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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Sileo (EMEA/V/C/003764/0000)

International non-proprietary name: dexmedetomidine

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

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Introduction

The applicant Orion Corporation submitted on 23 September 2013 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Sileo, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 11 April 2013 as the applicant showed that the product would constitute a significant therapeutic innovation due to the proposed indication.

The rapporteur appointed was F. Hasslung Wikström and co-rapporteur D. Murphy.

The applicant applied for the following indication: "Alleviation of acute anxiety and fear associated with noise in dogs."

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

The active substance of Sileo is dexmedetomidine hydrochloride, a selective alpha-2 adrenergic receptor agonist (alpha-2 agonist), which works by attaching to receptors in the brain called alpha-2 receptors and causes a reduction in the activity of the sympathetic nervous system which is involved in controlling anxiety, arousal and sleep as well the blood pressure and heart rate. By reducing the activity of the sympathetic nervous system, dexmedetomidine helps to make the dog calm or sleepy.

Sileo oromucosal gel contains 0.1 mg/ml dexmedetomidine hydrochloride and is presented in 3 ml oral syringes which are individually packaged in child-resistant cartons. The route of administration is oromucosal use.

The CVMP adopted an opinion and CVMP assessment report on 10 April 2015.

On 10 June 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Sileo.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The finished product, Sileo 0.1 mg/ml oromucosal gel, is manufactured and packaged in an approved site. The European Union (EU) batch release site is Orion Corporation, Espoo, Finland. A manufacturing authorisation, issued on 23 May 2013 by the Finnish Inspectorate, which shows that these sites are authorised for the manufacture and batch release (respectively) of such veterinary dosage forms is provided.

The active substance dexmedetomidine hydrochloride is manufactured in the EU.

A declaration signed by the Qualified Person (QP) at Orion, confirming that the active substance is manufactured at the specified site in line with Article 46(f) of Directive 2001/83/EC (as amended by Directive 2004/27/EC) has been provided. A GMP certificate issued 25 July 2008 by the Finnish Inspectorate has also been provided for the active substance manufacturing site.

No concerns have been raised during the assessment that would give rise to any manufacturing site inspection prior to authorisation.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status and manufacturing authorisation for both the active substance and dosage form manufacturing sites have been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product, Sileo 0.1 mg/ml oromucosal gel, is a homogenous, translucent, green oromucosal gel which contains the active substance dexmedetomidine hydrochloride and the excipients hyprolose (hydroxypropylcellulose), propylene glycol, sodium laurilsulfate, hydrochloric acid 10%, sodium hydroxide 2M, brilliant blue FCF (E133), tartrazine (E102) and purified water.

Container

The primary packaging is 4 ml high density polyethylene (HDPE) oral syringes fitted with a plunger, dosing ring and end cap. The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The nominal filling volume is 3 ml. The syringes are graduated to permit delivery of the product in 0.25 ml increments to facilitate the dosing of dogs weighing from 2 kg to 100 kg.

Each oral syringe is packed into a 2-piece child-resistant carton which is used to minimise the risk for accidental intake of the oral gel by children. In each carton there is an accompanying package leaflet. The outer package in combination with the protective cap on the oral syringe can be accepted as a container-closure system.

Development pharmaceutics

The aim of the formulation development was to develop an oromucosal water-based gel in which the active substance dexmedetomidine hydrochloride is dissolved. Other aims of the formulation development were to enable the dose to be administered oromucosally from an oral syringe with a variable dose capacity and 0.25 ml increments.

The formulation development work was based on experience from previously marketed products within the EU. All the components used are typical for such gel products. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the summary of product characteristics (SPC).

The formulation used during clinical studies was very similar to the final formulation, differing only in the colouring agents used.

A preservative efficacy test was performed and results are provided. The finished product was demonstrated to be self-preserving therefore no preservatives were needed in the formulation. Sileo 0.1 mg/ml oromucosal gel is a multi-dose product and the microbiological stability during dosing has been verified with a real-time in-use study.

Development work also focussed on the need for the product to be in a child-resistant package. This led to the selection of the oral syringe design used (with an end cap which requires considerable strength to remove it) and also to selection of the secondary packaging (2-piece carton, which necessitates various tabs being pressed whilst pulling open the carton simultaneously).

Method of manufacture

The manufacturing process can be considered a standard process comprising of mixing and homogenizing, then filling into the oral syringes and packaging.

The manufacturing method has been described in sufficient detail, and all the critical steps in the process have been identified and controlled.

The gel is manufactured from a mixture of the excipients and active substance dissolved and dispersed in purified water using heat. The gel is then cooled, its pH is adjusted and filled into the primary packaging (oral syringes). Adequate details have been provided and appropriate in-process controls have been presented.

Control of starting materials

Active substance

Dexmedetomidine hydrochloride is an almost white or white crystalline powder that is freely soluble in water. It is a known active substance, already included in EU centrally authorised veterinary and human medicinal products, and is manufactured as the S-enantiomer. The information for the active substance is presented in an active substance master file (ASMF).

