ÚSKVBL
Ústav pro státní kontrolu veterinárních biopreparátů a léčiv

Institute for State Control of Veterinary Biologicals and Medicines
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

NALGOSED 10 MG/ML SOLUTION FOR INJECTION

Date: 28/04/2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0142/001/MR
Name, strength and pharmaceutical form	Nalgosed 10 mg/ml solution for injection
Applicant	Bioveta, a. s. Komenského 212/12 683 23 Ivanovice na Hané Czech Republic Tel: 00420 517 318 500 E-mail: registrace@bioveta.cz
Active substance(s)	Butorphanol 10 mg (as butorphanol tartrate 14.58 mg)
ATC Vetcode	QN02AF01
Target species	Horses, dogs, cats
Indication for use	The product is indicated for the management of analgesia and sedation in horses; for the management of analgesia, sedation and preanaesthesia in dogs and cats.

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).

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

NALGOSED 10 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of the solution for injection contains:

Active substances:
Butorphanol 10 mg
(as butorphanol tartrate 14.58 mg)

Excipients:
Benzethonium chloride 0.1 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Target species

Horses, dogs, cats.

4.2. Indications for use, specifying the target species

The product is indicated for the management of analgesia and sedation in horses; for the management of analgesia, sedation and preanaesthesia in dogs and cats.

HORSE:

As an analgesic: For relief of moderate to severe abdominal pain of gastrointestinal origin including a colic. The product alleviates pain related to a colic or labour.

As a sedative: For sedation after administration of certain alpha2-adrenoceptor agonists (detomidine hydrochloride, romifidine). Sedation in therapeutic and diagnostic procedures in standing animals.

DOG:

As an analgesic: For relief of moderate to severe pain associated with postoperative procedures, especially after orthopaedic surgery or soft tissue surgery.

As a sedative: In combination with medetomidine hydrochloride.

As a preanaesthetic: Preanaesthetic administration of the product reduces the dose of general anaesthetic, especially sodium thiopental. The product is administered as a part of the anaesthesia protocol in combination with medetomidine hydrochloride and ketamine.

CAT:

As an analgesic: For relief of moderate to severe pain associated with surgery procedures, especially with castration, orthopaedic surgery or soft tissue surgery.

As a sedative: In combination with medetomidine hydrochloride.

As a preanaesthetic: Preanaesthetic administration of the product reduces the dose of general anaesthetic, especially sodium thiopental. The product is administered as a part of the anaesthesia protocol in combination with medetomidine hydrochloride and ketamine.

4.3. Contraindications

Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

Do not use in animals with severe dysfunction of the kidneys.

Use of butorphanol is contraindicated in case of cerebral injury or organic brain lesions and in animals with obstructive respiratory diseases, heart dysfunction or spastic conditions.

HORSE
As a sole agent and in any combination:
Do not use in horses with a history of liver disease.

Butorphanol/detomidine hydrochloride combination:
Do not use in horses suffering from colic.
Do not use in horses with a pre-existing cardiac dysrhythmia or bradycardia.

DOG & CAT
Do not use in dogs and cats with a history of liver disease.

4.4. Special warnings (for each target species)

Butorphanol is intended for use where short duration analgesia (horse, dog) or short to medium duration analgesia (cat) is required.
In cats, individual response to butorphanol may be variable. In the absence of an adequate analgesic response, an alternative analgesic agent should be used.
In cats increasing of the dose will not increase intensity or duration of desired effects.

4.5. Special precautions for use

Special precautions for use in animals

Before using the product in combination with any other medicines, the contraindications and warnings stated in SPCs of the respective medicines should be taken into account.

Butorphanol is a morphine derivative and thus it exhibits opiate activity. Safety of the product in puppies, kittens and foals has not been established. The use of the product in these groups should be based on the benefit-risk assessment by the responsible veterinarian.

Due to its antitussive properties, butorphanol may lead to an accumulation of mucous in the respiratory tract. Therefore, in animals with respiratory diseases associated with increased mucous production, butorphanol should only be used after a risk-benefit evaluation by the responsible veterinarian.

Routine cardiac auscultation should be performed prior to use in combination with α2-adrenoceptor agonists. The combination of butorphanol and α2-adrenoceptor agonists should be used with caution in animals with cardiovascular disease. The concurrent use of anticholinergic drugs, e.g. atropine should be considered.

