1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Butorgesic 10 mg/ml solution for injection (FR, HU)
Butorgesic 10 mg/ml solution for injection for horses, dogs and cats (AT, IT)
Butorgesic vet 10 mg/ml solution for injection (DK, FI, NO, SE)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains:

Active substance:

butorphanol	10.00 mg
(as butorphanol tartrate)	14.58 mg

Excipients:

benzethonium chloride	0.10 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

Horse, dog and cat.

4.2 Indications for use, specifying the target species

HORSE

As an analgesic
Relief of abdominal pain caused by colic of gastrointestinal origin.

As a sedative (in combination)
For sedation in combination with certain α2-adrenoceptor agonists (detomidine, romifidine). For therapeutic and diagnostic measures such as minor surgical procedures on the standing horse.

DOG

As an analgesic
Relief of mild to moderate visceral pain and mild to moderate pain after soft tissue surgery.

As a sedative in (in combination)
For deep sedation in combination with medetomidine.

As a pre-anaesthetic

Pre-anaesthetic use of the product has resulted in a dose related reduction in the dose of induction anaesthetic agents.

As an anaesthetic (in combination)
As part of anaesthesia in combination with medetomidine and ketamine.

CAT

As an analgesic
To alleviate moderate postoperative pain after soft tissue surgery and minor surgical procedures.

As a sedative (in combination)
For deep sedation in combination with medetomidine.

As an anaesthetic (in combination)
As part of anaesthesia in combination with medetomidine and ketamine.

4.3 Contraindications

All target species
Do not use in cases hypersensitivity to the active substance or to any of the excipients.
Do not use in cases of severe dysfunctions of liver or/and kidney.
Do not use in cases of cerebral injury or organic brain lesions as well in animals with obstructive respiratory disease, heart dysfunctions 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.

See also section 4.7

4.4 Special warnings for each target species

Butorphanol is intended for use in situations where short-lasting analgesia (horse, dog) or a short to medium persistence of analgesia (cat) is required.

The response to butorphanol may vary individually in cats. In case of lack of proper analgesic effect another analgesic should be used.
Marked sedation does not occur when butorphanol is used as a sole agent in cats.
A dose increase causes no gain or result in extension of the desired effect in cats.

4.5 Special precautions for use

Special precautions for use in animals
The safety of the product in puppies, kitten and foals has not been established. Therefore, in these animals the product should only be used according to a benefit-risk assessment by the responsible veterinarian.

Due to its antitussive properties, butorphanol may lead to an accumulation of mucous in the respiratory tract (see section 4.8). Therefore, in animals with respiratory diseases associated with increased

mucous production, butorphanol should only be used after benefit-risk assessment by the responsible veterinary surgeon.

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.
The combination of butorphanol and an α2-adrenoceptor agonist should be used with caution in animals with mild to moderate dysfunction of the liver or the kidney.
Take care when administering butorphanol to animals concomitantly treated with central nervous depressants (see section 4.8).

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

CAT
Cats should be weighed to ensure that the correct dose is calculated. Use of either insulin syringes or 1 ml graduated syringes is recommended. If repeated administrations are required, use different injection sites.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Butorphanol has opioid-like activity. Precautions should be taken to avoid accidental injection or self-injection with this potent drug. If accidental self-injection occurs, seek immediate medical attention showing a copy of the package leaflet or the label to the physician.

The most frequent adverse effects of butorphanol in humans are drowsiness, sweating, nausea, dizziness and vertigo and these may occur following unintended self-injection.

Do not drive, since sedation, dizziness and confusion may occur. Effects can be reversed by the administration of an opioid antagonist (e.g. naloxone).

Accidental spillage on the skin and eyes should be washed immediately with 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 the veterinary medicinal product has not been established during pregnancy and lactation in the target species.

The use of butorphanol is not recommended during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

When butorphanol is used in combination with particular sedatives such as adrenergic α2-agonists (romifidine or detomidine in horses, medetomidine in dogs and cats) synergistic effects occur which require a reduction in butorphanol dose (see section 4.9).

Butorphanol has antitussive properties and should not be used in combination with an expectorant, as this can lead to accumulation of mucus in the respiratory tract.

Butorphanol has antagonistic properties towards mi opiate receptors (μ) and can remove the analgesic effect of pure μ-opioid agonists (eg morphine / oxymorphine) in animals that have already received these agents.

The concomitant use of other central nervous system sedatives is expected to potentiate the effects of butorphanol, so these drugs should be used with caution. A reduced dose of butorphanol should be given when these agents are administered simultaneously.

See also section 4.5.

4.9 Amounts to be administered and administration route

Horse: intravenously (IV).
Dog and Cat: intravenous (IV), subcutaneous (SC) and intramuscular (IM).
When administering as an intravenous injection, do no inject as a bolus.
If repeat SC or IM administrations are required, use different injection sites.
The rubber stopper should not be pierced more than 20 times.

