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:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Methyl parahydroxybenzoate (E218)	1.8 mg
Propyl parahydroxybenzoate	0.2 mg
Carbomer (974P)	
Sucrose	
Macrogol 400	
Glycerol (E422)	
Ethanol 96%	
Trolamine (for pH adjustment)	
Water, purified	

Oral solution
Slightly viscous, colourless to slightly yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Horses.

3.2 Indications for use for each 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.

3.3 Contraindications

Do not use in cases of known 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 3.7.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:
In cases accompanied by bacterial infection the administration of antimicrobial agents is recommended.
In case of glaucoma the veterinary medicinal product must only be used after a careful benefit-risk assessment by the attending veterinarian.
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 veterinary medicinal product do not eat, drink or smoke to avoid accidental intake of the veterinary medicinal 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 veterinary medicinal product may cause embryotoxicity. Pregnant women should take care when handling the veterinary medicinal product. Wear gloves to avoid skin contact.
This veterinary medicinal 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 veterinary medicinal product. In case of

hypersensitivity reactions or if irritation persists, seek medical advice and show the package leaflet or label to the physician.
This veterinary medicinal 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.

3.6 Adverse events

Horses

Rare (1 to 10 animals / 10,000 animals treated):	Sweating* Muscle tremor Tachycardia Hypotension** Restlessness

*mainly neck region
**slight

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 and lay

Pregnancy:
If used during pregnancy, treatment must be discontinued a minimum of 4 days before the expected time of delivery, 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.

3.8 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 anaesthesia.
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 is subsequently neutralised by β-blockers.

3.9 Administration routes and dosage

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 kilogram 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 veterinary medicinal product is administered orally, through or over food.
This veterinary medicinal product is intended for individual animal treatment.

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

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.

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

Meat and offal: 28 days
Do not use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QR03CC13

4.2 Pharmacodynamics

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 with minimum effect on the cardiovascular system. The veterinary medicinal product has been shown to inhibit histamine release from mast cells in the lungs, and enhance mucociliary clearance in horses.

4.3 Pharmacokinetics

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%).

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 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

5.3 Special precautions for storage

Do not store above 30 °C.

5.4 Nature and composition of immediate packaging

White HDPE bottle with white polypropylene child-resistant screw cap and LDPE syringe inlay.

The veterinary medicinal 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 veterinary medicinal product.

Each bottle contains 360 ml.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater <or household waste>.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Floris Holding B.V.

7. MARKETING AUTHORISATION NUMBER

Vm 56190/3003

8. DATE OF FIRST AUTHORISATION

25 August 2022

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

November 2023

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (*https://medicines.health.europa.eu/veterinary*).

Approved 17 November 2023