The manufacturing process is a three-step chemical synthesis and the process is described in an acceptable level of detail. The justification for the designation of the two starting materials is considered appropriate. Appropriate specifications for both starting materials are provided and are satisfactorily justified. Specifications for other materials used are also satisfactory. Critical steps in the manufacturing process are described and controlled. A comprehensive review of the origin and control of all potential impurities arising in the process is provided and is satisfactory. The impurity levomedetomidine hydrochloride has been toxicologically qualified. The specification for the active substance controls critical parameters for the quality of the active substance. Descriptions for all analytical methods are presented and the methods for assay, purity, chloride and residual solvents have been appropriately validated in accordance with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guidelines. Other test methods are standard pharmacopoeial methods. Batch analysis data for three production scale batches are provided and all parameters comply with the active substance specification and the results demonstrate consistency from batch to batch.

Excipients

The Ph. Eur. excipients hydroxypropylcellulose, propylene glycol, sodium laurilsulfate, hydrochloric acid 10% and purified water are used in the formulation. These Ph. Eur. excipients are tested according to, and comply with, the requirements of the respective monographs.

Sodium hydroxide 2M, brilliant blue FCF (E133) and tartrazine (E102) are used in the formulation and are not the subject of Ph. Eur. monographs. Sodium hydroxide 2M is used for pH adjustment. Brilliant blue and tartrazine are used as colouring agents. In-house specifications are provided for these three excipients and are considered appropriate.

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

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

Control tests during production

Not applicable.

Control tests on the finished product

The description of the methods used for the control of the finished product and the specifications were provided. The specifications proposed at release and at the end of shelf life are in accordance with current EU and VICH guidance and are appropriate to control the quality of the finished product.

High-performance liquid chromatography (HPLC) analytical methods and their validation are described for analysis of the identity (colouring agents and active substance), assay, purity, content uniformity and optical purity. Microbiological control is performed according to standard pharmacopoeial methods.

The results of the analysis of three consecutive production scale batches were presented which comply with the finished product release specification.

Stability

Stability studies have been performed on six batches of the active substance in accordance with VICH GL3 on stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/899/99-Rev.1). Results of the tests demonstrate the active substance to be stable with no adverse trends in any of the parameters investigated. The proposed retest period is considered to be adequately supported.

Stability studies on the finished product have also been conducted in accordance with VICH GL3 on stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/899/99-Rev.1). Data up to 18 months at long-term, intermediate and 6 months at accelerated conditions have been provided for three commercial scale batches. In addition, supportive data for a laboratory scale batch has been provided. The analytical methods used are stability indicating. The proposed shelf life of 24 months is accepted.

Stress test studies show that the finished product degrades under light exposure. The storage condition "Keep the oral syringe in the carton in order to protect from light." is therefore included in the SPC and other product information.

An in-use stability study has been performed and supports the proposed in-use shelf life of 48 hours, which is in-line with the recommendations for the product's use.

Based on the available stability data, the shelf life, in-use shelf life and storage conditions as stated in the SPC (and other product information) are acceptable.

Overall conclusions on quality

The finished product is manufactured according to a validated standard process comprising mixing, homogenizing, filling and packaging. The gel is manufactured from a mixture of the excipients and the active substance dissolved and dispersed in purified water using heat. The gel is then cooled, pH-adjusted and filtered before being filled into the oral syringes.

The excipients in the formulation are commonly used in this type of formulation and their use has been justified.

The finished product is tested according to acceptable specifications, and the analytical methods used in the control of the product have been satisfactorily validated. Details on the batches used in the clinical studies have been provided.

The manufacturing process for the active substance is a three step chemical synthesis and details of the process and its control are adequately described. Stability studies for the active substance support the retest period.

The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product. Analytical methods and their validation are adequately described. A child-resistant outer package (2-piece carton) is used to minimise the risk for accidental intake of the oral gel by children. The outer package in combination with the protective cap on the oral syringe can be accepted as a container-closure system.

Suitable stability studies have been carried out according to current VICH guidelines. The stability data provided support a shelf life of 2 years and an in-use shelf life of 48 hours when stored in the outer carton.

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate the 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.

Part 3 – Safety

Safety documentation

Pharmacodynamics

The active substance, dexmedetomidine hydrochloride, is an alpha-2 adrenergic receptor (adrenoceptor) agonist (alpha-2 agonist). Dexmedetomidine is authorised in the EU for use in humans as a sedative in an intensive care setting. Intravenous (IV) and intramuscular (IM) dexmedetomidine is used as a sedative/analgesic agent for dogs and cats. Reports and publications have been provided to support the alpha-2 adrenoceptor mediated sedation, analgesia and anxiolysis caused by dexmedetomidine, both in vitro and in vivo. Dexmedetomidine also exhibits typical alpha-2 adrenoceptor mediated haemodynamic effects. Other alpha-2 adrenoceptor mediated pharmacodynamic effects include hypothermia, decreased intestinal motility, increased diuresis and natriuresis, and increased blood glucose through inhibition of insulin secretion.

