Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

Date Created: November 2010

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Vetergesic Multidose, 0.3 mg/ml Solution for Injection for Dogs, Cats and Horses
Applicant	Ceva Animal Health Ltd Unit 3 Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB UK
Active substance	Buprenorphine Hydrochloride
ATC Vetcode	QN02AE01
Target species	Dogs, Cats and Horses
Indication for use	Post-operative analgesia in the dog, cat and horse. Potentiation of the sedative effects of centrally-acting agents in the dog and horse. When used in horses, an intravenous sedative should be administered within five minutes prior to injection of buprenorphine.

MODULE 2

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

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Informed consent application in accordance with Article 13c of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	13th February 2009

I. SCIENTIFIC OVERVIEW

This application was for an extension to an existing authorisation, Vetergesic Multidose, 0.3 mg/ml Solution for Injection for Dogs and Cats, to add the minor species horses in accordance with Article 12(3) of Directive 2001/82/EC as amended. It can therefore be considered a MUMS[1] application.

Vetergesic Multidose, 0.3 mg/ml, Solution for Injection for Dogs, Cats and Horses contains the active substance buprenorphine as buprenorphine hydrochloride. The product is indicated for use in post-operative analgesia in dogs, cats and horses, and the potentiation of the sedative effects of centrally-acting agents in dogs and horses. In dogs, the dose rate is 10-20 µg/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 µg/kg or 5-6 hours with 20 µg/kg. For potentiation of sedation, the dose rate is 10-20 µg/kg (0.3-0.6 ml per 10 kg). In cats, the dose rate is 10-20 µg/kg (0.3-0.6 ml per 10 kg) for post-operative analgesia, repeated once if necessary, after 1-2 hours. The route of administration for dogs and cats is via intramuscular or intravenous injection. In horses, the dose rate for post-operative analgesia is 10 µg/kg (3.3 ml per 100kg), given intravenously five minutes after administration of an intravenous sedative. The dose may be repeated if required after 1-2 hours. For the potentiation of sedation, the dose is 5 µg/kg (1.7 ml per 100kg), given 5 minutes after administration of an intravenous sedative. The dose may be repeated if necessary after 10 minutes.

Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC.

[1] MUMS - minor use minor species.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

Product Development and Composition

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

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

Active Substance

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 were provided for the original dossier[2] in the form of an Active Substance Master File. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

Other Substances

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. The excipients are chlorocresol, glucose anhydrous, hydrochloric acid and water for injections.

Packaging Materials

The product is packaged in 10 ml amber type I glass vials with a chlorobutyl rubber stopper. The particulars of the containers and controls performed are provided and conform to the regulation.

Finished Product Quality Control

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.

[2] Vetergesic Multidose 0.3 mg/ml Solution for Injection for Dogs and Cats.

Stability of the Product

Finished Product

Stability data on the original product were provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life. The shelf life of 3 years is justified.

In-Use

Shelf life after opening the immediate packaging: 28 days. Keep the vial in the outer carton in order to protect from light. Shake well before use.

II. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

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 included a review of published literature on the pharmacology and toxicology of buprenorphine hydrochloride. Safety data were originally supplied for Vetergesic Multidose, 0.3 mg/ml Solution for Injection for Dogs and Cats, and this data is included in this section. No further information for this extension application was required.

Pharmacology

The applicant provided literature references for the original dossier to support the pharmacokinetics of buprenorphine. The published literature indicated 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-dealkylation 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.

Toxicology

Single Dose toxicity

References were provided for the original dossier with regard to studies conducted in rats, mice, dogs and baboons when the product was administered by the oral, intravenous, intraperitoneal, intramuscular and subcutaneous routes. These studies indicated the very low toxicity of buprenorphine.

- Repeated Dose toxicity

References were provided in the original dossier 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 subcutaneous or oral administration, reported no abnormalities. However, after intravenous administration, histological changes were observed in the adrenals, spleen and testes of dogs and in lungs of baboons.

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Reproductive toxicity

The applicant submitted studies in the original dossier on groups of rats, whereby the test substance or control were administered subcutaneously. No effects on male or female fertility were observed but there was a high neonatal mortality. The SPC carries appropriate warnings.

