SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

SUBESTIN 25 microgram/ml oral solution for horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:

Active Substance:
Clenbuterol Hydrochloride 25 microgram
(equivalent to 22 microgram clenbuterol)

Excipients:

Methyl parahydroxybenzoate (E218) 1.8 mg
Propyl parahydroxybenzoate 0.2 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution
Slightly viscous, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Horses.

4.2 Indications for use, specifying the target species

Treatment of respiratory disease in horses where it is considered that airway obstruction due to bronchospasm and/or accumulation of mucus is a contributing factor, and improved mucociliary clearance is desirable.
To be used alone or as adjuvant therapy.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or any of the excipients.
Do not use in horses with known cardiac disease.
For use during pregnancy or lactation see section 4.7.

4.4 Special warnings for each target species

None

4.5 Special precautions for use

Special precautions for use in animals
In cases accompanied by bacterial infection the administration of antimicrobial agents is recommended.
In case of glaucoma the product must only be used after a careful risk-benefit assessment.
Special precautions should be taken in case of halothane anaesthesia, since the heart function can show increased sensitivity to catecholamines.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This veterinary medicinal product contains clenbuterol, a beta-agonist, which may cause adverse effects such as increased heart rate.
Dermal exposure and accidental ingestion, including hand-to-mouth contact should be avoided. When using this product do not eat, drink or smoke to avoid accidental intake of the product.
To avoid accidental ingestion by or exposure to a child, do not leave the filled syringe unattended and close the bottle immediately and properly after use.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Wash hands after use.
This product may cause embryotoxicity. Pregnant women should take care when handling the product. Wear gloves to avoid skin contact.
This product may cause hypersensitivity reactions. People with known hypersensitivity to any of the excipients (parabens, polyethylene glycol and/or triethanolamine) should avoid exposure to the product. In case of hypersensitivity reactions or if irritation persists, seek medical advice and show the package leaflet or label to the physician.
This product may be irritating to the skin and/or eyes. Avoid skin and/or eye contact. In case of accidental skin contact, wash skin thoroughly. In case of accidental eye contact, flush thoroughly with clean water.

4.6 Adverse reactions (frequency and seriousness)

Clenbuterol may cause side effects such as sweating (mainly neck region), muscle tremor, tachycardia, slight hypotension, restlessness or lethargy. These are typical for β-agonists and occur rarely.

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

Pregnancy:
If used during pregnancy, treatment must be discontinued a minimum of 4 days before the expected time of delivery or at signs of approaching parturition, since uterine contractions may be abolished or labour may be prolonged.

Lactation:
Avoid administration to nursing mares because of excretion in the milk. The safety of the veterinary medicinal product has not been established during lactation.
A nursing foal ingests a high volume of milk relative to its body weight. Therefore, during lactation an effect of the active substance excreted in milk in the nursing foal cannot be definitely excluded.

4.8 Interaction with other medicinal products and other forms of interaction

Effects including side effects may be enhanced with simultaneous use with glucocorticoids, ß2-sympathomimetics, anticholinergics and methylxanthines.
The veterinary medicinal product should not be used concomitantly with other sympathomimetics or vasodilators.
In animals treated with clenbuterol disturbances of the heart rhythm can be expected upon anesthesia.
Simultaneous administration of narcotics containing halogens (isoflurane, methoxyflurane) increases the risk of ventricular arrhythmias.
During the use of both local and general anaesthetics one cannot exclude a further vascular dilatation and fall of blood pressure, particularly if used in combination with atropine.
Increased risk of arrhythmia with simultaneous administration of digitalis glycosides.
The veterinary medicinal product can reduce or neutralise the effects of prostaglandin F2α and oxytocin on the uterus.
Clenbuterol hydrochloride is a β -adrenergic agonist and subsequently neutralized by β-blockers.

4.9 Amounts to be administered and administration route

Oral use
The veterinary medicinal product should be administered twice a day with approximately 12 hours (minimum 8 hours) in between according to the following dosage:
Administer 0.8 micrograms clenbuterol hydrochloride per kilo body weight (i.e. 0.7 micrograms clenbuterol per kg bodyweight), corresponding to 4 ml oral solution / 125 kg body weight, twice daily.
The duration of the treatment is a maximum of ten consecutive days.
The product is administered orally, through or over food.
This veterinary medicinal product is intended for individual treatment.

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

Doses of clenbuterol hydrochloride up to 4 times the therapeutic dose (orally administered) administered for 90 days caused only temporary side effects typical for

$ß_2$-adrenoceptor agonists (sweating, tachycardia, muscle tremor) which did not require treatment.

In case of accidental overdose, a ß-blocker (such as propranolol) may be used as antidote.

4.11 Withdrawal period(s)

Meat and offal: 28 days
Not authorised for use in animals producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: $ß_2$-sympaticomimeticum
ATC vet code: QR03CC13

5.1 Pharmacodynamic properties

The veterinary medicinal product contains clenbuterol hydrochloride, which is a sympathomimetic amine which preferentially binds to ß2- adrenoreceptors on cell membranes of the bronchi. This subsequently activates the enzyme adenylate cyclase in smooth muscle cells, thus providing intense bronchodilating properties and decreasing airway resistance. The veterinary medicinal product has been shown to inhibit histamine release from mast cells in the lungs, and enhance mucociliary clearance in horses.

5.2 Pharmacokinetic particulars

The bioavailability of clenbuterol hydrochloride in horses after oral administration is 100%. Maximum plasma concentrations (C_{max}) of clenbuterol are reached 2 hours after administration.
After the first dose of the recommended repeated treatment, C_{max} values of 0.4 to 0.9 ng/ml are expected. Steady state levels in the plasma are achieved after 3 - 5 days of treatment. At that point, the C_{max} values of clenbuterol vary between 0.6 and 1.6 ng/ml.
The substance is rapidly distributed to tissues and primarily metabolised in the liver. Not more than 45% of the portion of the dose excreted via the urine consists of parent clenbuterol.
Clenbuterol is eliminated from the plasma in different phases and has an average final elimination half-life of ten to twenty hours.
The largest part of the dose administered is eliminated unchanged via the kidneys (70 – 91%), the remainder via the faeces (± 6 – 15%).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate

Carbomer (974P)
Sucrose
Macrogol 400
Glycerol
Ethanol 96%
Trolamine (for pH adjustment)
Water, purified

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: 3 years.
Shelf life after first opening the immediate packaging: 3 months

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and composition of immediate packaging

White HDPE bottle with white polypropylene child-resistant screw cap and LDPE syringe inlay.
The product is supplied in a carton box with a measuring device, a 25 ml syringe with polypropylene body and polyethylene plunger, capable of delivering 4 to 24 ml of the product.

Each bottle contains 360 ml.

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

Floris Holding B.V.
Kempenlandstraat 33 / 35
5262 GK Vught
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 56190/5003

9. DATE OF FIRST AUTHORISATION

28 April 2022

10. DATE OF REVISION OF THE TEXT

June 2024

PROHIBITION OF SALE, SUPPLY AND/OR USE

POM-V

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Gavin Hall

Approved: 27 June 2024