SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Torphadine 10 mg/ml solution for injection for dogs, cats and horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Butorphanol 10.0 mg
Equivalent to 14.58 mg of butorphanol tartrate

Excipient:
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

Dogs, cats and horses.

4.2 Indications for use, specifying the target species

Dog:
As an analgesic:
- For relief of mild to moderate visceral pain.

As an sedative:
- 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.

As an anaesthetic:
- 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.

As a sedative:

- For sedation when used in combination with certain alpha2-adrenoceptor agonists (medetomidine).

As an anaesthetic:

- For anaesthesia, when used in combination with medetomidine and ketamine, suitable for short painful anaesthetic procedures.
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Horse:

As an analgesic:

- For the relief of moderate to severe abdominal pain associated with colic of gastrointestinal origin.

As a sedative:

- For sedation, given after the administration of certain alpha2-adrenoceptor agonists (detomidine, romifidine).

4.3 Contraindications

All target species:
Do not use in cases of hypersensitivity to the active substance or any of the excipients.
Do not use in animals with severe dysfunction of the liver or kidneys.
Do not use in animals with cerebral injury or organic brain lesions.
Do not use in animals with obstructive respiratory disease, heart dysfunction or spastic conditions.

Horse:
Butorphanol/detomidine hydrochloride combination:
Do not use in horses with a pre-existing cardiac dysrhythmia or bradycardia.
Do not use in cases of colic associated with impaction as the combination will cause a reduction in gastrointestinal motility.
Do not use in horses with emphysema due to a possible depressive effect on the respiratory system.
Do not use in pregnant mares.

Butorphanol/romifidine combination:
Do not use during the last month of pregnancy.

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 (see section 5.1). In cases where longer duration analgesia is likely to be required, an alternative therapeutic agent should be used.
Marked sedation does not occur when butorphanol is used as a sole agent in cats.
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

All target species:
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 according to a benefit-risk assessment by the responsible veterinary surgeon.
Prior to use of the product in combination with α2-adrenoreceptor agonists routine cardiac auscultation should be performed and the concurrent use of anticholinergic drugs, e.g. atropine should be considered.
The combination of butorphanol and an α2-adrenoceptor agonists should be used with caution in animals with mild to moderate dysfunction of the liver or kidney.
Take care when administering butorphanol to animals concurrently treated with other central nervous depressants (see section 4.8).
The safety of the product in puppies, kitten and foals has not been established and therefore in these animals the product should only be used according to a benefit-risk assessment by the responsible veterinary surgeon.

Dog:
When administering as an intravenous injection, do not inject rapidly as a bolus.
In dogs with MDR1 mutation reduce dose by 25-50%

Cat:
Use of either insulin syringes or 1 ml graduated syringes is recommended.

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.

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

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.

4.6 Adverse reactions (frequency and seriousness)

All target species:
There may be some pain on intramuscular injection.
Sedation may be noted in treated animals.

Dog:
Respiratory and cardiac depression (as evidenced by a decrease in respiratory rate, development of bradycardia and a decrease in diastolic pressure) may occur (see section 4.5). The degree of depression is dose-dependent. If respiratory depression occurs, naloxone may be used as an antidote. Moderate to marked cardiopulmonary depression may occur if butorphanol is given rapidly by intravenous injection.
When using butorphanol as a pre-anaesthetic, the use of an anticholinergic such as atropine, will protect the heart against possible narcotic-induced bradycardia.
Transient ataxia, anorexia and diarrhoea have been reported as occurring rarely.
Reduction in gastrointestinal motility may occur.

Cat:
Respiratory depression may occur. If respiratory depression occurs, naloxone may be used as an antidote.
Mydriasis is likely to occur.
Butorphanol administration may cause excitation, anxiety, disorientation and dysphoria.

Horse:
The most common side effect is mild ataxia which may persist for 3 to 10 minutes.
An increase in motor activity and ataxia produced by butorphanol lasted 1 – 2 hours in some cases.
Restlessness, and shivering and sedation followed by restlessness have both been observed in some horses.
A bolus i.v. injection at the maximum label dose (0.1 mg/kg body weight) may result in excitatory locomotor effects (e.g. pacing) in clinically normal horses.
Mild to severe ataxia may be encountered in combination with detomidine, but horses are unlikely to collapse. Normal precautions should be observed to prevent injury(see section 4.5).
Mild sedation may occur in approximately 15% of horses following administration of butorphanol as a sole agent.
Butorphanol may also have adverse effects on gastrointestinal tract motility in normal horses, although there is no decrease in gastrointestinal transit time. These effects are dose-related, and generally minor and transient.
Depression of the cardiopulmonary system may occur. When used in combination with alpha2-adrenoceptor agonists, cardiopulmonary system depression may be fatal in rare cases.

