College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fentadon 50 microgram/ml, solution for injection for dogs

NL/V/0155/001

April 2014

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0155/001/DC
Name, strength and pharmaceutical form	Fentadon 50 microgram/ml, solution for injection for dogs
Applicant	Eurovet Animal Health B.V. Handelsweg 25, 5531 AE, Bladel The Netherlands
Active substance(s)	Fentanyl (as citrate).
ATC Vetcode	QN02AB03
Target species	Dog
Indication for use	For intra-operative analgesia during surgical procedures such as soft tissue- and orthopaedic surgery. For the control of post-operative pain associated with major orthopaedic and soft tissue surgery.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13a - Well established veterinary use - of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure.	20 January 2012
Concerned Member States for original procedure	AT, BE, DE, DK, ES, FR, IT, LU, NO, PL, PT, SE, UK.

I. SCIENTIFIC OVERVIEW

The application for Fentadon 50 µg/ml was submitted in accordance with Article 13a of Directive 2001/82/EC as amended. The active substance, fentanyl citrate has well established veterinary use.

Indications are for intra-operative analgesia during surgical procedures such as soft tissue- and orthopaedic surgery and for the control of post-operative pain associated with major orthopaedic and soft tissue surgery.

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

II. QUALITY ASPECTS

A. Composition

The product contains 78.5 µg/ml fentanyl citrate (equivalent to 50 µg/ml fentanyl) and the following excipients: methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium hydroxide, hydrochloric acid, sodium chloride and water for injections. Hydrochloric acid and sodium hydroxide are used for pH adjustment.

The solution for injection is packed in clear, colourless type I glass vials, fitted with Teflon coated halogenated type I rubber stoppers with aluminium caps. Vials are packed individually in boxes.

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 products represent an established pharmaceutical form and their 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 products are manufactured using conventional manufacturing techniques. Process validation data on the products have been presented in accordance with the relevant European guidelines.

The tests performed during production are described. Adequate in-process specifications are provided.

C. Control of Starting Materials

The active substance is Fentanyl citrate, 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.

Two suppliers are used, Certificates of Suitability have been provided for both.

The excipients are in conformity with compendial requirements. The glass vials and stoppers are in conformity with the regulations.

D. 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.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specifications control 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.

G. Stability

Stability data on the active substance were provided in accordance with applicable European guidelines, confirming the retest period of the active substance from each supplier 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.

The claim of a 28 day stability after broaching is based on the demonstration of stability for two batches broached and stored 28 days at +25 □C.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL).

III.A Safety Testing Pharmacological Studies

The applicant has provided bibliographical data which show that fentanyl citrate is a synthetic opioid that is selective for the μ-opioid receptor. Fentanyl citrate has the ability to produce profound analgesia. It causes only minor heart and circulatory depression.

The applicant has also provided bibliographical data which show that after intravenous injection the fentanyl plasma concentrations decrease rapidly primarily due to redistribution. In dogs 60% of fentanyl is bound to plasma proteins. Fentanyl has a large volume of distribution of more than 5 l/kg. The plasma kinetics of fentanyl are independent of the dose in the range of the recommended doses. Fentanyl has a relatively long elimination half-life: 45 min to more than 3 hours in dogs. The clearance is high about 40 to 80 ml/min/kg. It is primarily eliminated by metabolism, with hydroxylation and dealkylation being the primary mechanisms, and less than 8% of the total dose is eliminated as unchanged drug. In addition to hepatic metabolism fentanyl may be metabolized in extra hepatic sites and eliminated by extra renal routes.

Toxicological Studies

The applicant has provided bibliographical data which show that acute toxicity of fentanyl is high and fentanyl has a narrow therapeutic index. The applicant has performed studies in dogs which show that the product is well tolerated at dosages up to two times the maximum recommended dose rate.

- Single Dose Toxicity

In

mice, the LD_{50} following subcutaneous injection is in the range of 4.97 to 7.57 mg/kg. After intraperitoneal injection the LD_{50} has been reported to be 16 mg/kg.

