ANNEX I

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 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 and 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:
Applythe accurately calculated dose volume. The dose should be calculateda 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. Safety 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 use.
DOG, CAT: Intravenous, subcutaneous or intramuscular use.
Rapid intravenous administration must be avoid. Different injection sites should be used for repeated subcutaneous or intramuscular administration.

HORSE
As an analgesic:
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 intravenous injection.
The dose may be repeated as necessary. The analgesic effect is seen within 15 minutes post injection.

As a sedative:
Butorphanol in combination with detomidine hydrochloride:
Administer detomidine hydrochloride at a dose of 0.012 mg/kg bw by intravenous 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 intravenous injection.
Butorphanol in combination with romifidine:
Administer romifidine at a dose of 0.04-0.12 mg/kg bw by intravenous 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 intravenous 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 intravenous, intramuscular or subcutaneous 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 intravenous or intramuscular injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.01–0.025 mg/kg bw, by intravenous or intramuscular 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 intravenous, intramuscular or subcutaneous 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 intravenous or intramuscular injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.01 mg/kg bw by intravenous or intramuscular 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 intramuscular injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.025 mg/kg bw by intramuscular 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 intramuscular 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 intramuscular or subcutaneous injection.
When intravenous induction of anaesthesia is used, administer butorphanol 15-30 minutes before administering the induction agent.
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 recovery.

As a postoperative analgesic:
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 subcutaneous or intramuscular injection.

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 intravenous injection.
Administer 15 minutes before the planned end of the 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 intramuscular or subcutaneous injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.05 mg/kg bw, by subcutaneous or intramuscular 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 of the medetomidine, 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: ***Intravenous administration:***
Administer butorphanol at a dose of 0.1 mg/kg bw, equivalent to 0.01 ml of the product/kg bw, by intravenous injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.04 mg/kg bw by intravenous injection and ketamine at a dose of 1.25-2.5 mg/kg bw by intravenous injection; ketamine should be titrated to the effect in order to aquire an adequate induction and depth of the 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, but often almost immediatelly after induction with the ketamine. Loss of pedal reflex occurs 3 minutes after administration of ketamine. To reverse the anaesthetic effects of the medetomidine, atipamezole should be administered at a dose of 0.2 mg/kg bw. After reversal the pedal reflex returns in approximately 2 minutes, sternal recumbency is attained approximately 6 minutes later followed by standing position a further 18 minutes later.
Intramuscular administration:
Administer butorphanol at a dose of 0.4 mg/kg bw, equivalent to 0.04 ml of the product/kg bw, by intramuscular injection. Immediately thereafter administer medetomidine hydrochloride at a dose of 0.08 mg/kg bw by intramuscular injection and ketamine at a dose of 5 mg/kg bw by intramuscular 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. If no addiotional medication is used, anaesthesia may last up to 60 minutes and at that point animal starts to attain the sternal recumbency. The patient stands up in 70–83 minutes. To reverse the anaesthetic effects of the medetomidine, 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 combinations where butorphanol is used together with α2-adrenoceptor agonists (e.g. xylazine, medetomidine), with the exception of intramuscular administration of the butorphanol/medetomidine/ketamine combination in dogs.

4.11 Withdrawal period(s)

Horses:
Meat and offal: Zero days.
Milk: Zero hours.

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 chlorobutyl 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

For animal treatment only.
Veterinary medicinal product subject to prescription.