A compilation of published papers on the effects of alpha-2 agonists in the locus coeruleus in the brain in rats and mice have been provided. It appears from these reports that selective alpha-2 agonists decrease the amount of noradrenaline in the locus coeruleus, resulting in sedation and hypnosis. It is further stated that lower exposures to dexmedetomidine are anxiolytic.

The anxiolytic effect is mediated by the same central nervous system (CNS) centre as for sedation, however smaller doses are needed. From the submitted documentation it seems as the anxiolytic effect is more pronounced in mice than in rats. However, the methodology used does not render the studies fully comparable. Furthermore, when compared to doses causing sedation, benzodiazepines appear more efficacious than dexmedetomidine for the relief of anxiety in the studied animal models; however a lower dose is needed for dexmedetomidine. In addition there are gaps in the understanding of fear and anxiety among species, at least as presented in this application.

There are no studies in experimental animals on the application of alpha-2 agonists for the proposed indication (anxiolysis) in non-rodent species.

The submitted studies in rodents justify the rationale for the attempt to develop the use of an alpha-2 agonist for the indication of alleviation of anxiety and fear in dogs. Furthermore, the applicant has submitted a clinical study where the use of clonidine for the alleviation of fear in dogs was described, this study can be considered sufficient to bridge that gap.

The unwanted effects of dexmedetomidine are well known, and briefly summarised by the applicant. Dexmedetomidine may induce sedation, diuresis, hypothermia, bradycardia, changes in arterial blood pressure (initial increase followed by decrease after IV injection), hyperglycaemia and hypoinsulinaemia.

In conclusion, the applicant has provided information that it may be possible for low dose dexmedetomidine to have an anxiolytic effect with a less pronounced sedative effect. The difference in effects is caused by the dose dependent action in the locus coeruleus in the brain, where a small reduction in noradrenaline release results in anxiolysis and a larger reduction in hypnosis. There is no experimental evidence of this dose dependent difference in the target species, but it is extrapolated from rodent models of fear and anxiety, which is accepted.

Pharmacokinetics

Dexmedetomidine is rapidly absorbed following subcutaneous (SC) or intramuscular (IM) administration and exhibits non-linear kinetics. Bioavailability following IM administration in the dog is 60%. In humans the oral, buccal and dermal bioavailabilities are reported to be about 16%, 82% and 51%, respectively. Dexmedetomidine is extensively bound to plasma proteins with little difference between species. In the rat dexmedetomidine is rapidly distributed to the liver, adrenals, lungs and kidneys. Most of the dexmedetomidine related radioactivity was eliminated from other tissues in 3 days, but was retained longer in the adrenal glands where the elimination half-life was more than 10 hours. The peak radioactivity in brain was 5- to 7-fold higher than the corresponding level in plasma. In pigmented rats the average peak concentration in the eyes was 28-fold higher than in non-pigmented rats suggesting that some drug-related component might bind to melanin.

The elimination of dexmedetomidine occurs almost exclusively by biotransformation in the liver with a relatively high clearance. The elimination half-life is about 2 hours. The metabolism is similar in the rat and the dog. There are slight differences in the human metabolic pathways and in levels of circulating metabolites compared with the dog and the rat. All known metabolites of dexmedetomidine are either devoid of pharmacological activity or show negligible activity. In the dog, dexmedetomidine metabolites are excreted mainly in the urine. In rats dosed IV or SC with 20 µg/kg of ^{3}H-dexmedetomidine, 64.7% or 50.1% respectively of the dose appeared in the urine, and the rest in the faeces.

Toxicological studies

Single-dose toxicity

Single-dose good laboratory practice (GLP)-compliant toxicity studies were performed in the rat and the mouse. One single-dose non GLP toxicity study was performed in the Beagle dog. The highest single-dose non-lethal dose observed was 1,000 µg/kg following IV bolus administration of dexmedetomidine to the rat, the mouse and the dog. The lowest LD_{50} was 5,000 µg/kg in both the rat and the mouse following both IV bolus and SC administration.

Repeat-dose toxicity

The repeat-dose toxicity of dexmedetomidine was investigated in studies of up to 28 days in the rat and the dog using doses from 10 µg/kg up to 500 µg/kg following intravenous, intramuscular or subcutaneous injection. The main pharmacological effect, sedation, was observed in all dose groups in all studies. There were no deaths observed at any dose level. In the dog studies slowed or irregular respiration rates were observed from 10 µg/kg and 250 µg/kg, respectively. Sedation and slowed respiration rates were not considered as adverse effects, but as pharmacological effects. No effects on electrocardiograms (ECG) were observed, however recordings were only made 24 hours post-dose. The observed lowest no observed adverse effect levels (NOAELs) were 10 µg/kg in the dog (IM and IV) and 20 µg/kg in the rat (IM and SC).

