ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Vetergesic Multidose, 0.3 mg/ml, Solution for Injection for Dogs and Cats

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0337/001/MR
Name, strength and pharmaceutical form	Vetergesic Multidose, 0.3 mg/ml, Solution for Injection for Dogs and Cats
Applicant	Sogeval UK Limited
Active substance(s)	Buprenorphine As Buprenorphine hydrochloride
ATC Vetcode	QN02AE01
Target species	Dogs and Cats
Indication for use	Post-operative analgesia in the dog and cat. Potentiation of the sedative effects of centrally-acting agents in the dog.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	MRP application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	07 July 2009
Date product first authorised in the Reference Member State	11 April 2008
Concerned Member States for original procedure	Austria Belgium Czech Republic Denmark Finland France Germany Hungary Iceland Ireland Luxembourg Netherlands Norway Poland Slovakia Spain Sweden

I. SCIENTIFIC OVERVIEW

Vetergesic Multidose, 0.3mg/ml, solution for injection for dogs and cats contains the active substance buprenorphine as buprenorphine hydrochloride. The product is authorised to be used in dogs and cats. The product is indicated for use in post-operative analgesia in the dog and cat and the potentiation of the sedative effects of centrally-acting agents in the dog. In dogs, the dose rate is 10-20 micrograms per kg (0.3-0.6 ml per 10 kg) for post operative analgesia. For further pain relief, repeat if necessary after 3-4 hours with 10 microgram per kg or 5-6 hours with 20 microgram per kg. For potentiation of sedation, the dose rate is 10-20 micrograms per kg (0.3-0.6 ml per 10 kg). In cats, the dose rate is 10-20 microgram per kg (0.3-0.6 ml per 10 kg) for post-operative analgesia, repeated if necessary, once, after 1-2 hours. The route of administration is intramuscular or intravenous injection.

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 and the slight reactions observed are indicated 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.

II. QUALITY ASPECTS

A. Composition

The product contains buprenorphine (as buprenorphine hydrochloride) as active substance and chlorocresol, glucose anhydrous, hydrochloric acid and water for injection as excipients.

The product is packaged in 10 ml amber type I glass vials with chlorobutyl rubber stopper.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

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.

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

C. Control of Starting Materials

The active substance buprenorphine as buprenorphine hydrochloride is the subject of monographs in the European Pharmacopoeia and in the United States Pharmacopeia. The supporting data have been provided in the form of Active Substance Master File. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

There are four excipients used in the formulation and each has been used previously in veterinary medicines. All excipients have monographs in the Ph. Eur. and each complies with the requirements of the current edition of the Ph. Eur.

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 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. The satisfactory validation data for the analytical methods have been provided.

G. Stability

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. The shelf life of 2 years is justified when stored below 25ºC.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years

In-use shelf life
Shelf life after opening the immediate packaging: 28 days

Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

Shake well before use.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Buprenorphine, the active ingredient of the product, is an opioid analgesic used extensively in human medicines and the safety information submitted by the company therefore includes a review of published literature on the pharmacology and toxicology of buprenorphine hydrochloride. Refer to the SPC for contraindications and special precautions for use in animals.

Pharmacological Studies

The applicant provided literature references to support the pharmacokinetics of buprenorphine. The published literature indicates that buprenorphine is rapidly absorbed following intramuscular injection with a maximum plasma concentration in 10-15 minutes post administration in rat, rabbit and primates. In humans, absorption is very rapid with average peak plasma concentrations 2-5 minutes after intramuscular injection. Bioavailability is very low due to first pass metabolism. Metabolism is by N-dealylation and conjugation of N-dealkyl buprenorphine and the parent substance. Approximately 70% of the administered dose, oral or intravenous routes, is eliminated in faeces and the remainder in the urine.

Toxicological Studies

Single Dose toxicity
References were provided to studies conducted in rats, mouse, dog and baboon when the product was administered by oral, intravenous, intraperitoneal, intramuscular and subcutaneous route. These studies indicated very low toxicity of buprenorphine.

Repeated Dose toxicity
References were provided to studies conducted subcutaneously, intramuscularly and intravenously in rats, dogs and baboons. Multiples of the recommended dose of buprenorphine were administered over varying time periods. The studies in which the test substance was administered by sub-cutaneous or oral administration, reported no abnormalities. However, after intravenous administration, histological changes were observed in adrenals, spleen and testes of dogs and in lungs of baboons.

Other Studies

Reproductive toxicity
The applicant submitted studies in groups of rats whereby the test substance or control was administered sub-cutaneously. No effects on male or female fertility were observed but there was a high neonatal mortality.

Embryotoxicity/fetotoxicity, including teratogenicity
A number of reports were provided and there were no adverse effects on fertility or general reproductive function in rats, although at the highest dose administered intramuscularly, the mothers experienced some difficulty in parturition and there was a high neonatal mortality. There was no effect on male fertility. It was concluded from teratogenicity studies that buprenorphine was not embryotoxic, was not a teratogen and did not have any marked effects on weaning potential. The data submitted were considered satisfactory.

Mutagenicity
The applicant submitted mutagenicity data that were compliant with VICH guidance and clearly indicated that buprenorphine hydrochloride is not mutagenic. The data submitted were considered satisfactory.

Carcinogenicity
The applicant submitted information from which it can be concluded that there is no evidence to suggest any carcinogenic potential for buprenorphine in rat or mouse studies. The data submitted were considered satisfactory.

