IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

DOMOSEDAN GEL 7.6 mg/ml oromucosal gel

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PRODUCT SUMMARY

EU Procedure number	IE/V/0218/001/DC
Name, strength and pharmaceutical form	Domosedan Gel 7.6 mg/ml oromucosal gel
Active substance(s)	Detomidine Hydrochloride
Applicant	Orion CorporationP.O Box 65 FI 02101 EspooFinland Street address: Orionintie 1 FI-02200 Espoo Finland
Legal basis of application	Decentralised application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of procedure	1st October 2008
Target species	Horse
Indication for use	Sedation to facilitate restraint for non-invasive veterinary procedures (e.g. passage of naso-gastric tube, radiography, rasping teeth) and minor husbandry procedures (e.g. clipping, shoeing).
ATC vet code	QN05CM90
Concerned Member States	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IS, IT, LV, LT, LU, MT, NL, NO, PL, PT, RO, SK, SI, SE, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

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The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended.Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A.Qualitative and Quantitative Particulars

The product contains:
Active substance
6.4 mg/ml Detomidine (equivalent to 7.6 mg/ml Detomidine hydrochloride)

Excipients
Brilliant blue FCF (E133) (as colourant)
Hydroxypropylcellulose
Propylene glycol
Sodium laurilsulphate
Sodium hydroxide
Hydrochloric acid
Purified water
The container/closure system is a pre-filled, single-dose syringe, enabling doses from 1.0 to 3.0 ml, packed in an outer carton.
The syringes consist of a syringe barrel (HDPE), cap (LDPE), plunger (HDPE) and a locking ring.The particulars of the containers and controls performed are provided and conform to the regulation.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B.Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques.Process validation for full-scale batches will be performed post-authorisation.

C.Control of Starting Materials

The active substance is Detomidine hydrochloride, an established active substance described in the European Pharmacopoeia.
The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

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Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D.Control on Intermediate Products

Not applicable.

E.Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.
Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F.Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing<?xml:namespace prefix = o ns = urn:schemas-microsoft-com:office:office />

Pharmacological Studies

The applicant has conducted studies as well as provided bibliographical data which show that detomidine acts as an alpha-2 adrenoceptor agonist with a central effect by inhibiting the transmission of noradrenalin-mediated nervous impulses. In the animal, the level of consciousness is lowered and the pain threshold is increased.
The applicant has also conducted studies which show that at a dose of 40 micrograms/kg of the product, the mean C_{max} was 4.3 ng/ml and mean t_{max} was 1.83 hours (range from 1 to 3 hours). Following sublingual administration, clinical signs of sedation were evident at approximately 30 minutes after dosing.

The bioavailability of detomidine administered as the sublingual gel in the horse is about 22%. If the product is swallowed the bioavailability is significantly decreased.

Elimination of detomidine occurs by metabolism with a half-life of about 1.25 hours. Metabolites of the drug are eliminated mainly in the urine.

Toxicological Studies

The applicant has provided bibliographical data which show that the toxicological profile of detomidine in laboratory and domestic animal species is well characterised. Acute toxicity was related to the pharmacological action, with laboratory studies in rats and rabbits demonstrating no evidence of teratogenic, foetotoxic or maternotoxic effects. The bibliographic data provided concur with the conclusions on toxicity of detomidine documented in the CVMP MRL Summary Report for that molecule.

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Other Studies (if relevant – or delete)

The applicant has conducted additional studies which show that Domosedan Gel 7.6 mg/ml oromucosal gel is at most mildly irritant when applied to skin and eyes and would not be regarded as a skin sensitiser.

Observations in Humans

The applicant has provided information which show that symptoms reported after accidental human exposure to an alpha-2 adrenoceptor agonist have included drowsiness, hypotension, hypertension, bradycardia, tingling sensation, numbness, pain, headache, somnolence, dilated pupils, and vomiting.

No human toxicology data available.

