Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Gerichtstraße 49
13347 Berlin
(Germany)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

Date: 16.04.2025

PRODUCT SUMMARY

EU procedure number	DE/V/0354/001 (formerly IE/V/0194/001/MR)
Name, strength and pharmaceutical form	Dolorex 10 mg/ml solution for injection
Applicant	Intervet Deutschland GmbH Feldstr. 1a 85716 Unterschleißheim Germany
Active substance(s)	Butorphanol 10 mg/ml as tartrate
ATC vetcode	QN 02AF01
Target species	Horse, dog, cat
Indication for use	Short duration analgesia and sedation

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Bibliographical application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	28th February 2007
Concerned Member States for original procedure	BE, DE, DK, EL, FI, FR, HU, LU, NL, NO, PT, SE, SK, UK(NI)

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) 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 veterinary medicinal product can be safely used in the target species; any potential adverse effects are detailed in the SPC.

The veterinary medicinal 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 veterinary medicinal product was demonstrated according to the claims made in the SPC.

The overall benefit/risk analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

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 VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

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

Process validation data on the VMP have been presented in accordance with the relevant European guidelines.

C. Production and 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 VMP.

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 tests

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.

3. SAFETY DOCUMENTATION (safety and residues tests)

A. Safety tests

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.

B. Residues 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.

Maximum Residue Limits

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.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

A. Pre-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.

B. Clinical trials

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.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

Sequence of significant variations

Safety/Efficacy Changes

Summary of change (Application number)	Approval date
Addition of target species - cats (IE/V/0194/001/II/002)	17th December 2008
Change of RMS due to withdrawal in IE	16th April 2025