It is however worthy of note that in the target animal safety (TAS) study (IM and IV) decreased respiratory rates, decreased rectal temperatures, and decreased heart rates were observed in all dose groups (20, 60, and 100 µg/kg). ECGs were recorded both before dosing and up to 8 hours post-dosing. The ECG results post-dosing identified bradycardia, associated with prolonged QT intervals, without ventricular arrhythmias. First and second degree atrioventricular block was noted sporadically in all dose groups.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

The applicant has provided several studies on the effects on reproduction in the rat and the rabbit. The proposed product is only intended for use in the dog, a non-food producing species, and information from these studies is useful in the user risk assessment.

In a 2-generation study in the rat fertility was not affected at doses of dexmedetomidine of up to 54 µg/kg (SC). The NOEL for foetal toxicity is considered to be 6 µg/kg, based on the reduced number of live offspring observed from 18 µg/kg. In the rat embryo-foetal toxicity study the NOAEL for maternal toxicity is considered to be 20 µg/kg (SC), based on the deaths, heavy sedation and body weight loss observed at 200 µg/kg. The NOEL is considered to be 2 µg/kg, based on the slight sedation observed at 20 µg/kg. The NOEL for foetal toxicity in this study is considered to be 20 µg/kg, based on the effects on early embryonic deaths, number of living foetuses, placental and foetal weights and delayed skeletal ossification observed at 200 µg/kg. In the previous study effects were observed at 18 µg/kg, therefore the overall NOEL for foetal toxicity in the rat is considered to be 6 µg/kg. In the rabbit embryo-foetal study sedation was observed in the dams at all dose levels. There were no foetal effects observed at any dose level. Dexmedetomidine was not teratogenic in the rat or rabbit at doses up to 200 µg/kg (SC) and 96 µg/kg (IV), respectively. There were no effects observed in peri- or post-natal development including maternal function in the rat at doses of dexmedetomidine up to 32 µg/kg (SC). Slight effects on body weight gain were seen in the F0 females at 32 µg/kg during gestation and in the F1 pups during lactation at 8 µg/kg and 32 µg/kg.

Mutagenicity/genotoxicity

Dexmedetomidine was not mutagenic in the Ames test or in the mouse lymphoma thymidine kinase (TK) locus test in the presence or absence of metabolic activity (S9). Dexmedetomidine did not demonstrate clastogenic activity in the human lymphocyte cell system and was negative in the micronucleus test in mouse bone marrow. It can be concluded that dexmedetomidine is not genotoxic.

Carcinogenicity

No carcinogenicity study was conducted for dexmedetomidine. There are no concerns for mutagenicity and no preneoplastic changes have been observed. The lack of carcinogenicity studies is accepted.

Studies of other effects

Data were provided on the individual ingredients which indicate that the final formulation is not a skin or ocular irritant and does not cause dermal sensitisation. No other special studies were provided. This is considered acceptable since there is no indication of immunotoxicity, neurotoxicity or endocrine dysfunction.

Dexmedetomidine has been used in humans since 1999. It is indicated for the sedation of mechanically ventilated adult patients in an intensive care setting and in non-intubated adult patients prior to and/or during surgical and other procedures. Observations in humans reported in the literature are of

relevance for the user risk assessment. An oral dose of 2.5 µg/kg induced a slight sedation in children from 6 to 8 years old, whereas a dose of 1 µg/kg had no effects. It is estimated that 3 µg/kg (150 µg/human) is the highest human oral dexmedetomidine dose that is unlikely to cause pharmacological effect (sedation) in adult humans. The most frequently reported adverse reactions with dexmedetomidine (following IV infusion) are hypotension, hypertension and bradycardia. In addition, the most common adverse reactions reported in conjunction with overdose included bradycardia, hypotension, over sedation, somnolence and cardiac arrest.

User safety

A user risk assessment consisting of an exposure assessment, summary of toxicological effects, and a risk characterisation was provided according to the CVMP Guideline on user safety (EMEA/CVMP/543/03-Rev.1). The exposure scenarios identified by the applicant are accidental dermal exposure, accidental oral exposure and accidental ocular exposure. The worst case scenario suggested by the applicant is a 20 kg child accessing the used and discharged dexmedetomidine oromucosal gel syringe and ingesting 1.0 ml giving an exposure of 5 µg/kg. This dose will cause sedation with an induction time of 24 minutes. The worst case scenario was not entirely agreed on. Given that the product could be administered by the dog owner and stored in the home the exposure of a small child (10 kg) getting hold of the oral syringe before, during, or after administration was considered worst case. The worst case will thus be a 10 kg child ingesting the whole content of a full oral syringe (3.0 ml containing 0.1 mg/ml of dexmedetomidine). This would give an oral dose of 30 µg/kg. However, this scenario is considered unlikely based on the difficulty for such a small child to operate the syringe and plunger. A child NOAEL of 1 µg/kg was derived from the results of paediatric safety studies. The exposure estimate is higher than the NOAEL, therefore a risk for the user is identified. To mitigate this, the product is packaged in a child-resistant secondary package. If a child gets access to a partly used oral syringe of the product, the likelihood of exposure is very small as the syringe cap is hard to remove and the locked ring-stop prevents ejection of the gel from the syringe. This measure, together with the instructions to put the used syringe back into the secondary package, is considered sufficient.

