Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Torphadine 10 mg/ml Solution for Injection for Dogs, Cats and Horses

Date Created: 30 November 2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0588/001/DC
Name, strength and pharmaceutical form	Torphadine 10 mg/ml Solution for Injection for Dogs, Cats and Horses
Applicant	Le Vet Beheer B.V.
Active substance(s)	Butorphanol tartrate
ATC Vetcode	QN02AF01
Target species	Cats, Dogs and Horses
Indication for use	Horse: As an analgesic: - For the relief of moderate to severe abdominal pain associated with colic of gastrointestinal origin. For sedation: - For sedation, given after the administration of certain alpha2-adrenoceptor agonists (detomidine, romifidine). Dog: As an analgesic: - For relief of mild to moderate visceral pain. For sedation: - For sedation, when used in combination with certain alpha2-adrenoceptor agonists (medetomidine). As a premedicant prior to general –anaesthesia: - For use in combination with acepromazine to provide analgesia and sedation prior to induction of general anaesthesia. A dose-related reduction in the dose of induction-anaesthetic agent (propofol or thiopentone) is also provided. - For premedication, give as the sole pre-anaesthetic agent.

	For anaesthesia: - For anaesthesia, when used in combination with medetomidine and ketamine Cat: As an analgesic for the relief of moderate pain: - For pre-operative use to provide analgesia during surgery. - For post-operative analgesia after small surgical procedures. For sedation: - For sedation when used in combination with certain alpha2-adrenoceptor agonists (medetomidine). For anaesthesia: - For anaesthesia, when used in combination with medetomidine and ketamine, suitable for short painful anaesthetic procedures.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original <mutual recognition> <decentralised>procedure	30th September 2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, BG, HR, CY, CZ, DK, EE, FI, FR, EL, HU, IS, IE, IT, LV, LT, LU, NL, NO, PL, PT, RO, SK, SI, ES, SE.

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, submitted in accordance with Article 13 (1) of Directive EC 2001/82/EC as amended. The reference product is Torbugesic 10 mg/ml Solution for Injection authorised in the UK since May 1991. Exemption was claimed from the requirement for bioequivalence studies in accordance with 7.1.a) and 7.1.b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2).

This product is indicated for use in cats, dogs as an analgesic, sedative and anaesthetic. In dogs it may also be used for pre-medication prior to anaesthetic. In horses, this product is indicated as an analgesic and sedative. For cats and dogs, the product can be administered via intravenous, intramuscular and subcutaneous use. In horses the product is administered by intravenous injection only. For amounts to be administered please refer to Section 4.9 of the SPC[1].

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 [2] 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.

[1] SPC – Summary of product Characteristics.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 10.0 mg of butorphanol per 1 ml (equivalent to 14.58 mg of butorphanol tartrate) and excipients benzethonium chloride, citric acid (anhydrous), sodium citrate (dehydrate), sodium chloride and water for injections.

The container/closure system consists of a clear Type I glass vial of either 10 ml or 20 ml packsize, with a coated bromobutyl rubber stopper and aluminium cap in a cardboard box. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are justified.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple mixing process in which the active substance, preservative and excipients are added to the water for injections and mixed at high speed before being filtered and filled into pre-sterilised vials. The vials are then further sterilised by moist heat in accordance with the Ph. Eur. Monograph. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

II.C. Control of Starting Materials

The active substance is butorphanol (as butorphanol tartrate) an established active substance described in the United States National Formulary. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance is manufactured in accordance with an ASMF[3]. The specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients used in the manufacture of the product are supplied in accordance with Ph. Eur. Monographs and certificates of analysis have been provided for each excipient.

[2] Efficacy – The production of a desired or intended result.
[3] ASMF – Active Substance Master File.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include those for appearance, visible particles, volume, pH and impurities.

II.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. The stability data supports a 5 year re-test period.

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. The product does not require any special storage conditions.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening the immediate packaging: 28 days.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and a biowaver absolving the applicant from the need to provide bioequivalence tests with a reference product on the basis of essential similarity was accepted, the results of pharmacological and toxicological tests are not required. Warnings and precautions as listed on the product literature are in line with the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Documentation

User Safety

A user risk assessment was provided showing that the probability of exposure is considered low when used by veterinary staff. Minor amendments to the user warnings and risk mitigation measures were proposed compared to those of the reference product in order to improve readability, which were supported. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Butorphanol has opioid activity.
- The most frequent adverse effects of butorphanol in humans are drowsiness, sweating, nausea, dizziness and vertigo and these may occur following unintended self-injection.
- Care should be taken to avoid accidental injection/self-injection.
- If accidental self-injection occurs, seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive. An opioid antagonist (e.g. naloxone) may be used as an antidote.
- Wash any splashes from skin and eyes immediately.

Environmental Safety

A Phase I environmental risk assessment (ERA) in line with the relevant VICH guideline (CVMP/VICH/592/98-FINAL) was submitted. As the product will be used in a small number of individual animals the active substance or any degradation products to the environment will be limited. Therefore the risk assessment stopped at question 5 of the VICH decision tree. A Phase II assessment was not required.

III.B.2 Residues documentation

As essential similarity to the reference product has been accepted, no residues depletion studies have been provided, which is acceptable. The proposed methods of administration and dosage regime for use in horses are identical to the reference product and therefore, the same withdrawal period is proposed and considered acceptable.

Withdrawal Periods

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

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1) and bioequivalence with a reference product has been established on the basis of essential similarity ((7.1.a) and 7.1.b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2)), efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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 of the product is favourable.

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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