HORSE

As an analgesic
Monotherapy:
0.1 mg of butorphanol /kg (1 ml of product /100 kg) IV. The dose may be repeated as required. Analgesic effects are seen within 15 minutes of injection.

As a sedative
With detomidine:
Detomidine hydrochloride: 0.012 mg/kg IV, followed within 5 minutes by
Butorphanol: 0.25 ml/100 kg IV

With romifidine:
Romifidine: 0.04 - 0.12 mg/kg IV, followed within 5 minutes by
Butorphanol: 0.2 ml/100 kg IV.

DOG

As an analgesic
Monotherapy:
0.2-0.3 mg butorphanol /kg (0.02-0.03 ml of product /kg) IV, IM or SC injection.
Administer 15 minutes before terminating anaesthesia to provide analgesia in the recovery phase.
Repeat dose as required.

As a sedative
With medetomidine:
Butorphanol: 0.01 ml/kg IV or IM
Medetomidine: 0.01-0.025 mg/kg IV or IM.
Allow 20 minutes for sedation to develop before commencing the procedure.

As a pre-anaesthetic
Monotherapy for canine analgesia:
0.1-0.2 mg butorphanol /kg (0.01-0.02 ml of product /kg) IV, IM or SC given 15 minutes prior to induction.

As an anaesthetic
In combination with medetomidine and ketamine:
Butorphanol: 0.01 ml/kg IM
Medetomidine: 0.025 mg/kg IM, followed after 15 minutes by
Ketamine: 5 mg/kg IM.
It is not advisable to reverse this combination in the dog with atipamezole.

CAT

As an analgesic
Pre-operative:
0.4 mg butorphanol /kg (0.04 ml of product/ kg) IM or SC
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. See also section 5.1. for duration of analgesia.

Post-operative:
Administer 15 minutes before terminating anaesthesia to provide analgesia in the recovery phase:

either 0.4 mg butorphanol /kg (0.04 ml of product /kg) SC or IM
or: 0.1 mg butorphanol /kg (0.01 ml of product /kg) IV.

As a sedative
With medetomidine:
Butorphanol: 0.04 ml/kg IM or SC.
Medetomidine: 0.05 mg/kg SC.
Additional local anaesthesia should be used for wound suturing.

As an anaesthetic
In combination with medetomidine and ketamine:

IM administration:
Butorphanol: 0.04 ml/kg IM
Medetomidine: 0.08 mg/kg IM.
Ketamine: 5 mg/kg IM.

IV administration:
Butorphanol: 0.01 ml/kg IV.
Medetomidine: 0.04 mg/kg IV.
Ketamine: 1.25-2.50 mg/kg IV (depending on depth of anaesthesia required).

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 effect of combinations with detomidine/medetomidine, atipamezole may be used, except when a combination of butorphanol, medetomidine, and ketamine has been used intramuscularly to produce anaesthesia in the dog. In this case, atipamezole should not be used.

Other possible signs of overdose in horses include restlessness / excitability, muscle tremor, ataxia, hypersalivation, decreased gastrointestinal motility and convulsions. In cats, the main signs of overdose are disrupted coordination, salivation and mild convulsions.

4.11 Withdrawal period(s)

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

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

Butorphanol tartrate is a centrally acting analgesic. Its action is agonist-antagonist at the opiate receptors in the central nervous system; agonist at the kappa (*k*) opioid receptor subtype and antagonist at the mu (μ) receptor subtype. The kappa (*k*) receptors control analgesia, sedation without depression of cardiopulmonary system and body temperature, whereas the mu (μ) receptors control supraspinal analgesia, sedation and depression of cardiopulmonary system and body temperature. The agonist component of butorphanol activity is ten times more potent than the antagonist component.

Onset and duration of analgesia:

Analgesia generally occurs within 15 minutes following administration in horse, dog and cat. After a single intravenous dose in the horse, analgesia usually lasts for 15 –60 minutes. In the dog, it lasts for 15 - 30 minutes after a single intravenous administration. In cats with visceral pain, analgesic effect for 15 minutes up to 6 hours after butorphanol administration has been demonstrated. In cats with somatic pain, the duration of analgesia has been considerably shorter.

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 (< 1.32 L/h.kg). It has a relatively 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 metabolized 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

Benzethonium chloride
Citric acid, anhydrous (for pH-adjustment)
Sodium citrate, dihydrate
Sodium chloride
Water for injections

6.2 Major incompatibilities

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

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

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

6.5 Nature and composition of immediate packaging

Colourless glass vial (Type I) with bromobutyl rubber stopper, covered with an aluminum cap.

Pack sizes:
Cardboard box containing 1 vial of 10 or 20 ml.
Cardboard box containing 5 vials of 10 or 20 ml.
Cardboard box containing 10 vials of 10 or 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

CP-Pharma Handelsgesellschaft mbH
Ostlandring 13
31303 Burgdorf
Germany

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE