IRISH MEDICINES BOARD ACT 1995

EUROPEAN COMMUNITIES (ANIMAL REMEDIES) (No. 2) REGULATIONS 2007

(S.I. No. 786 of 2007)

VPA: **10801/002/001**
Case No: 7005642

The Irish Medicines Board in exercise of the powers conferred on it by Animal Remedies (No. 2) Regulations (S.I. No. 786 of 2007) hereby grants to:

Richter Pharma AG

Feldgasse 19, **4600 Wels**, **Austria**

an authorisation, subject to the provisions of the said Regulations and the general conditions of the attached authorisation, in respect of the Veterinary Medicinal Product:

Nargesic 10 mg/ml Solution for Injection for horses

The particulars of which are set out in Part 1 and Part 2 of the said Schedule. The authorisation is also subject to any special conditions as may be specified in the said Schedule.

The authorisation,unless revoked, shall continue in force from **16/05/2008** until **15/05/2013**.

Signed on behalf of the Irish Medicines Board

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A person authorised in that behalf by the said Board.

(NOTE: This authorisation replaces any previous authorisation in respect of this product which is now null and void.)

Part II

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Nargesic 10 mg/ml Solution for Injection for horses

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains:

Active substance:
10 mg butorphanol as tartrate

Excipient:
0.1 mg benzethonium chloride

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to almost colourless solution

4 CLINICAL PARTICULARS

4.1 Target Species

Horses

4.2 Indications for use, specifying the target species

Monotherapy

As an analgesic
For the short term relief of moderate to severe abdominal pain such as colic. For information on the duration of analgesia that can be expected following treatment, see section 5.1

Combination-therapy:

As a sedative
In combination with alpha2-adrenoceptor agonists (detomidine, romifidine or xylazine):
Standing chemical restraint for therapeutic and diagnostic procedures such as minor standing surgery and restraint of intractable patients.

As a pre-anaesthetic
Premedication to general anaesthesia.

4.3 Contraindications

Do not use in case of hypersensitivity to the active substance, or to any of the excipients.
Do not use in horses with severe dysfunction of liver and kidneys.

Use in combination with α2-adrenoceptor agonists:
Do not use combination in horses with a pre-existing cardiac dysrhythmia or bradycardia.
The combination will cause a reduction in gastrointestinal motility and consequently should not be used in cases of colic associated with impaction.
Do not use combination during pregnancy.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

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

Safety and efficacy of butorphanol in foals have not been established. In foals use only according to the benefit/risk assessment by the responsible veterinarian.

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

Before using any combinations consult the contra-indications and warning that appear on the other product's Summary of Product Characteristics or data sheets.

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.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Care should be taken to avoid accidental self-injection. In case of accidental self-injection, seek medical advice immediately and show the package insert or the label to the physician. Do not drive. The effects of butorphanol include sedation, dizziness and confusion. An opioid antagonist (e.g. Naloxone) may be used as an antidote.
Wash splashes from skin and eyes immediately.

4.6 Adverse reactions (frequency and seriousness)

Monotherapy
Undesirable effects are generally related to the known activity of opioids. In published trials with butorphanol, transient ataxia occurred in about 20 % of horses, lasting about 3 to 15 minutes. Mild sedation occurred in about 10 % of horses. Restlessness may occur ½ to 2 hours after administration. Gastrointestinal motility may be reduced.

Combination-therapy:
Any reduction of gastrointestinal motility caused by butorphanol may be enhanced by the use of concomitant alpha2-agonists. The respiratory depressive effects of alpha2-agonists may be enhanced by concomitant butorphanol, particularly if respiratory function is already impaired. Other undesirable effects (e.g. cardiovascular) are likely to be related to the alpha2-agonist.

4.7 Use during pregnancy, lactation or lay

Butorphanol crosses the placental barrier and penetrates into milk.