It is agreed that the possible exposures should be compared with exposure levels having a pharmacological effect; or rather the NOAEL since the pharmacological effect in this case could be of a severe nature when not closely monitored.

It is agreed that dermal exposure is not likely to result in any pharmacological effect. It is agreed that any risk following accidental oral or ocular exposures caused by a dog’s cough or sneeze is negligible. It is also agreed that dermal exposure is easily detected because of the colour of the product. The local intramuscular irritation study provided is not relevant for the dermal exposure scenarios. However, since the local tolerance data in dog oral mucosa were considered acceptable in the clinical studies further local dermal irritation data is not required. Dexmedetomidine is therefore not considered as a dermal irritant. Based on knowledge of the individual ingredients lack of potential for dermal and ocular irritation and dermal sensitisation, the finished product is not considered as a dermal or ocular irritating or dermal sensitising product. The instruction to wear gloves and to wash off any spilled product is considered as a sufficient measure, even though a MOE for the dermal scenario was not calculated. This would also be the case for a pregnant woman. However, because uterine contractions and foetal effects may occur following systemic exposure to dexmedetomidine a warning has been included in the SPC.

Based on the data presented, the product does not pose an unacceptable risk to users, which are pet-owners (administering the product) and children (when getting access to the product accidentally), when used in accordance with the SPC.

Environmental risk assessment

An environmental risk assessment (ERA) in accordance with VICH GL6 on environmental impact assessment for veterinary medicinal products - Phase I (CVMP/VICH/592/98) and the CVMP Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) was provided. The veterinary medicinal product will only be used in non-food animals.

Based on the data provided the ERA can stop at Phase I. Sileo is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

In single-dose and repeated dose toxicity studies in the rat and the mouse with dexmedetomidine, the main effect observed was sedation. The lowest LD_{50} was 5,000 µg/kg in both the rat and the mouse. In the TAS study in the dog decreased respiratory rate, decreased rectal temperature, and decreased heart rate was observed.

Dexmedetomidine is not genotoxic and there is no identified carcinogenicity concern. Dexmedetomidine did not affect fertility in the rat and is not a teratogen in the rat or the rabbit. Embryotoxicity was however observed in the rat but not in the rabbit.

Data were provided on the individual ingredients which indicate that the final formulation is not a skin or ocular irritant and does not cause dermal sensitisation. No other special studies were provided. This is considered acceptable since there is no indication of immunotoxicity, neurotoxicity or endocrine dysfunction.

Observations in humans are of relevance for the user risk assessment. An oral dose of 2.5 µg/kg induced a slight sedation in 6–8 year old children, whereas a dose of 1 µg/kg had no effect.

In the user risk assessment a risk was identified for a small child. The worst case would be a 10 kg child ingesting the whole contents of a full oral syringe, which would give an oral dose of 30 µg/kg. This is much higher than the oral dose of 2.5 µg/kg which is capable of inducing sedation in 6–8 year old children. In addition, the margin of exposure to the lowest non-lethal single-dose (IV bolus or SC) in the rat is only about 30. Taking into consideration intra- and interspecies variability the margin should be at least 100. Consequently, over sedation, hypothermia, hypotension, bradycardia, and cardiac arrest (which when out of an intensive care setting could lead to death) may be caused by oral ingestion of the full contents of an oral syringe of the product. Even ingestion of 0.5 ml of the contents would result in an exposure of 5 times the human no observed effect level of 1 µg/kg. This risk is adequately mitigated by providing a secondary child-resistant packaging to prevent children from accessing the product. Furthermore, there are suitable instructions in the package insert that the product should be replaced, with the tight syringe cap replaced, back into the secondary packaging after each use.

When used in accordance with the SPC, the product is not expected to pose an unacceptable risk to the user.

Based on the data provided the ERA can stop at Phase I. Sileo is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

See Part 3.

Pharmacokinetics

In the dog dexmedetomidine has a volume of distribution of approximately 0.9 l/kg and the elimination half-life is less than one hour. The substance is mainly metabolised by hydroxylation, conjugation and methylation in the liver. The metabolites can generally be considered inactive, or with very weak activity, are largely excreted via the urine. As the excretion is dependent upon biotransformation in the liver, hepatic blood flow will affect the rate of excretion. In the context of this application this should be of minimal consequence, as treated animals have to be clinically healthy for being considered candidates for owner administered treatment in the home.

