1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
Butorphanol 10 mg
(as Butorphanol tartrate 14.7 mg/ml)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzethonium chloride	0.1 mg
Citric acid monohydrate	
Sodium citrate	
Sodium chloride	
Water for injections	

A clear and colourless solution.

3. CLINICAL INFORMATION

3.1 Target species

Horses, dogs, cats.

3.2 Indications for use for each target species

Horses:
As an analgesic
For short term relief of pain associated with colic of gastrointestinal tract origin.
As a sedative
For sedation in combination with certain α2-adrenoceptor agonists.

Dogs:
As an analgesic
For relief of mild to moderate visceral pain and pain associated with post-surgical procedures.
As a sedative
For sedation in combination with medetomidine hydrochloride.
As a pre-anaesthetic
Pre-anaesthetic use of the product has resulted in a dose related reduction in the dose of induction anaesthetic agents, such as thiopentone sodium or propofol.
As an anaesthetic
For anaesthesia in combination with medetomidine and ketamine.

Cats:
As an analgesic
For relief of mild to moderate visceral pain. For pre-operative use to provide analgesia during surgery. For post-operative analgesia after a variety of surgical procedures.
As a sedative
For sedation in combination with medetomidine hydrochloride.
As an anaesthetic
For anaesthesia in combination with medetomidine and ketamine.

3.3 Contraindications

Horses, dogs and cats:
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in cases of cerebral injury or organic brain lesions (e.g. lesions following cranial trauma) and in animals with obstructive respiratory diseases, heart dysfunction or spastic convulsions.
Do not use in animals with severe dysfunction of the liver or kidneys.

Horses:

Butorphanol / detomidine hydrochloride combination:
The combination should not be used in pregnant animals.
Do not use the combination in horses with a pre-existing cardiac dysrhythmia or bradycardia.
Do not use in horses with emphysema due to a possible depressive effect in the respiratory system.

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

Butorphanol / xylazine combination:
The combination should not be used in pregnant animals.

Any reduction in gastrointestinal motility caused by butorphanol may be enhanced by the concomitant use of α2-adrenoceptor agonists. Consequently, such combinations should not be used in cases of colic associated with impaction.

3.4 Special warnings

Butorphanol is intended for use where short duration analgesia (dog, horse) is required. However, repeat treatments of butorphanol may be administered. For cases where longer duration analgesia is likely to be required, an alternative therapeutic agent should be used.

In the cat, butorphanol is intended for use where short to medium duration analgesia is required. For information on the duration of analgesia that can be expected following treatment see section 4.2. Depending on the clinical response, product administration may be repeated within six hours. In the absence of an adequate analgesic response, use of an alternative analgesic agent, such as another suitable opioid analgesic and/or a non-steroidal anti-inflammatory drug, should be considered. Increasing the dose may not increase the intensity or duration of analgesia. Any alternative analgesia should take account of the action of butorphanol on opioid receptors, as described in section 3.8.

Sedation, especially in cats, may not be sufficient when the product is used as a sole agent.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Rapid intravenous injection should be avoided.

Safety and efficacy of butorphanol in puppies, kittens and foals has not been established. Use the veterinary medicinal product in these groups only according to 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 or in animals that are being treated with expectorants, butorphanol should only be used on the basis of a risk-benefit analysis 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.

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

Dogs:
In dogs with MDR1 mutation reduce dose by 25-50%.

Cats:
Cats should be weighed to ensure that the correct dose is calculated. Use of either insulin syringes or 1 ml graduated syringes is recommended.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Direct contact with skin or eye of the user should be avoided since the veterinary medicinal product might induce irritation and sensitization. Accidental spillage on the skin should be washed immediately with soap and water. When the veterinary medicinal product comes into contact with the eyes, rinse immediately with plenty of water.

Care should be taken when handling the veterinary medicinal product to avoid self-injection. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician, and DO NOT DRIVE, since drowsiness, nausea and dizziness may occur. Effects can be reversed by the administration of an opioid antagonist.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Horses, dogs, cats:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Injection site pain[1]

[1]On intramuscular injection

Horses:

Very common (>1 animal / 10 animals treated):	Ataxia[1,2]
Very rare	Pacing[3]

(<1 animal / 10,000 animals treated, including isolated reports):	Digestive tract hypomotility Cardiac depression Respiratory depression[4]
Undetermined frequency (cannot be estimated from the available data):	Sedation[5]

[1]Mild; may persist for 3 to 10 minutes
[2]Mild to severe; 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.
[3] Excitatory locomotor effects.
[4]When used in combination with α2-adrenoceptor agonists; fatality may occur rarely.
[5] Mild and may occur following the administration of butorphanol as a sole agent.

Dogs:

Rare (1 to 10 animals / 10,000 animals treated):	Diarrhoea Ataxia[1] Anorexia
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Cardiac depression[2] Respiratory depression[2] Digestive tract disorder[3]

[1] Transient.
[2] 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.
[3] Reduction in gastrointestinal motility.

Cats:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	anxiety excitation disorientation mydriasis respiratory depression dysphoria

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. The use of butorphanol during pregnancy and lactation is not recommended.

3.8 Interaction with other medicinal products and other forms of interaction

Butorphanol may be used in combination with other sedatives such as α2-adrenoceptor agonists (e.g. romifidine, detomidine, xylazine in horses, medetomidine in dogs and cats) where synergistic effects can be expected. Therefore, an appropriate reduction in dose is necessary when used concomitantly with such agents (see section 3.9).