Embryotoxicity/fetotoxicity, including teratogenicity

A number of reports were provided for the original dossier, and there were no adverse effects on fertility or general reproductive function in rats, although at the highest dose administered intramuscularly, females 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, and the SPC carries appropriate warnings.

Mutagenicity

The applicant submitted mutagenicity data for the original dossier 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 for the original dossier from which it could 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 for the original dossier, which gave information on undesirable effects and special warnings for use. These data were considered acceptable.

Residues

The product is not to be used in horses intended for human consumption. Treated horses must never be slaughtered for human consumption. Horses must be declared as not intended for human consumption under National Horse Passport regulations. No data were provided for dogs or cats in the original dossier, as these are not food-producing animals.

Environmental Safety

The safety of the product for the environment was previously established for Vetergesic Multidose, 0.3 mg/ml Solution for Injection for Dogs and Cats, and these are applicable to the extended product. 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 DOCUMENTATION

Data were previously provided for the original dossier. Further data with regard to clinical aspects were provided with regard to the use of the extended product in horses.

Clinical Pharmacology

Pharmacodynamics

The applicant provided literature references for the original dossier, characterising the pharmacodynamic effects of buprenorphine in both laboratory animals and in 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. Literature references were submitted in relation to the extended product, referring to the use of buprenorphine in horses for the extended product. Opioids are commonly used in conjunction with additional sedatives in horses, in order to avoid the occurrence of excitation rather than sedation in this species during anaesthesia.

Pharmacokinetics

In vitro pharmacokinetic (PK) studies in the original dossier demonstrated that buprenorphine generally shows slow association kinetics and even slower dissociation kinetics. 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. In horses, the extended product is indicated only for intravenous use.

For the analysis of pharmacokinetics in the extended product, a suitable number of horses received 10 μg/kg buprenorphine intravenously in a non-blinded study. Blood samples were taken at various time-points and plasma levels of buprenorphine and nor-buprenorphine were measured by liquid chromatography tandem mass spectrometry. A long-lasting antinociceptive effect without significant side effects was seen, and blood plasma concentrations of buprenorphine were within acceptable levels. No adverse reactions were noted.

Tolerance in the Target Species

The applicant presented several literature references for the original dossier 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. As the references in the safety section of the dossier were supportive of intravenous and intramuscular administration, no further safety studies were required.

The clinical documentation previously submitted by the applicant indicated 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.

For the extended product which may be used in horses, a further study was conducted in order to ensure that the product is well tolerated in clinical practice in this species. The product was therefore administered 5-10 minutes after a premedicant (detomidine at 20µg/kg). A suitable number of horses were divided into groups and subjected to one of the following treatment regimes: three treatments with 5% glucose, (as negative controls), three treatments with 10 µg/kg Vetergesic Multidose, 0.3 mg/ml Solution for Injection for Dogs, Cats and Horses, three treatments of the product at 30 µg/kg and three treatments of the product at 50 µg/kg. Clinical and haematological assessments were made at suitable time-points. The study demonstrated that the product was well tolerated.

Clinical Efficacy

Several literature references were presented for the original dossier which demonstrated 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 supported 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 is administered post-operatively.

When administered alone at the proposed dose, buprenorphine does not appear to produce a significant 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.
For the extended product, three dose titration studies were conducted in horses in order to determine the dose of buprenorphine required for sedation. An additional study was provided to demonstrate antinociceptive effects of the

active substance. Two clinical field trials were also conducted in order to exhibit the efficacy of buprenorphine as a post-operative analgesic, and to demonstrate the efficacy of the product following the use of an intravenous sedative.