For the final product formulation, there are three non-GLP studies supporting the absorption of dexmedetomidine across the oral mucous membrane. During the product development it was demonstrated that there were less pronounced physiological effects for the oromucosal gel compared to the same dose administered intramuscularly. In an explanatory study the bioavailability was investigated and found to be approximately 28%. Lastly, repeated administration was assessed in a supportive study. From the latter study it was concluded that the terminal half-life is somewhat prolonged after repeated administration. The kinetics of dexmedetomidine are adequately characterised to support the dosage intended for the proposed product.

Dose determination/justification

The applicant has submitted two dose determination studies where doses recommended for intramuscularly administered dexmedetomidine intended for sedation were compared to two oromucosal doses. The choice of doses appear to be based on data in rodents regarding the anxiolytic effects of alpha-2 agonists when used in doses lower than those effective for sedation.

The bridge between preclinical studies in rodents and the clinical use in dogs was made by a small study where the alpha-2 agonist clonidine (at a dose of up to 0.05 mg/kg) was successfully used to relieve anxiety and aggression in dogs.

No dose-titration studies for the anxiolytic versus sedative effects of dexmedetomidine in dogs were provided. However, the few small, dose finding studies indicate that lower exposure to dexmedetomidine, obtained by a combination of a lower dose and oromucosal administration, will result in a lower level of sedation than seen with doses used for sedation.

It is acceptable that there are no classical dose finding studies. Instead, two doses - 125 or 250 µg/m^2 - were tested in the pilot field trial.

Target animal tolerance

The current application does not include a conventional target animal safety study with the proposed product and dose. A study investigating higher doses of dexmedetomidine than those intended for this product was submitted; however it does not investigate the repeated administration of the proposed product.

In a safety study (WEL Study 00-008) intravenous and intramuscular injections of dexmedetomidine were repeatedly administered at 24 hour intervals to dogs at 0, 1, 3 and 5 times the dose used for sedation. The most notable effects seen in experimental animals were sedation, decrease in heart rate and body temperature and a dose dependent increase in the duration of signs. There were no long term negative effects or mortalities. The doses recommended for sedation are 3 times higher than the 125 µg/m^2 dose proposed in the present application. In addition, the bioavailability after oromucosal administration is less than 50% (average 28%), resulting in lower exposure from oromucosal use compared to injections. Consequently, the applicant has sufficiently characterised the safety of dexmedetomidine used at clinically relevant dose levels. Doses required to cause serious adverse events are indeed higher than doses used in the safety studies. A high dose of around 5 times the sedative dose will result in prolonged sedation, however with complete recovery.

The repeated use of oromucosal dexmedetomidine, at the same dose rate as indicated for the proposed product, was investigated in a non-GLP study in 9 dogs. The results indicate that a 2 hour dosing interval will result in higher plasma concentrations when compared to single-dose administration. Unwanted physiological and sedative effects were minimal, indicating acceptable safety of repeated administration by the oromucosal route.

Furthermore, the repeated administration of a dose twice that of the intended dose was investigated in a laboratory study. In this study 4 dogs were sedated to some degree, increasingly so after repeated doses.

All studies have been performed in healthy, non-pregnant animals. Therefore, only healthy individuals should be treated. Safety during pregnancy or lactation has not been investigated. The adverse reactions seen in experimental studies have mainly been sedation, emesis, decreased heart rate, decreased body temperature and possible incontinence. These adverse reactions are described in the product information.

Studies on the continuous infusion of dexmedetomidine in Beagle dogs were provided (study nos. R&D/00/234-235). The plasma concentrations obtained in these studies were 3–13 ng/ml plasma while the estimated concentration after proposed use of the intended product will be an estimated 1 ng/ml. In these studies dogs showed bradycardia, sedation, gastrointestinal signs and decreased body temperature. All signs were reversible and there were no mortalities.

In the event of a large overdose in a small dog, the exposure will be lower than that seen in the experimental target animal safety study (WEL Study 00-008). Thus, it is likely that a small dog exposed to a large overdose will be sedated, however on the basis of study results this is expected to be transient and lead to full recovery in a healthy dog.

The oral dosing syringe is intended to be used in the home environment by the dogs' owners. It is of paramount importance that correct dosing is easily achieved. Due to a number of dosing errors observed in the field study, the markings on the final oral dosing syringe have been improved. In addition, should a dosing mistake occur a quick reference for the dosage of a specific antidote is included in the product information.

The product is not intended for sick, pregnant or lactating animals and this is reflected in the SPC (sections 4.5 and 4.7).

Based on the totality of data provided, the CVMP concluded that the product is well tolerated in the target species, dogs, when used as recommended in the SPC.

Field trials

In a pilot dose-confirmation field study, two doses of dexmedetomidine (125 and 250 µg/m^2) were administered to dogs to characterise the known physiological effects of dexmedetomidine after administration via the oromucosal route, as compared to the intramuscular route. Both dose levels were found to have effects on heart rate, body temperature and sedation. However, the effects were smaller than those seen with intramuscular dexmedetomidine at the same or lower doses.

