IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Dolorex 10 mg/ml Solution for Injection for horse, dog and cat

PRODUCT SUMMARY

EU Procedure number	IE/V/0194/001/MR
Name, strength and pharmaceutical form	Dolorex 10 mg/ml solution for injection for horse, dog and cat
Active substance(s)	Butorphanol 10 mg/ml as tartrate
Applicant	Intervet International bv Wim de Korver Straat 35; NL-5831 AN Boxmeer The Netherlands
Legal basis of application	Bibliographical application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of procedure	28th Feb 2007
Target species	Horse, dog, cat
Indication for use	Short duration analgesia and sedation
ATCvet code	QN 02AF01
Concerned Member States	BE, DE, DK, EL, FI, FR, HU, LU, NL, NO, PT, SE, SK, UK(NI)

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.

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; any potential adverse effects are detailed 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

· Active substance
Butorphanol (as butorphanol tartrate) 10 mg/ml
Excipients
Benzethonium chloride
Sodium citrate
Sodium chloride
Citric acid monohydrate
Water for injection

The container is a cardboard box with 1 glass vial of 10 or 50 ml with a rubber stopper and an aluminium cap.
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 at a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C.Control of Starting Materials

The active substance is butorphanol as butorphanol tartrate, an established active substance. 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.
Other substances in the product comply with pharmacopoeia monographs.
10 ml and 50 ml multidose, clear Ph. Eur. type I (Ph. Eur 3.2.1) glass vials with halogenated butyl rubber stopper (Ph. Eur. 3.2.9) and aluminium overseal.

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 Studies on the Active Substance
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 Tests on the Finished Product
Stability data on the 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.ASafety Testing

Pharmacological Studies

· Pharmacodynamics
The applicant has provided bibliographical data which show that butorphanol is a synthetic opioid analgesic. Its action is agonist-antagonist at the opiate receptors in the central nervous system.
· Pharmacokinetics
The pharmacokinetic profile is well documented especially in humans. Data relating to horses, dogs and cats have been obtained from proprietary studies and the published literature. Information relating to intravenous use in horses, intramuscular use in dogs and subcutaneous use in cats was presented. The data are sufficient for the purposes of this dossier, which is based on well established use.

Toxicological Studies

The applicant has provided bibliographical data describing the toxicological effects in a variety of species by several different routes of administration. Butorphanol has a wide therapeutic margin with opioid-related side effects.
· Single Dose Toxicity
Signs of acute toxicity include ataxia, nervousness, convulsions and death. These were more severe and occurred at lower doses following intravenous administration than by other routes. Oral administration, even at high doses (up to 100 mg/kg) resulted in minimal adverse effects.
· Repeated Dose Toxicity
Repeated daily oral doses of up to 10 mg/kg for 90 days resulted in mild behavioural signs and weight loss. Slight changes in the liver and associated blood biochemical parameters, which were reversible, occurred in dogs at 5 mg/kg.
· Reproductive Toxicity, including Teratogenicity:
Lower pregnancy rates were reported when male and female rats were treated daily from 63 days (males) or 14 days (females) before conception with doses of up to 160 mg/kg. In females the treatment continued until 21 days after giving birth. Pup mortality and pup weight were affected at this high dose, but there was no change to gestation period, litter size and foetal loss. The 'no effect level' for embryotoxicity was 40 mg/kg/day.
There were no adverse effects on litter size, foetal loss, litter and mean pup weight, embryonic or foetal development when butorphanol was administered to female rats at daily doses up to 160 mg/kg between days 6 and 15 of gestation.
· Mutagenicity and carcinogenicity
There is no evidence of any mutagenic or carcinogenic potential.

Other Studies

The applicant has provided bibliographical data which show that butorphanol is frequently used in humans for post operative analgesia and for chronic pain (IM every 3-4 hours for up to 34 weeks). The recommended dose is 1 – 4 mg IM (standard dose 2 mg; 0.5 – 2 mg IV; 4 – 8 mg oral).
The safety profile is good. Major side effects are sedation, nausea, elevated pulmonary vascular pressure, CNS excitation (rare). There is minimal cardiopulmonary depression compared with other opioids. In case of overdosage, expected problems would

arise from CNS depression with associated respiratory and cardiovascular depression. Naloxone will reverse such effects. Butorphanol has a low potential for abuse compared with other opioids.

User Safety

The applicant has provided an adequate user safety assessment.

The end user will usually be a veterinarian. The major risk of exposure will be via accidental self-injection or spraying onto skin or mucosae. Accidental needle stick injury leading to injection of 0.2 ml, or nasal exposure to a similar amount, will deliver 2 mg butorphanol. This is within the human recommended dose range. Mild sedation could therefore be expected. Effects of butorphanol can be reversed in healthy individuals with naloxone (dose 0.2 – 0.8 mg to reverse effects of up to 0.06 mg/kg butorphanol). Medical consultation and monitoring of cardiorespiratory parameters are warranted.
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.

III.BResidues Documentation

Residue Studies

No residue depletion studies were conducted because

- butorphanol is used in a small number of individual animals for an infrequent and non-regular treatment
- treated animals are unlikely to be sent for slaughter immediately after treatment
- oral bioavailability on humans is low
- after IV administration butorphanol is rapidly eliminated
- IV use in horses should not result in residues at pharmacologically or toxicologically relevant concentrations.
- Pharmacokinetic knowledge and calculations show that the acceptable daily intake (0.3 mg/kg/day) will not be exceeded.

MRLs

Butorphanol is listed in Annex II of Council Regulation 2377/90. No MRL is required for intravenous use in horses.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat is justified.

IV. CLINICAL ASSESSMENT

IV.APre-Clinical Studies
Pharmacology
See section IIIA
Tolerance in the Target Species of Animals
Theapplicant has presented a discussion of published and proprietary target animal tolerance studies using multiples of the recommended dose rate in the target species. Side effects are due to pharmacological effects of the active, with classic opioid effects. The product literature accurately reflects the type and incidence of adverse effects which might be expected.
IV.B Clinical Studies
Laboratory Trials

The applicant has provided bibliographical data relating to dose determination studies, which have been conducted in laboratory animals and the target species, examining the effect of butorphanol on visceral, articular and cutaneous pain.
Field Trials

The applicant has presented published and proprietary reports of field trials using butorphanol. Field trials have been conducted in target species with a range of single or repeated doses and a variety of routes of administration. Analgesia generally occurs within 15 minutes following administration in horse, dog and cat. After a single intravenous dose in the horse, analgesia usually lasts for 15 – 60 minutes. In the dog, it lasts for 15-30 minutes after a single intravenous administration. In cats with visceral pain, analgesic effect for 15 minutes up to 6 hours after butorphanol administration has been demonstrated. In cats with somatic pain, the duration of analgesia has been considerably shorter..
A selection of published reports is also provided supporting the safe use of butorphanol in combination with other classes of compounds (e.g. a2 agonists, benzodiazepines, acepromazine, NSAIDs) and other opioids. The data are sufficient to confirm the effects of butorphanol in combination with a2 agonists and the reports can also be applied to Dolorex.

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 risk benefit 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.

Safety/Efficacy Changes

Summary of change **(Application number)**	**Approval date**
Addition of target species - cats (IE/V/0194/001/II/002)	17th December 2008