Microbiological Studies

Detomidine was not tested for anti-microbial activity but alpha-adrenergic agonists are not known to possess such activity**.**

Excipients are commonly used in topical and/or oral veterinary pharmaceuticals as well as human medicines, cosmetics and foodstuffs.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that when administering Domosedan Gel 7.6 mg/ml oromucosal gel that:
·The most likely routes of exposure are via the skin and the eye.
·It may cause local skin irritation following prolonged skin contact.
·It may cause sedation, somnolence, decreased blood pressure and decreased heart rate in humans.
·Pregnant women should avoid contact with the product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that no significant environmental risks are expected to arise from the use of Domosedan Gel 7.6 mg/ml oromucosal gel for horses based on the proposed pattern of use.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted using Domosedan Gel 7.6 mg/ml oromucosal gel because data presented in support of the product relating to the depletion of detomidine residues were considered by CVMP in the context of the maximum residue limit application.
·The equine residue depletion data considered by CVMP when assessing the MRL file for detomidine were based on studies in which detomidine solution for injection was administered by the intravenous and intramuscular routes at the highest recommended dose of 80 micrograms detomidine/kg. With reference to these data, the CVMP concluded that the drug and its metabolites are rapidly excreted such that residues present in tissues by 24 h after dosing are below the proposed acceptable intake.

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·It is anticipated that tissue residues achieved following the sublingual administration of detomidine will be less than those detected following either intravenous or intramuscular administration because 1) the recommended treatment dose for the oromucosal gel is 40 micrograms/kg, and 2) bioavailability following sublingual administration is estimated to be < 30%.

In addition, it is acknowledged that the major effects are pharmacological not toxicological and that the drug is intended for single use on individual animals.

MRLs

Detomidine is listed in Annex II of Council Regulation 2377/90. Tissue maximum residue limits are not required to ensure consumer safety.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat in horses and zero hours for milk are justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies Tolerance in the Target Species of Animals

The applicant has conducted a GLP compliant blinded controlled target animal tolerance study using multiples of the recommended dose in the target species. A control group of animals received no treatment.
Parameters evaluated were clinical signs, degree of sedation, changes to the oral mucosa, bodyweight, food and water consumption, clinical chemistry, haematology analysis, urine analysis and physiological parameters including heart rate, respiration rate, capillary refill time, gut motility, ECG parameters and rectal temperature.
Adverse effects consisting of swelling around the eyes, nasal and ocular discharges, excessive or erratic urination, muscle tremors and shivering, and erythema of the site of administration were seen following administration of up to 5 times the recommended dose. All of these effects were transient and none were considered toxicologically significant. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies Laboratory Trials

The applicant conducted a series of 10 laboratory trials between 2002 and 2004 (using from 3 to 11 horses in each trial) to determine a satisfactory dose and formulation of the product.During these studies samples were collected to determine serum detomidine concentrations and clinical parameters (including degree of sedation, heart rate, local tolerance and adverse events) were evaluated. These data were considered as supportive information for the determination of a final formulation and dose rate.

Field Trials

The applicant has conducted field studies which show that the optimal dose rate of the product to facilitate completion of various veterinary and husbandry procedures is 40µg/kg bodyweight.
A randomised, blinded, single-centre study was conducted in Finland from October 2004 to January 2005.Sixty privately owned horses with a mean age of 9 years and a mean bodyweight of 534kg were included in the study. The effects of the oral test product were compared with a currently authorised injectable product.The level of sedation obtained using the test product at a dose rate of 40µg/kg bodyweight was adequate to allow minor procedures including clipping of the hair coat, shoeing and rasping of the teeth to be performed and was at least as good as that achieved with the injectable product.
Another randomised, blinded, placebo controlled field study was conducted in the USA using the patients of nine equine veterinary practices. Two hundred seventy horses of various breeds, from 1 to 36 years of age were enrolled in the study from October 2006 to June 2007. The horses were to be sedated to facilitate grooming (including cleaning of the prepuce), hoof care, floating teeth (manually), passage of a nasogastric tube or endoscope, or radiography. In the All Randomized set of 270

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horses,161 detomidine-treated horses (79%) and only 6 placebo-treated horses (8%) successfully completed the procedures, confirming the efficacy of the 40micrograms/kg bodyweight dosage.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the HPRA website.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Changes:
None.

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