HORSE:

The use of the product at the recommended dose may lead to transient ataxia and/or excitement. Therefore, to prevent injuries, in the patient and people when treating horses, the location for the treatment should be chosen carefully.

DOG:

Intravenous application should be slow, not a rapid bolus.
In dogs with MDR1 mutation reduce dose by 25-50%.

CAT:

Observe the exact dosage. The dose should be administered based on the precisely determined body weight of the animal. A syringe with an appropriate scale (e.g. an insulin syringe) should be used for accurate dosing.

Naloxone can be used as an antidote in case of respiratory depression.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Care should be taken to avoid accidental self-injection. A guarded needle should preferably be used until the moment of injection. In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician.

DO NOT DRIVE as sedation, dizziness and disorientation may occur. An opioid antagonist may be used as an antidote.

Avoid accidental contact with skin and eyes. In case of accidental spillage on the skin or contact with eyes, rinse immediately with plenty of water.

4.6. Adverse reactions (frequency and seriousness)

ALL TARGET SPECIES:
In very rare cases, pain on intramuscular injection may be observed.

HORSE
The most commonly side effect is mild ataxia which may persist for 3 to 10 minutes.
Mild to severe ataxia may be encountered in combination with detomidine, but clinical studies have shown that horses are unlikely to collapse. Normal precautions should be observed to prevent self-injury.
In very rare cases, butorphanol may also have adverse effects on gastrointestinal tract motility in horses, although there is no decrease in gastrointestinal transit time. These effects are dose-related and generally minor and transient.
Very rarely, butorphanol may cause excitatory locomotor effects (pacing).
When used in combination with α2-adrenoceptor agonists, cardiopulmonary system depression may occur very rarely. In these cases, fatality may occur rarely.

DOG
Transient ataxia, anorexia, and diarrhoea have been reported as occurring rarely.
In very rare cases, respiratory and cardiac depression (as evidenced by a decrease in respiratory rate, development of bradycardia and a decrease in diastolic pressure) may occur. The degree of depression is dose dependent.
In very rare cases, reduction in gastrointestinal motility may occur.

CAT
In very rare cases, respiratory depression may occur.
Very rarely, butorphanol may cause excitation, anxiety, disorientation, dysphoria and mydriasis.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7. Use during pregnancy, lactation or lay

The safety of this veterinary medicinal product has not been established in the target species during pregnancy and lactation. The use of butorphanol during pregnancy and lactation is not recommended.

4.8. Interaction with other medicinal products and other forms of interaction

When butorphanol is used in combination with certain α2-adrenoceptor agonists (romifidine or detomidine in horses, medetomidine in dogs and cats) synergistic effects occur requiring a butorphanol dose reduction (see section 4.9).
Butorphanol is antitussive and should not be used in combination with an expectorant as it may lead to an accumulation of mucous in the airways.
Butorphanol has antagonist properties at the opiate mu (μ) receptor which may remove the analgesic effect of pure opioid mu (μ) agonists (e.g. morphine/oxymorphine) in animals that have already received these agents.
The concomitant use of other central nervous depressants would be expected to potentiate the effects of butorphanol and such drugs should be used with caution. A reduced butorphanol dose should be used when administering these agents concurrently.

4.9. Amounts to be administered and administration route

HORSE: Only for intravenous (IV) administration

DOG, CAT: Intravenous (IV), subcutaneous (SC) or intramuscular (IM) administration

Avoid bolus application where IV administration is used. Avoid too rapid IV administration. Different injection sites should be used for repeated SC or IM administration.

HORSE

<u>As an analgesic:</u>

Butorphanol alone:

Administer a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, i.e. 1 ml/100 kg bw, by IV injection.

The dose may be repeated as necessary. The analgesic effect is seen within 15 minutes post injection.

<u>As a sedative:</u>

Butorphanol in combination with detomidine hydrochloride:

Administer detomidine hydrochloride at a dose of 0.012 mg/kg bw by IV injection. Five minutes later administer butorphanol at a dose of 0.025 mg/kg bw, equivalent to 0.0025 ml of the product/kg bw, i.e. 0.25 ml/100 kg bw, by IV injection.

Butorphanol in combination with romifidine:

Administer romifidine at a dose of 0.04-0.12 mg/kg bw by IV injection. Five minutes later administer butorphanol at a dose of 0.02 mg/kg bw, equivalent to 0.002 ml of the product/kg bw, i.e. 0.2 ml/100 kg bw, by IV injection.

DOG

As an analgesic:

Butorphanol alone:

Administer a dose of 0.2-0.3 mg/kg bw, equivalent to 0.02-0.03 ml of the product/kg bw, i.e. 0.2-0.3 ml/10 kg bw, by IV, IM or SC injection.

Administer the product 15 minutes before the end of anaesthesia to provide an analgesic effect in the recovery phase. The analgesic effect can be observed in 15 minutes. For continuous analgesia, the product dose can be repeated as needed.

As a sedative:

Butorphanol in combination with medetomidine:

Administer butorphanol at a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, by IV or IM injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.01–0.025 mg/kg bw, by IV or IM injection. Both agents should be administered separately, not in a single syringe (see section 6.2 Incompatibilities).

Before initiating the therapeutic procedure, wait for 20 minutes after the administration for sufficient sedation.

To reverse the anaesthetic effects, atipamezole should be administered at a dose of 0.05-0.125 mg/kg bw. Sternal recumbency is attained approximately 5 minutes later followed by standing a further 2 minutes later.

As a preanaesthetic:

Butorphanol alone:

Administer a dose of 0.1-0.2 mg/kg bw, equivalent to 0.01-0.02 ml of the product/kg bw, by IV, IM or SC injection.

Administer 15 minutes before inducing anaesthesia.

As a sedative and preanaesthetic – premedication of barbiturate anaesthesia:

Butorphanol in combination with medetomidine:

Administer butorphanol at a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, by IV or IM injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.01 mg/kg bw by IV or IM injection. Both agents should be administered separately, not in a single syringe (see section 6.2 Incompatibilities).

As a part of the anaesthesia protocol:

Butorphanol in combination with medetomidine and ketamine:

Administer butorphanol at a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, by IM injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.025 mg/kg bw by IM injection. Both agents should be administered separately, not in a single syringe (see section 6.2 Incompatibilities). 15 minutes later administer ketamine at a dose of 5 mg/kg bw by IM injection.

Sedation and the onset of anaesthesia develop approximately in 6 minutes from the first administration. Loss of pedal reflex occurs in approximately 14 minutes. Anaesthesia subsides approximately in 53 minutes from ketamine administration – the pedal reflex returns. Sternal recumbency is attained approximately 35 minutes later followed by standing a further 36 minutes later.

It is not advisable to reverse the butorphanol/medetomidine/ketamine combination with atipamezole.

CAT

As a preoperative analgesic:

Butorphanol alone:

Administer a dose of 0.4 mg/kg bw, equivalent to 0.04 ml of the product/kg bw, i.e. 0.2 ml/5 kg bw, by IM or SC injection.

When intravenous induction of anaesthesia is used, administer butorphanol 15-30 minutes before administering the anaesthetic.

When intramuscular induction of anaesthesia is used (acepromazine/ketamine or xylazine/ketamine), administer butorphanol 5 minutes before administering the anaesthetic. The use of butorphanol has no distinct effect on the time of awakening.

As a postoperative analgesic:

i) **Intramuscular, subcutaneous administration:** Administer a dose of 0.4 mg/kg bw, equivalent to 0.04 ml of the product/kg bw, i.e. 0.2 ml/5 kg bw, by SC or IM injection.
ii) **Intravenous administration:** Administer a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, i.e. 0.05 ml/5 kg bw, by IV injection.

Administer 15 minutes before awakening from anaesthesia.

As a sedative:

Butorphanol in combination with medetomidine:

Administer butorphanol at a dose of 0.4 mg/kg bw, equivalent to 0.04 ml of the product/kg bw, by IM or SC injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.05 mg/kg bw, by SC or IM injection. Both agents should be administered separately, not in a single syringe (see section 6.2 Incompatibilities).

Local anaesthesia should be used for surgical suturing of wounds.

To reverse the anaesthetic effects, atipamezole should be administered at a dose of 0.125 mg/kg bw. Sternal recumbency is attained approximately 4 minutes later followed by standing a further 1 minute later.