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 and lactation

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. See also section 4.3.

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 4.5 and 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

Dog and cat: Intravenous, intramuscular and subcutaneous use.
Horse: Intravenous use.

Animals should be weighed to establish an accurate body weight prior to calculation of the appropriate treatment dose.

Dog:

For analgesia:

Route	Dose butorphanol	**Dose product**
IV,IM or SC	0.20-0.30 mg/kg bw	**0.02-0.03 ml/kg bw**
Comment	IV injection should be slow. Analgesic effects are seen within 15 minutes of injection. Administer 15 minutes before terminating anesthesia to provide analgesia in the recovery phase. For continuous analgesia repeat dose as required.	

For sedation in combination with medetomidine hydrochloride:

Route	Dose butorphanol	**Dose product**	Dose medetomidine hydrochloride
IM or IV	0.1 mg/kg bw	**0.01 ml/kg bw**	0.01*-0.025**mg/kg bw
Comment	Allow 20 minutes for profound sedation to develop before commencing the procedure. Where compatibility is accepted, products containing medetomidine and butorphanol may be combined and administered in the same syringe (see section 6.2).		

*Depending on degree of sedation required**:** 0.01 mg/kg: For sedation and as a premedicant to barbiturate anaesthesia

**Depending on degree of sedation required 0.025 mg/kg: For profound sedation and as a premedicant to ketamine anaesthesia

For use as a premedicant/pre-anaesthetic:
- When the product is used as the sole agent:

Route	Dose butorphanol	**Dose product**
IV, IM or SC	0.1-0.20 mg/kg bw	**0.01-0.02 ml/kg bw**
Comment	15 minutes prior to induction	

- When the product is used together with 0.02 mg/kg acepromazine:

Route	Dose butorphanol	**Dose product**
IV or IM	0.10 mg/kg bw*	**0.01 ml/kg bw***
Comment	Allow at least 20 minutes before the onset of action but the time between pre-medication and induction is flexible from 20-120 minutes. Where compatibility is accepted, products containing butorphanol and acepromazine may be combined and administered in the same syringe (see section 6.2).	

* The dose may be increased to 0.2 mg/kg (equivalent to 0.02 ml/kg) if the animal is already experiencing pain before the procedure commences or if a higher plane of analgesia is required during surgery.

For anaesthesia in combination with medetomidine and ketamine:

Route	Dose butorphanol	**Dose product**	Dose medetomidine	Dose ketamine
IM	0.10 mg/kg bw	**0.01 ml/kg bw**	0.025mg/kg bw	5.0mg/kg bw*
Comment	**Reversal with atipamezole is not recommended** Where compatibility is accepted, products containing medetomidine and butorphanol may be combined and administered in the same syringe (see section 6.2).			

* Ketamine should be administered 15 minutes after the IM administration of the butorphanol/medetomidine combination.

Cat:
For pre-operative analgesia:

Route	Dose butorphanol	**Dose product**
IM or SC	0.4 mg/kg bw	**0.04 ml/kg bw**
Comment	Administer 15-30 minutes prior to the administration of IV induction anaesthetic agents Administer 5 minutes before induction with IM induction anaesthetic agents such as combinations of IM acepromazine/ ketamine or xylazine/ketamine	

For post-operative analgesia:

Route	Dose butorphanol	**Dose product**
SC or IM	0.4 mg/kg bw	**0.04 ml /kg bw**
IV	0.1 mg/kg bw	**0.01 ml /kg bw**
Comment	Administer 15 minutes before recovery	

For sedation in combination with medetomidine hydrochloride:

Route	Dose butorphanol	**Dose product**	Dose medetomidine hydrochloride
IM or SC	0.4 mg/kg bw	**0.04 ml/kg bw**	0.05 mg/kg bw
Comment	Local anaesthetic infiltration should be used for wound suturing. Where compatibility is accepted, products containing medetomidine and butorphanol may be combined and administered in the same syringe (see section 6.2).		

For anaesthesia in combination with medetomidine and ketamine:

Route	Dose butorphanol	**Dose product**	Dose medetomidine	Dose ketamine

IM	0.40 mg/kg bw	**0.04 ml/kg bw**	0.08 mg/kg bw	5.0 mg/kg bw*
IV	0.10 mg/kg bw	**0.01 ml/kg bw**	0.04 mg/kg bw	1.25-2.50 mg/kg bw (depending on depth of anaesthesia required)
Comment	Where compatibility is accepted, products containing medetomidine, butorphanol and ketamine may be combined and administered in the same syringe (see section 6.2).			

Horse:
For analgesia:

Route	Dose butorphanol	**Dose product**
IV	0.10 mg/kg bw	**1 ml/100 kg bw**
Comment	Analgesic effects are seen within 15 minutes of injection. Dose may be repeated as required.	

