing of animals with lower weights. The new strength is presented in vials of 20 ml filled with 15 ml of solution for injection.

Reference is therefore made to the clinical assessment for the currently approved Dexdomitor 0.5 mg/ml.

The racemate medetomidine has been on the market worldwide for a number of years and the efficacy of the approved doses are supported by a number of studies. The efficacy of dexmedetomidine is sufficiently supported by the submitted documentation in which dexmedetomidine was compared to the racemate in the target species. In these studies, the dextro-enantioner was as effective as the racemate, medetomidine. Minor differences in onset of effects were observed, but are of less importance, as there were no significant differences at 15-30 min after administration.

Similar to the racemate, sufficient (rated as good or excellent) analgesia was only reached in about 40 – 50 % of the animals. Hence, dexmedetomidine should only be used when slight analgesia is required.

There is one clinical aspect to cover were information cannot be bridged from the higher strength and this is a possible tolerance issue related to the larger volume to be administered. The applicant has provided a safety assessment of the higher amounts of the preservatives methyl parahydroxybenzoate and propyl parahydroxybenzoate per dose when using the new formulation with respect to local- and systemic- toxicity. It is concluded that the higher amounts of preservatives do not add any risk when the product is used in accordance with the SPC.

An upper limit for the volume to be administered was proposed by the applicant for the new dosing solution, with a lower strength, since higher dosing strengths are also available. This was acceptable to the CVMP.

Overall conclusions on efficacy

The CVMP concluded that due to the fact that the dose in the target animal will remain the same with the added benefit of a more accurate dosing in animals with lower weight the efficacy of the product remains unchanged and the efficacy part of this extension application is therefore acceptable.

Part 5 – Benefit risk assessment

Introduction

The extension application is to add a new strength containing 0.1 mg/ml dexmedetomidine hydrochloride. This lower concentration presentation will have the same indication and use information

as the currently approved Dexdomitor 0.5 mg/ml. The new presentation has been developed to facilitate accurate dosing of animals with lower weights.

Benefit assessment

Direct therapeutic benefit

Dexdomitor 0.1 mg/ml is a lower strength of the currently approved Dexdomitor 0.5 mg/ml solution for injection.

Dexdomitor 0.1 mg/ml is of value to support accurate dosing of smaller weight animals with the currently approved lower range dose.

Indirect or additional benefits

None

Risk assessment

No added risk has been identified for the lower strength presentation Dexdomitor 0.1 mg/ml.

Evaluation of the benefit risk balance

The formulation and manufacture of Dexdomitor 0.1 mg/ml is well described and specifications set will ensure that product of consistent quality will be produced. Based on the date provided the CVMP concluded that the change of the amount of the active pharmaceutical ingredient as well as the concentration of methyl parahydroxybenzoate have not led to a change in overall quality of the product. The quality part of the dossier for this extension was therefore considered to be acceptable.

The CVMP concluded that due to the fact that the dose in the target animal will remain the same with the added benefit of a more accurate dosing in animals with lower weight the safety profile and efficacy of the product remain unchanged and the safety and efficacy part of this extension application are therefore acceptable.

Given the clear benefit of the more accurate dosing for animals with lower weights compared to the fact that no added risks could be identified the CVMP concluded that the overall evaluation of the benefit risk balance was positive.

Conclusion on benefit risk balance

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for the Dexdomitor 0.1 mg/ml extension is approvable.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Dexdomitor 0.1 mg/ml can be considered to be in accordance with the requirements of Directive 2001/82/EC, as amended and that the benefit-risk balance is favourable.