As a part of the anaesthesia protocol:

Butorphanol in combination with medetomidine and ketamine:

i) **Intravenous administration:**
Administer butorphanol at a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, by IV injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.04 mg/kg bw by IV injection and ketamine at a dose of 1.25-2.5 mg/kg bw by IV injection; ketamine should be dosed based on the required depth of anaesthesia. The agents should be administered separately, not in a single syringe (see section 6.2 Incompatibilities).

The patient lies down in 2-3 minutes after administration. Loss of pedal reflex occurs 3 minutes after administration. To reverse the anaesthetic effects, atipamezole should be administered at a dose of 0.2 mg/kg bw. Pedal reflex returns in approximately 2 minutes, sternal recumbency is attained approximately 6 minutes later followed by standing a further 18 minutes later.

ii) **Intramuscular administration:**
Administer butorphanol at a dose of 0.4 mg/kg bw, equivalent to 0.04 ml of the product/kg bw, by IM injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.08 mg/kg bw by IM injection and ketamine at a dose of 5 mg/kg bw by IM injection. The agents should be administered separately, not in a single syringe (see section 6.2 Incompatibilities).

The onset of effect and its subsiding depend on the administered dose of ketamine. The patient lies down in 1 minute including the loss of pedal reflex. Anaesthesia lasts up to 60 minutes without any additional medication (sternal recumbency) and the patient stands up in 70–83 minutes. To reverse the anaesthetic effects, atipamezole

should be administered at a dose of 0.1 mg/kg bw. Pedal reflex returns in approximately 4 minutes, sternal recumbency is attained approximately 7 minutes later followed by standing a further 18 minutes later.

The stopper can be punctured up to 50 times.

4.10. Overdose (symptoms, emergency procedures, antidotes), if necessary

Respiratory depression is the most important consequence of overdose. Opioid receptor antagonists (e.g. naloxone) are suitable antidotes.

Atipamazole is a suitable antidote in case of overdose of butorphanol in combination with medetomidine hydrochloride or ketamine, with the exception of intramuscular administration of the butorphanol/medetomidine/ketamine combination in dogs.

4.11. Withdrawal period(s)

Horse:
Meat and offal: Zero days.
Milk: Zero days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: analgesics, morphinan derivatives.
ATCvet code: QN02AF01.

5.1 Pharmacodynamic properties

The product contains butorphanol, an opioid centrally acting analgesic. Butorphanol belongs to the group of agonists and antagonists. Its analgesic effect is 4-7 times higher than that of morphine and its narcotic antagonist activity corresponds to 1/40 of the naloxone effect. Its analgesic activity is dose-dependent, in horses it lasts 15-90 minutes.

In combination with medetomidine, detomidine or romifidine, butorphanol helps to induce a deep sedation. It is suitable for pre-operative analgesia prior to induction of anaesthesia with various formulations. At high doses, respiratory depression, followed by cardiovascular depression, can be observed.

5.2 Pharmacokinetic particulars

In the horse, butorphanol has a high clearance (on average 1.3 L/h.kg) after intravenous administration. It has a short terminal half-life (mean <1 hour), indicating that 97% of a dose will be eliminated after intravenous administration in, on average, less than 5 hours.
In the dog, butorphanol administered by the intramuscular route has a high clearance (around 3.5 L/h.kg). It has a short terminal half-life (mean <2 hours), indicating that 97% of a dose will be eliminated after intramuscular administration in,

on average, less than 10 hours. Repeated dose pharmacokinetics and the pharmacokinetics following intravenous administration have not been studied.
In the cat, butorphanol administered by the subcutaneous route has a low clearance (<1320 mL/kg.h). It has a relative long terminal half-life (around 6 hours) indicating that 97% of the dose will be eliminated in approximately 30 hours. Repeated dose pharmacokinetics have not been studied.

Butorphanol is metabolised extensively in the liver and excreted in the urine. The volume of distribution is large, suggesting wide distribution into tissue.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium citrate dihydrate
Sodium chloride
Citric acid monohydrate
Benzethonium chloride
Water for injection

6.2. Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3. Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.
Protect from light.

6.5. Nature and composition of immediate packaging

10 ml vial from clear glass of type I, with a pierceable rubber stopper and aluminium cap, wrapped in carton.

Pack size: 1 x 10 ml.

