IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Morphasol 4 mg/ml solution for injection for dogs and cats

PRODUCT SUMMARY

EU Procedure number	IE/V/0232/001/DC
Name, strength and pharmaceutical form	Morphasol 4 mg/ml solution for injection for dogs and cats
Active substance(s)	Butorphanol (as Butorphanol tartrate)
Applicant	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany
Legal basis of application	Bibliographical application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of procedure	30th September 2009
Target species	Dogs and cats
Indication for use	**Dogs:** As an analgesic: for the relief of mild to moderate visceral pain. As a sedative: in combination with medetomidine. **Cats:** As an analgesic: for the relief of mild to moderate visceral pain. Butorphanol is intended for use where short (dog) and short to medium (cat) analgesia is required.
ATCvet code	QN02AF01
Concerned Member States	AT, BE, DE, ES, FI, FR, HU, LU, NL, NO, PL, SE, UK, IS

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 reactions observed are indicated in the SPC.

The product is safe for the user 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 4 mg/ml butorphanol (as butorphanol tartrate) as the active substance and the excipients chlorocresol, citric acid monohydrate, sodium citrate, sodium chloride and water for injections.

The container/closure system is a 10 ml multidose clear Type I glass vial with a grey butyl rubber stopper, laminated with fluoropolyethylene, 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.

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

Pharmacological Studies

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.

The applicant has also provided bibliographical data which show that the volume of distribution is large suggesting wide distribution into tissues. The terminal half-life is short in cats and dogs. Butorphanol is metabolised extensively in the liver and is mainly excreted in urine.

Toxicological Studies

The applicant has provided bibliographical data and conducted studies describing the toxicological effects in a variety of species by several different routes of administration.

Single Dose Toxicity
The following clinical signs were observed in rats and mice following intravenous administration with an observed LD_{50} of 18.7 mg/kg and 31 mg/kg, respectively: ataxia, sedation, convulsions, dyspnoea and death. Oral administration in rats, even at high doses (up to 100 mg/kg) resulted in minimal adverse effects.

Repeated Dose Toxicity

Repeated daily oral doses to rats of up to 10 mg/kg for 2 weeks resulted in weight loss and transient mild sedation. Slight changes in the liver and associated blood biochemical parameters occurred at 10 mg/kg.

Reproductive Toxicity, including Teratogenicity:

Lower pregnancy rates were reported for rabbits treated orally with up to 60 mg/kg. The ‘no effect level’ for maternotoxicity was 30 mg/kg/day with neither embryotoxic nor teratogenic effects observed.

The applicant has not provided any bibliographical data for the target species. Warnings and precautions as listed on the product literature are adequate to ensure safety to the target species.

Mutagenicity and carcinogenicity:

There is no evidence of any mutagenic or carcinogenic potential.

Observations in Humans

The applicant has provided bibliographical data which show that in humans, the most frequent adverse effects of butorphanol are drowsiness, sweating, nausea, dizziness and vertigo. Prolonged use of butorphanol may lead to opioid dependence. It may precipitate withdrawal symptoms if given to patients who have recently used other opioid analgesics

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product will only be administered by or under the direction of a veterinary practitioner. The major risk of exposure will be via accidental self-injection or spraying onto skin or mucosae. Drowsiness, nausea and dizziness may occur following exposure. Effects of butorphanol can be reversed by the administration of an opioid antagonist.

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.

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

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

See Section III.A

Tolerance in the Target Species of Animals

The applicant has provided data on target animal tolerance study using the recommended dose in the target species. A placebo was used as a control. The dose was administered by intravenous route on a single occasion.

Adverse effects in dogs including mild sedation were seen following the recommended dose. In cats, adverse effects including sedation, mydriasis, behavioural effects were seen following the recommended dose.

Bibliographical data have also been provided which shows that respiratory and cardiovascular depression may occur in both species. Transient ataxia, anorexia and diarrhoea are also rarely reported in dogs.

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 and somatic pain as well as sedation when used in combination with medetomidine.

Field Trials

The applicant has conducted field studies and provided bibliographical data which show that the analgesic effect of butorphanol occurs within 15 minutes following intravenous administration in dogs and cats and lasts from 15 minutes up to 30 minutes in dogs. The duration of effect lasts for 15 minutes up to 6 hours in cats. Duration of effect in cats relates to visceral pain only. In cats with somatic pain the duration of effect is likely to be considerably shorter.

A selection of published reports is also provided supporting the safe use of butorphanol in combination with medetomidine (α_2 agonist) and other central nervous depressants. However, an appropriate reduction in dose is necessary when used concomitantly with such agents. The data are sufficient to confirm the sedative effects of butorphanol in combination with medetomidine. Butorphanol may remove the analgesic effect in animals that have already received pure opioid mu agonists (morphine/oxymorphine) because of its antagonist properties at the opiate mu receptor.

Based on the data presented, the following indications/dose rates have been justified:

Dogs:
As an analgesic: for the relief of mild to moderate visceral pain:
intravenous administration of 0.2-0.4 mg/kg bodyweight (BW) butorphanol (equivalent to 0.05-0.1 ml/kg BW Morphasol). For postoperative analgesia intravenous administration of 0.2-0.4 mg/kg BW butorphanol is recommended 20 minutes prior to end of soft tissue surgery.

Sedation in combination with medetomidine:
Intravenous administration of 0.1-0.2 mg/kg BW butorphanol (equivalent to 0.025-0.05 ml/kg BW Morphasol) with 10-30 µg/kg BW medetomidine, depending on degree of sedation required.

Cats:
As an analgesic: for the relief of mild to moderate visceral pain:
intravenous administration of 0.1-0.2 mg/kg BW butorphanol (equivalent to 0.025-0.05 ml/kg BW Morphasol)

Butorphanol is intended for use where short (dog) and short to medium (cat) analgesia is required. However, repeat treatments of butorphanol may be administered. The need for, and timing of repeat treatment should be based on clinical response. For cases where longer duration analgesia is likely to be required, an alternative therapeutic agent should be used.

In the absence of an adequate analgesic response, use of an alternative analgesic agent, such as another suitable opioid analgesic and/or a non-steroidal anti-inflammatory drug, should be considered.

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.