Observations in humans

Buprenorphine is widely used in human medicine for the treatment of moderate to severe pain and for the treatment of opioid dependency. It is available under two human authorisations. The applicant submitted abbreviated copies of the SPCs for these products which give information on undesirable effects and special warnings for use. These data were considered adequate.

User Safety

The applicant provided a satisfactory user risk assessment, identifying the risk to the users of the product and the potential routes of exposure. This showed that the most likely routes of exposure to the product would be via skin or eye contact, or by accidental self-injection. In addition to the pharmacological effects which could occur in people in the event of accidental self-injection, it is known that chlorocresol is an irritant. The risks have been identified and appropriate warnings are included in the SPC and product literature. These are:

Wash hands/affected area thoroughly after any accidental spillage.

As buprenorphine has opioid-like activity, care should be taken to avoid self-injection. In case of accidental self-injection or ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Following eye contamination or skin contact, wash thoroughly with cold running water. Seek medical advice if irritation persists.

Ecotoxicity

The environmental risk assessment was carried out in accordance with VICH Phase I guidelines and using the CVMP guidance in support of VICH guidelines.
The environmental risk assessment demonstrated that use of Vetergesic multidose injection would not result in extensive environmental exposure.
Warnings and precautions as listed on the SPC and 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

Pharmacodynamics

The applicant provided literature references characterising the pharmacodynamic effects of buprenorphine in both laboratory animals and the target species. Buprenorphine is an opiate and *in vitro* studies have shown that its analgesic properties are mediated through its action as a partial agonist at the μ-receptor. The clinical analgesic effect can, however, only be demonstrated in clinical trials. Buprenorphine can cause respiratory depression, but data from laboratory animal studies indicate that the ceiling for this effect occurs at a much lower dose than the ceiling for its analgesic effect.

Pharmacokinetics

In vitro pharmacokinetic (PK) studies demonstrated that buprenorphine generally shows slow association kinetics and even slower dissociation kinetics and this may explain its slow onset of action but prolonged duration of effect. The product is intended for administration by the intravenous and intramuscular routes in both cats and dogs. The studies conducted in the cat suggested that bioavailability following intramuscular administration was close to 100%.

The PK studies in the cat and many of the clinical studies have been conducted using other buprenorphine containing product. Vetergesic Multidose formulation is identical to the other buprenorphine containg product with the exception that it contains the preservative chlorocresol. Chlorocresol is an established preservative used in human and veterinary medicines. Vetergesic Multidose formulation is unlikely to affect physical properties or biopharmaceutical factors which may influence the bioavailability of buprenorphine. In accordance with exemption 4(f) of the CVMP bioequivalence guideline it was not necessary to conduct an *in vivo* BE study, and equivalent pharmacological effect between the two formulations had been demonstrated.

Tolerance in the Target Species of Animals

The applicant presented several literature references which investigated the safety of experimental formulations of buprenorphine in the dog, and an acute toxicity study using this product. The applicant also conducted an acute toxicity study using this formulation in cats. Buprenorphine has a very good acute and chronic toxicity profile, although slowing of the heart rate may be noted in dogs at high doses. The data presented were considered adequate to determine the margin for safety and toxicity profile for buprenorphine in relation to the proposed clinical use of the product.

Local tolerance has been demonstrated for the Vetergesic Multidose formulation administered to both cats and dogs by the intramuscular route at up to four times the recommended dose at a single site. No injection site reactions were reported. Chlorocresol is an established preservative used in both human and veterinary medicinal products formulated for parenteral, oral or topical administration. The concentration included in Vetergesic Multidose is well within the established range. As the references in the safety section of the dossier are supportive of intravenous and intramuscular administration, no further safety studies are required.

The clinical documentation submitted by the applicant indicates that safety for both cats and dogs is very good when used in practice. In cats there were no clinically significant suspected adverse reactions which could be directly attributed to buprenorphine. In dogs there was one report of bradycardia and some evidence for respiratory depression, although the latter did not appear to be clinically significant. The safety studies suggested that at severe overdose buprenorphine may cause liver damage and therefore the product should be used with caution in dogs with liver disease. It is considered that appropriate SPC warnings adequately mitigate against the risks associated with use of the product.

IV.B Clinical Studies

Several literature references have been presented which demonstrate that buprenorphine administered to dogs at doses between 0.01 – 0.02 mg/kg, intramuscularly, provided effective analgesia after soft tissues and orthopaedic surgical procedures which would be expected to produce moderate-severe pain.

Literature references and an extensive field study conducted by the applicant also support the analgesic efficacy of buprenorphine administered at a dose of 0.01 – 0.02 mg/kg, intramuscularly, to cats undergoing mild to severely painful surgical procedures. There was some variability in response between individuals and in one study it was demonstrated that repeat doses may need to be given after 1 - 2 hours. These aspects are adequately addressed in the SPC. The onset of analgesia could be delayed where buprenorphine was administered post-operatively.

When administered at the proposed dose on its own, buprenorphine does not appear to produce much sedative effect. However, literature references demonstrated that buprenorphine, when used in combination at a dose of 0.01

mg/kg, potentiates the sedative effects of medetomidine and acepromazine in the dog.

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.

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.
(www.gov.uk/check-animal-medicine-licensed)

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.
(www.gov.uk/check-animal-medicine-licensed)