6.6. Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such product

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bioveta, a. s.
Komenského 212/12
683 23 Ivanovice na Hané
Czech Republic
tel: 00420 517 318 500
e-mail: registrace@bioveta.cz

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application According to Article 13(1) of Directive 2001/82/EC
Date of completion of the original <mutual recognition> <decentralised>procedure	28/02/2018
Date product first authorised in the Reference Member State (MRP only)	14/07/2016
Concerned Member States for original procedure	RMS: CZ CMS: BG, EE, EL, HU, LT, LV, PL, RO, SK

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range:

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, <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.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

For applications based on informed consent to another authorisation:

The quality / safety / efficacy aspects of this product is/are identical to <original product>. <The initial application for <original product> was assessed before there was a requirement to have a public assessment report; therefore no details in this section are available>.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains active substance butorphanol (as tartrate) 10 mg/mL and the excipients benzethonium chloride, sodium citrate dehydrate, citric acid monogydrate, sodium chloride and water for injection.

The product is packed in glass vials (type I) an closed with injection stopper and aluminium caps. One 10mL glass vial is put into paper box.

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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is butorphanol, 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.

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 substancehave 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 2 years.

The claim of a 28 days stability after broaching the vial is based on the demonstration of stability for a batch broached and stored 28 days.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and chemical equivalence with a reference product has been demonstrated, results toxicological and other studies are not required.
Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users / the environment / consumers.

III.A Safety Testing

Pharmacological Studies

The applicant has conducted studies / has provided bibliographical data which show that <active> acts by <insert brief description of mode of action – from SPC.> <Describe any specific peculiarities e.g. isomers>

The applicant has also <conducted studies><has provided bibliographical data> which show that <brief description of main pharmacokinetic features from SPC>– in each target species.>

If bioequivalence studies were conducted, name reference product and summary of results

Toxicological Studies

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and chemical equivalence with a reference product has been demonstrated, results toxicological and other studies are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because the product belongs to the group of injectable anaesthetics and sedatives and therefore the Phase I stops at question no. 5. – the product is used to treat a small number of animals in herd. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues documentation

Residue Studies

The applicant has submitted the generic application in accordance with Article 13(1) of Directive 2001/82/EC, as amended.

MRLs

Butorphanole tartrate is an allowed substance as described in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRL**	**Target tissues**	**Other provisions**
Butorphanole tartrate	Not applicable	*Equidae*	No MRL required	Not applicable	For intravenous administration only.

Withdrawal Periods

Based on information above, the following withdrawal periods were approved:

Horse:
Meat and offal: Zero days.
Milk: Zero days.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species of Animals

The tolerance of the product in the target animal species (in dogs and cats) is evaluated.
The applicant has conducted a controlled target animal tolerance study using the recommended dose in the target species, dogs and cats. A placebo was used as a control. All doses were administered by IM. Adverse effect consisting of pain was seen following the recommended dose in cats.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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>

or

Complete this section for extensions to the same VPA range or defined, significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- *Changes to pharmacokinetic data leading to a change in the SPC*
- *Changes to toxicological data leading to a change in the SPC*
- *Changes to user safety warnings*
- *Changes to ecotoxicological information as given in the SPC or changes to disposal warnings*
- *New residue studies in new target species or tissues*
- *Reassessment of residue data or new studies resulting from changes to MRL*
- *Changes to withdrawal period*
- *Changes to target species*
- *Changes to target species tolerance data leading to change in warnings/precautions for target species*
- *New or changed indications*

Significant changes in administrative or quality data include any Type II change, which affects the initial report. The following Type IA or IB changes may also apply:

- *Name of product [Type IA: 2]*
- *Name of active substance [Type IA: 3}*
- *MAH [Type IA: 1]*
- *Composition of the medicinal product [Type IB: 18, Type IA/B: 25, 34, 35, 39]*
- *Container/closure system [Type 1/B: 26, 28, 29, 36, 41, 43]*
- *Method of preparation [Type 1B: 33]*
- *Active substance specification [Type IB: 25]*
- *CEP [Type IA/B: 15]*
- *Re-test period or storage conditions of active substance [Type IB: 17]*
- *Excipient specifications [Type 1A/B: 25]*
- *Packaging materials[Type 1A/B: 28, 29, 36, 41, 43]*
- *TSE [Type 1A: 16, 22]*
- *Shelf-life or storage conditions of the finished product [Type 1B: 42]*

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	