Pregnancy:
Studies in laboratory species have not produced any evidence of teratogenic effects.
For safety reasons use is not recommended immediately before and during foaling. During the last month of pregnancy use only according to the benefit/risk assessment by the responsible veterinarian.

Lactation
No information is available concerning possible, undesirable effects in foals. Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Concomitant administration of butorphanol may enhance the effects of other sedative, anaesthetics or respiratory depressants, therefore an appropriate reduction in dose is necessary to avoid any adverse synergistic effect.
The concomitant administration of other drugs which are metabolised in the liver may enhance the effect of butorphanol.
Administration of butorphanol may remove the analgesic effect in animals, which have earlier received pure opioid agonists, such as morphine or fentanyl.

4.9 Amounts to be administered and administration route

Intravenous use only.

Monotherapy:

Butorphanol 0.1 mg/kg bodyweight (1 ml /100 kg) by intravenous injection. The dose may be repeated as required. The need for and timing of repeat treatment will be based on clinical response. For information on the duration of analgesia see section 5.1.

Combination-therapy:

With detomidine:
0.012 mg detomidine/kg bodyweight IV,
followed immediately by
0.025 mg butorphanol/kg bodyweight (0.25 ml /100 kg) IV.

With romifidine:
0.05 mg romifidine/kg IV,
followed within 5 minutes by
0.02 mg butorphanol/kg (0.2 ml /100 kg) IV.

With xylazine:
0.5 mg xylazine/kg IV,
followed after 3-5 minutes by
0.05 - 0.1 mg butorphanol/kg (0.5-1 ml /100 kg) IV.

The stopper should not be pierced more than 25 times.

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

Increased dosages could result in respiratory depression as a general opioid effect.
Intravenous doses of 1.0 mg/kg (10 x the recommended dose), repeated at 4-hourly intervals for 2 days, led to transient adverse effects, including pyrexia, tachypnoea, CNS signs (hyperexcitability, restlessness, mild ataxia leading to somnolence) and gastrointestinal hypomotility, sometimes with abdominal discomfort.

An opioid antagonist (e.g. Naloxone) may be used as an antidote.

4.11 Withdrawal Period(s)

Meat and offal: zero days
Milk: zero days

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Morphinan derivatives, ATCvet code: QN02AF01

5.1 Pharmacodynamic properties

Butorphanol is a central acting analgesic from the group of synthetic opioids with an agonistic-antagonistic effect and a potency 8 times that of morphine.
The onset of analgesia occurs within a few minutes after intravenous administration and peaks at 15 to 30 minutes.
Depending on individual metabolism, the analgesia may last up to 2 hours (mean duration approximately 60 minutes).
Increased doses do not correlate with increased analgesia, a dosage of about 0.4 mg/kg leads to a ceiling effect.

Butorphanol has minimal cardiopulmonary depressant activity in horses.
It does not cause histamine release in horses.
In combination with alpha2-agonists it causes additive and synergistic sedation.

5.2 Pharmacokinetic properties

It is highly bound to plasma proteins (up to 80%) and distributed rapidly (V_d on average 2.1 l/kg), major distribution tissues are lung, liver, kidneys, adrenals and intestine.

Metabolism is rapid and mainly ocurs in the liver. Two inactive metabolites are produced (hydroxybutorphanol and norbutorphanol).

The elimination ($T_{½el}$ 44 min) occurs mainly through urine (to a major extent) and faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Benzethonium chloride
Water for injection

6.2 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: 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 temperature storage conditions.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

10 ml or 50 ml clear type I glass vial with brombutyl rubber stopper and aluminium caps.
1 x 10 ml, 5 x 10 ml, 10 x 10 ml, 50 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials

Any unused product or waste material should be disposed of in accordance with national requirements.

7 MARKETING AUTHORISATION HOLDER

Richter Pharma AG,
Feldgasse 19, 4600 Wels,
AUSTRIA

8 MARKETING AUTHORISATION NUMBER(S)

VPA 10801/002/001

9 DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16th May 2008

10 DATE OF REVISION OF THE TEXT