Both dose levels were subsequently tested in a three-armed, placebo-controlled, double-blinded pilot clinical field study including a total of 36 dogs (n=12/group) to investigate the efficacy of dexmedetomidine in alleviating anxiety and fear in association with fireworks. End-points were assessed by the owner. In this study dexmedetomidine was superior to placebo in alleviating anxiety and fear. A good effect was seen for 9 out of 12 (75%) of the dogs treated with dexmedetomidine at a dose of 125 µg/m^2 and 8 (66.7%) treated with dexmedetomidine 250 µg/m^2 as compared to only 3 (25%) dogs in the placebo group. When dogs with good effects were compared with all other dogs, a statistically significant difference in favour of a treatment effect was seen between the dogs treated with dexmedetomidine (125 µg/m^2 or 250 µg/m^2) compared to the dogs receiving a placebo (p = 0.014). When analysed by treatment group, the difference in favour of treatment was statistically significant only for the dogs treated with the lower dose (dexmedetomidine 125 µg/m^2) (p = 0.0391), but tended to be significant also for the higher dose (250 µg/m^2) (p=0.0995). When the variable was dichotomised into responders and non-responders, the difference between the proportions of responders in the treated groups compared to placebo was not statistically significant (p = 0.1495) as there were non-responders in the higher dose group. Furthermore, there were fewer adverse events in the group dosed with 125 µg/m^2. Therefore the applicant interpreted the results of this pilot study to justify the evaluation of the lower dose rate of 125 µg/m^2 in the pivotal study.

In the pivotal GCP-compliant, multicentre, placebo-controlled, randomized, double-blinded field study of two parallel-group design, the efficacy of the product was investigated in a total of 182 dogs for the proposed indication at the proposed dose of 125 µg/m^2 repeated up to five times at intervals of two hours. In this study 89 dogs were treated with the final proposed product and 93 dogs were treated with a placebo gel. Both investigational product and placebo were administered on the oral mucosa. The dogs were recruited via veterinary clinics in Finland and Germany and the main evaluation was performed on New Year's Eve 2012. All observations were performed and recorded by the dogs' owners. Adequate numbers of dogs were easily recruited, and the demographic distribution appears comparable between the two treatment groups. A co-primary variable was used for investigating a treatment effect as distribution of the dog's behaviour compared to the previous year, in five different categories ranging from excellent to worse (1st co-primary variable), and as difference in owner-scored signs of anxiety and fear (2nd co-primary variable).

For the evaluation of the first co-primary variable, the owner assessed the effect of study treatment, where the dog's signs of anxiety at New Year's Eve were compared to the dog's reactions to fireworks in previous year(s) without treatment. The effect of study treatment was assessed once at minimum 2 hours after the last dosing, using a categorical scale. An "excellent" treatment effect was reported by the owners for 15 of the 89 (16.9%) dogs treated with dexmedetomidine and 9 of the 93 (9.7%) dogs on placebo. Similarly 49 (55.1%) of the dogs on dexmedetomidine and 25 (26.9%) of those on placebo were reported to have a "good effect". The treatment effect was statistically significant (p with generalised linear model <0.0001) favouring dexmedetomidine.

For the evaluation of the second co-primary variable, the owner observed the dog and assessed how the dog had been behaving within the previous 15 minutes on repeated occasions associated with each dosing. For each of the 12 signs of anxiety and fear, the owner assessed the extent (from 0 to 4) of

the sign, and the sums of scores were calculated (maximum sum for a dog/time point was 48). The scores for dogs on dexmedetomidine were numerically lower compared to those on placebo from the 1 hour time point after the first dosing until the fifth dosing. For example, one hour after the second dosing the mean ± SD score for the dexmedetomidine treated group was 4.5 ± 5.2 versus 8.8 ± 8.0 for the placebo group. For the second co-primary variable, the sum scores were analysed at 1 hour time points (from the first to fourth dosing), for which a statistically significant treatment effect ($p = 0.0134$ with RMANCOVA) favouring dexmedetomidine was found.

The outcome for both predefined co-primary variables was significantly different between the two groups favouring the dexmedetomidine treated group. Furthermore, a dichotomised variable, based on the first categorical variable, demonstrated that more dogs were classified as success in the dexmedetomidine treated group than in the placebo treated group.

In conclusion, the pivotal clinical trial was well designed and adequately sized to demonstrate differences among the groups and the data was analysed according to pre-set criteria in the study protocol. Results show that a clinically meaningful treatment effect is obtained in comparison to placebo when dexmedetomidine is administered to healthy dogs as necessary via the oromucosal route at a dose of 125 µg/m^2 with dosing intervals of not less than two hours for alleviating anxiety and fear in association with fireworks.