For sedation in combination with detomidine hydrochloride:

Route	Dose of detomidine hydrochloride	Dose butorphanol*	**Dose product**
IV	0.012 mg/kg bw	0.025 mg/kg bw	**0.25 ml/100 kg bw**
Comment	Detomidine should be administered up to 5 minutes before the butorphanol dose.		

*Clinical experience has shown that a total dose rate of 5 mg detomidine hydrochloride and
10 mg butorphanol affords effective, safe sedation in horses above 200 kg body weight.

For sedation in combination with romifidine:

Route	Dose of romifidine	Dose butorphanol	**Dose product**
IV	0.04-0.12 mg/kg bw	0.02 mg/kg bw	**0.2 ml/100 kg bw**
Comment	Romifidine should be administered up to 5 minutes before the butorphanol dose.		

Before this product is combined and administered in the same syringe as another veterinary medicinal product always refer to the section on 'Major incompatibilities' (section 6.2).
The maximum number of vial punctures when using needle sizes 21G and 23G should not exceed 100 and when using a 18G needle, the maximum should not exceed 40.

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

The main sign of overdose is respiratory depression, which can be reversed with naloxone.

To reverse the sedative effect of butorphanol/alpha-2 adrenoceptor agonist combinations, atipamezole may be used. To reverse adverse cardiopulmonary effects of these combinations, higher atipamezole doses may be required. Atipamezole should not be used in dogs treated with a combination of butorphanol, medetomidine, and ketamine used intramuscularly to produce anaesthesia.
Other possible signs of overdose in the horse include restlessness/excitability, muscle tremor, ataxia, hypersalivation, decrease of gastrointestinal motility and seizure. In the cat, the main signs of overdose are incoordination, salivation, and mild convulsions.

4.11 Withdrawal period

Meat and offal: zero days
Not authorised for use in mares producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Analgesics, Opioids, Morphinan derivatives
ATCvet code: QN02AF01

5.1 Pharmacodynamic properties

Butorphanol is a centrally acting opioid analgesic with agonist-antagonist activity at opiate receptors in the central nervous system. Activation of opioid receptors is coupled to changes in ion conductance and G protein interactions which lead to inhibition of pain transmission. Butorphanol has agonist activity at the kappa (κ) opioid receptor subtype and antagonist activity at the mu (μ) opioid receptor subtype. The agonist component of butorphanol activity is ten times more potent than the antagonist component.
Butorphanol as a sole agent provides dose-dependent analgesia and can also cause sedation (horses and dogs). Butorphanol in combination with certain alpha-2 adrenoceptor agonists results in profound sedation and in combination with certain alpha-2 adrenoceptor agonists and ketamine results in anaesthesia.
Onset and duration of analgesia:
Analgesia generally occurs within 15 minutes following intravenous administration.
After a single intravenous dose in the horse, analgesia usually lasts for 15-60 minutes.

5.2 Pharmacokinetic particulars

The volume of distribution after intravenous injection is large suggesting wide distribution into tissues. The volume of distribution is 7.4 L/kg in cats and 4.4 L/kg in dogs. Butorphanol is metabolised extensively in the liver and mainly excreted in urine.

In the dog, after intramuscular administration butorphanol has a high clearance (around 3.5 L/kg/hour) and a short terminal half-life (mean < 2 hours). This indicates that, on average, 97% of an intramuscular dose is eliminated in less than 10 hours.

In the cat, after subcutaneous administration, butorphanol has a relatively long terminal half-life (around 6 hours). This indicates that, on average, 97% of a subcutaneous dose is eliminated in approximately 30 hours.

In the horse, after intravenous administration, butorphanol has a high clearance (on average 1.3 L/kg/hour) and a short terminal half-life (mean < 1 hour).This indicates that, on average, 97% of an intravenous dose is eliminated in less than 5 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzethonium chloride
Citric acid
Sodium citrate
Sodium chloride
Water for injections

6.2 Major incompatibilities

Butorphanol must not be mixed with other veterinary medicinal products in the same syringe with the exception of the following combinations:

- butorphanol/medetomidine
- butorphanol/medetomidine/ketamine
- butorphanol/acepromazine

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 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.

6.5 Nature and composition of immediate packaging

Clear type I glass vials closed with a coated bromobutyl rubber stopper and aluminium cap in a carton box.

Pack sizes: 10 ml and 20 ml.

Not all pack sizes may be marketed.

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

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

Le Vet Beheer B.V.
Wilgenweg 7
3421 TV Oudewater
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 41821/4037

9. DATE OF FIRST AUTHORISATION

30 September 2016

10. DATE OF REVISION OF THE TEXT

October 2021

Approved: 08/10/21