 Repeated Dose Toxicity

In rats, intrathecal injection on alternate days over a thirty day period of 0.005% fentanyl was well tolerated. Rats recovered fully after thirty minutes. (NOEL not established).

- Mutagenicity

In one study (mouse lymphoma assay with S9 activation) a genotoxic potential of fentanyl.was found. However, mutagenicity tests performed on human lymphocytes (Ames Salmonella test, primary rat hepatocyte USD assay, BALB/c-3T3 transformation test and in vitro CHO chromosomal aberration assay) no evidence of mutagenicity of fentanyl was found.

Other Studies

The applicant has provided bibliographical data which show that fentanyl patches used in human medicine frequently result in irritation at the application site, mostly erythema. Although IgE antibodies to fentanyl exist, its allergenicity has not been shown.

Observations in Humans

The applicant has provided bibliographical data which show that fatalities in humans have occurred after intentional or accidental ingestion of fentanyl overdoses. Prolonged treatment of critically ill neonates with fentanyl results in narcotic withdrawal symptoms upon cessation of treatment.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product (an opioid) may cause adverse effects after internal exposure, including respiratory depression or apnoea, sedation, hypotension and coma. The product may cause hypersensitive reactions. Adverse effects on the fetus can not be excluded. The risk is however considered to be acceptable as the product will only be used by highly skilled professionals (veterinarians). It is expected that professionals will be aware of the dangers, will follow the advise in the product literature and they have access to appropriate personal protective equipment which will help avoid any unnecessary risks.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

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 Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using multiples of the recommended dose (lowest recommended dose 3 µg/kg; 2-fold overdose of highest recommended dose 20 µg/kg) in 4 male and 4 female dogs. All doses were administered by intravenous route once. The study was performed as a randomised, blinded, crossover study with a 3 week washout period. Parameters evaluated were respiratory rate, pulse rate and clinical signs. Sedation, reduced activity, bradycardia, hypothermia, tachypnoea and vocalisation were observed. These effects were all transient. In addition vomiting, scratching, tremors, irritability and overactivity were observed in some individuals, these effects were also transient.

Bibliographical data have also been provided which show that with doses up to 167.5 µg/kg administered over 20 minutes no respiratory arrest occurred and although respiratory rate, PaO_2, heart rate and cardiac output were almost halved, oxygen consumption remained above the basic metabolic rate.

In another study dogs were given extremely high doses of fentanyl (up to 1910 µg/kg) in an attempt to calculate the ED_{50} and establish duration of anaesthesia. Decreased heart rate, respiratory rate and PaO_2 as well as increased $PaCO_2$ were observed in all dogs. During the experiment dogs were not intubated and breathing room air spontaneously. All animals survived without sequelae.

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 which show therapeutic dose rates and routes of administration recommended for fentanyl in dogs. The use of fentanyl in multimodal anaesthesia techniques has been extensively described in the published literature. The dose of fentanyl must be adjusted depending on the combination used. The therapeutic effect of opioids is well described in the published literature. In clinical veterinary practice opioids are used for premedication and perioperative analgesia, to provide sedation, parenteral and regional analgesia for acute and chronic conditions, and to induce and/or maintain anaesthesia. They are used alone or in combination with other medicinal products. Fentanyl, as an opioid agonist, is indicated for severe pain, often associated with trauma and also to manage mild to moderate pain as for example in soft tissue surgery.

The safety and efficacy of fentanyl was assessed in Beagle dogs administered Fentadon by intravenous injection. One group of 4 male and 4 female dogs received either 3 µg/kg or 20 µg/kg administered in a randomised, blinded, crossover study. The effect was assessed by thermal and mechanical nociceptive tests. Fentanyl produced dose-dependant moderate to excellent analgesia at the

dose level of 3 and 20 µg/kg demonstrated by the threshold measurements, showing that fentanyl was a fast acting analgesic as the highest values were obtained within the first hour post dose.

Field Trials

The applicant has not conducted field studies, however clinical studies were performed and bibliographical data were provided which allowed evaluation of safety and efficacy.

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.

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 Heads of Vetrinary Medicines Agencies website (www.HMA.eu).

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.

None.