The first titration study conducted to GCP[3] consisted of a blind, randomised cross-over study, using three different doses of buprenorphine hydrochloride, (5, 7.5 and 10 µg/kg), in combination with a fixed dose of detomidine hydrochloride, at 10 µg/kg. Each animal received each treatment with a wash-out period of ten days. This assay was performed in order to evaluate the optimal dose for efficacy field trials, and to assess the combined effect of detomidine at 10 µg/kg and butorphanol at 25 µg/kg, (a commonly used sedative combination), and detomidine alone. A suitable number of animals were given one of the following treatments: saline (negative control), 10 µg/kg detomidine plus saline, 10 µg/kg detomidine plus 5 µg/kg buprenorphine, 10 µg/kg detomidine plus 7.5 µg/kg buprenorphine, 10 µg/kg detomidine plus 10 µg/kg buprenorphine, or 10 µg/kg detomidine plus 25 µg/kg butorphanol. Horses were assessed for degree and duration of sedation, physiological parameters were monitored and ataxia was clinically quantified. Assessments were made at various time-points, and the animals were observed for any adverse reactions post-treatment. No statistical difference was noted between the five groups receiving active treatment, however length of sedation differed moderately between groups. The SPC reflects the findings with regard to duration and depth of sedation when the product is used in combination with an appropriate sedative.

A similar study was performed in which the amounts of detomidine were increased in conjuction with two dose rates of buprenorphine. Saline was used as a negative control in this blind, randomised cross-over study. Results demonstrated that buprenorphine may be utilised at a dose of 10 µg/kg, where detomidine is given at 20 µg/kg. A final titration study investigated the difference between use of detomidine or romfidine in conjunction with buprenorphine. A satisfactory degree of sedation was achieved using both romfidine and buprenorphine, with no adverse effects being observed.

A study was performed demonstrating the antinociceptive effects of buprenorphine in horses. This was a blind, randomised cross-over study evaluating sensitivity to pain following three doses of buprenorphine, (5, 7.5 and 10 µg/kg), when used in conjunction with acepromazine. Acepromazine and butorphanol (100 µg/kg) were used as a positive control, and 5% glucose used as a negative control. The wash-out period was ten days. Three baseline sets of data were obtained prior to a suitable number of animals being subjected to one of each of the following treatments: 0.05 mg/kg acepromazine and 5% glucose, 0.05 mg/kg acepromazine and 5 µg/kg buprenorphine, 0.05 mg/kg acepromazine and 7.5 µg/kg buprenorphine, 0.05 mg/kg acepromazine and 10 µg/kg buprenorphine or 0.05 mg/kg acepromazine and 100 µg/kg butorphanol. Assessment of appropriate sedation was performed at different time-points, with physiological measurements also being performed. Duration of antinociception to thermal and mechanical stimuli following treatment was compared using

[3] GCP – Good Clinical Practice.

repeated ANOVA[4] measurements. End point was determined by leg lifting for the mechanical stimulus and head-turning or skin-twitching for the thermal device. Administration of acepromazine and buprenorphine produced antinociception for a significantly longer time than acepromazine and butorphanol.

A field study was conducted in horses in order to assess the use of Vetergesic Multidose 0.3 mg/ml Solution for Dogs, Cats and Horses as a post-operative analgesic. The product was administered pre-operatively to provide post-operative analgesia after castration. A suitable number of young horses were divided into two treatment groups. All animals received 0.03 mg/kg acepromazine. One group then received 0.02 mg/kg detomidine followed by 10 µg/kg buprenorphine, a second group received 5% glucose instead of buprenorphine. Following routine general anaesthesia and recovery, the animals were evaluated. Results demonstrated that post-operative pain control was improved in the buprenorphine-treated group, and that the product was safe and effective with regard to providing post-operative analgesia when given as a premedicant.

A second field study was conducted as a partially blind, randomised clinical trial, in order to evaluate the effect of buprenorphine at 5 µg/kg in combination with detomidine at 10 µg/kg for the standing sedation of horses. A large number of animals were subjected to one of two treatments: an initial injection of 10 µg/kg detomidine followed by 5 µg/kg buprenorphine, or 10 µg/kg detomidine and an equivalent volume of glucose solution. Depth of sedation and degree of ataxia were assessed at various time-points, and physiological measurements taken. Buprenorphine at a dose rate of 5 and 10 µg/kg enhanced sedation produced by two dose rates of detomidine. No adverse reactions were noted.

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.

[4] ANOVA – Analysis of Variance.

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)