Because of its antagonist properties at the opiate mu receptor, butorphanol may inhibit the analgesic effect in animals, which have already received pure opioid mu agonists (morphine/oxymorphine).
Because of the antitussive properties of butorphanol, it should not be used in combination with an expectorant, as this may lead to an accumulation of mucous in the airways.
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 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.

3.9 Administration routes and dosage

Horses: Intravenous use (i.v.).
Dogs and cats: Intravenous (i.v.), subcutaneous (s.c.) and intramuscular (i.m.) use.

To ensure a correct dosage, body weight should be determined as accurately as possible.
In dogs with MDR1 mutation reduce dose by 25-50%.
Intravenous injection should be slow, do not inject as a bolus.
If repeat SC or IM administrations are required, use different injection sites.
Rapid intravenous administration should be avoided.
For information on the duration of analgesia that can be expected following treatment, see section 4.2.

Horses
Analgesia
Monotherapy:
0.1 mg/kg (1ml / 100 kg bw) i.v. injection.
Butorphanol is intended for use where short duration analgesia is required. The dose may be repeated as required. The need for and timing of repeat treatment will be based on clinical response. For cases where longer duration analgesia is likely to be required, an alternative therapeutic agent should be used.

Sedation
With detomidine hydrochloride:
Detomidine: 0.012 mg/kg bw i.v. followed within 5 min by
Butorphanol: 0.025 mg/kg bw (0.25ml / 100 kg bw) i.v.

With romifidine:
Romifidine: 0.04 mg – 0.12 mg/kg bw i.v. followed within 5 minutes by
Butorphanol: 0.02 mg/kg bw (0.2ml / 100 kg bw) i.v.

With xylazine:
Xylazine: 0.5 mg/kg bw i.v. followed immediately by
Butorphanol: 0.025 – 0.05 mg/kg bw (0.25-0.5 ml/100 kg bw) i.v.

Dogs
Analgesia
Monotherapy:
0.2 – 0.3 mg/kg (0.02 – 0.03 ml/kg bw) i.v., i.m. or s.c. injection. Administer 15 minutes before terminating anaesthesia to provide analgesia in the recovery phase. Repeat dose as required.

Sedation
with medetomidine:
Butorphanol: 0.1 mg/kg (0.01 ml/kg bw) i.v. or i.m.
Medetomidine: 0.01 – 0.025 mg/kg i.v. or i.m.
Allow 20 minutes for sedation to develop before commencing the procedure.

Premedicant / pre-anaesthetic
for sedation and as premedicant to anaesthesia:
Butorphanol: 0.1 mg/kg (0.01 ml/kg bw) i.v. or i.m.
Medetomidine: 0.01 mg/kg i.v. or i.m.

Pre-anaesthetic
monotherapy for canine analgesia:
Butorphanol: 0.1 – 0.2 mg/kg (0.01 – 0.02 ml/kg bw) i.v., i.m. or s.c. given 15 minutes prior to induction

Anaesthesia
in combination with medetomidine and ketamine:
Butorphanol: 0.1 mg/kg (0.01 ml/kg bw) i.m.
Medetomidine: 0.025 mg/kg i.m., followed after 15 minutes by
Ketamine: 5 mg/kg i.m.
It is not advisable to reverse this combination in the dog with atipamezole.

Cats
Pre-operative analgesia
Butorphanol: 0.4 mg/kg (0.04 ml/kg bw) i.m. or s.c..
Administer 15 – 30 minutes prior to the administration of i.v. induction anaesthetic agents. Administer 5 minutes before induction with i.m. induction anaesthetic agents such as combinations of i.m. acepromazine / ketamine or xylazine / ketamine.

Post-operative analgesia
Administer 15 minutes before recovery:
Either Butorphanol: 0.4 mg/kg (0.04 ml/kg bw) s.c. or i.m.
or: 0.1 mg/kg (0.01 ml/kg bw) i.v.

Sedation
with medetomidine:
Butorphanol: 0.4 mg/kg (0.04 ml/kg bw) s.c. or i.m.
Medetomidine: 0.05 mg/kg s.c.
Additional local anaesthesia should be used for wound suturing.

Anaesthesia
in combination with medetomidine and ketamine:

i.m. administration: Butorphanol: 0.4 mg/kg (0.04 ml/kg bw) i.m.
Medetomidine: 0.08 mg/kg i.m.
Ketamine: 5 mg/kg i.m.

i.v. administration: Butorphanol: 0.1 mg/kg (0.01 ml/kg bw) i.v.
Medetomidine: 0.04 mg/kg i.v.
Ketamine: 1.25 – 2.50 mg/kg i.v. (depending on depth of anaesthesia required)

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

The main sign of overdose is respiratory depression which can be reversed with an opioid antagonist (naloxone). 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.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance.

Not applicable

3.12 Withdrawal periods

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

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code :

QN02AF01

4.2 Pharmacodynamics

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 opioid receptor subtype and antagonist at the mu receptor subtype. The kappa receptors control analgesia, sedation without depression of cardiopulmonary system and body temperature, whereas the mu 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.

4.3 Pharmacokinetics

In horses, butorphanol is well distributed in tissue after intravenous administration. Butorphanol is metabolised extensively in the liver and excreted in the urine. In horses, butorphanol administered by intravenous route has a high clearance (on average 1.3 L/h.kg) and a short terminal half-life (44 minutes), 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 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.