In the field studies only few adverse events were reported. The most commonly reported reactions were lack of efficacy, emesis and sedation. There were no serious adverse effects reported in any of the studies and this is consistent with experience from use of the substance as a sedative in animals. The product was well tolerated at the correct low doses used in the studies in healthy animals.

Overall conclusion on efficacy

Dexmedetomidine is a known alpha-2 agonist substance previously approved for sedation in small animals and humans.

Pre-clinical data has been submitted in support of an anxiolytic action of low doses of alpha-2 agonist substances. This effect has been suggested to be mediated by the decreased release of excitatory neurotransmitters in the locus coeruleus. The anxiolytic effects of various alpha-2 agonistic substances have been demonstrated in pre-clinical rodent models and in a published clinical study in dogs where clonidine was used. The dossier does not contain any pre-clinical canine models of anxiety and fear in which proof of concept of the treatment has been established. However, this is not considered pivotal for the evaluation of efficacy for the intended indication.

It was demonstrated that dexmedetomidine is absorbed across the oral mucosa in healthy dogs, but that the bioavailability is low, with an average of 28%.

Concerning target animal safety, it was demonstrated that high and repeated overdosing will result in an increased severity and duration of adverse effects but that mortality or long lasting effects are not expected in healthy dogs.

A clinically meaningful treatment effect has been demonstrated in comparison to placebo when dexmedetomidine is administered to healthy dogs as necessary via the oromucosal route at a dose of 125 µg/m^2 with dosing intervals of not less than two hours for alleviating anxiety and fear in association with fireworks, as assessed by the owners in dogs treated with dexmedetomidine compared to placebo, when dogs were exposed to fireworks. The field study was adequately sized and the study was well designed to provide reliable results.

Part 5 – Benefit-risk assessment

Introduction

This application is for Sileo, a product containing dexmedetomidine 0.1 mg/ml as an oromucosal gel which is to be presented in 3 ml multi-dose oral syringes.

Dexmedetomidine is an alpha-2 agonist that inhibits the release of noradrenaline from noradrenergic neurons, blocks the startle reflex and thus counteracts arousal.

The product is intended for the alleviation of anxiety and fear associated with noise in dogs. The route of administration is oromucosal use. The recommended starting dose is 125 mcg/m^2 body surface. The dose can be repeated after a minimum of two hours. The product can be dosed up to 5 times during each event.

This is a full application submitted in accordance with Article 12(3) of Directive 2001/82/EC. The product is presented as a significant therapeutic innovation as there are no products approved for the specified indication.

Benefit assessment

Direct therapeutic benefit

The active substance is a known sedative substance.

The mode of action is considered to be mediated in the central nervous system by the reduced release of noradrenaline.

A well conducted placebo-controlled clinical trial demonstrated that the product is efficacious in alleviating anxiety and fear in association with noise (fireworks) when the product is administered to healthy dogs via the oromucosal route at a dose of 125 µg/m^2 dexmedetomidine as necessary with dosing intervals of not less than two hours.

The efficacy in other than healthy animals is not documented.

Additional benefits

The product is easy to apply by the owner.

Risk assessment

Main potential risks:

Quality

The formulation and manufacture of the finished product Sileo oromucosal gel is well described and the specifications set will ensure that a product of consistent quality will be produced.

Target animal safety

The safety of Sileo has been investigated in healthy dogs when used according to the proposed dosing recommendations. Adverse reactions are of a non-serious nature. The most important expected adverse reactions are sedation, emesis and urinary incontinence. Accidental overdoses may cause reversible physiological effects and clinical signs such as a decrease in heart rate and body temperature. No data were submitted on reproductive toxicity in the target species and this is addressed in the product information.

User safety

A risk has been identified for a small child ingesting the whole contents or part of an oral syringe, with over sedation, hypothermia, hypotension, bradycardia, and cardiac arrest as a potential consequence. This risk is mitigated by using a child-resistant secondary packaging accompanied by instructions in the package insert on how to handle the product in order to avoid exposure in children.

Significant systemic exposure of a pregnant woman may cause uterine contractions and decreased foetal blood pressure. Therefore a warning for pregnant women not to handle the product is included in the product information.

Environmental safety

The product is not expected to pose a risk for the environment when used in accordance with the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks. User safety risks have been identified, mainly concerning the risks associated with exposure in children. This risk is managed by the presentation of the product in a primary packaging with a tight cap and a secondary packaging that is child-resistant.

Evaluation of the benefit-risk balance

The product has been demonstrated to alleviate anxiety and fear associated with noise in healthy dogs.

The formulation and manufacture of Sileo oromucosal gel is well described and the proposed specifications would ensure that a product of consistent quality will be produced.

It is well tolerated by the target animals.

The product represents an acceptable risk for the user and the environment when used as recommended and appropriate warnings have been included in the SPC.

The product has been shown to have a positive benefit-risk balance overall.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the CVMP concluded that the application for Sileo is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.