1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Aservo EquiHaler 343 micrograms/actuation inhalation solution for horses

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation (ex nostril adapter) contains:

Active substance:
Ciclesonide 343 micrograms

Excipients:
Ethanol: 7.9 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution.
Clear, colourless to yellowish solution.

4. CLINICAL PARTICULARS

4.1 Target species

Horse

4.2 Indications for use, specifying the target species

For the alleviation of clinical signs of severe equine asthma (formerly known as Recurrent Airway Obstruction– (RAO), Summer Pasture Associated Recurrent Airway Obstruction – (SPA-RAO)).

4.3 Contraindications

Do not use in known cases of hypersensitivity to the active substance, to corticosteroids or to any of the excipients.

4.4 Special warnings for each target species

Special care should be taken when administering the veterinary medicinal product. To ensure an efficacious administration, the breath indicator in the chamber wall of the nostril adapter needs to be observed: when the horse inhales, the membrane of the breath indicator curves inwards. During exhalation, the membrane of the breath indicator curves outwards. The spray should be released at the beginning of inhalation, i.e. when the breath indicator starts curving into the chamber. If the movement of the breath indicator cannot be observed, assure the correct positioning of the nostril adapter. If movement of the breath indicator is still not visible or the movement is too rapid, the product should not be administered.
Efficacy of the product has not been established in horses with acute exacerbations (<14 days duration) of clinical signs.

4.5 Special precautions for use

Special precautions for use in animals
Safety of the veterinary medicinal product has not been established in horses weighing less than 200 kg body weight, or in foals.

The prescribing veterinarian should assess if the horse has a temperament suitable for a safe and efficacious administration of the Aservo EquiHaler in agreement with good veterinary practice. Horses might not adapt to an easy and safe application of the Aservo EquiHaler within a couple of days. In such cases, an alternative treatment should be considered.

The onset of clinical improvement may take several days. The use of concomitant medication (such as bronchodilators) and environmental control may need to be considered in cases of severe clinical signs of respiratory obstruction, at the discretion of the attending veterinarian (see also section 4.8).

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Follow closely the instructions for handling and use of the Aservo EquiHaler as provided in the package leaflet section "Other Information".

Administration of the product should take place in well ventilated surroundings.

People with known hypersensitivity to ciclesonide or any of the excipients should avoid contact with the veterinary medicinal product.

Inhalative or intranasal corticosteroids may cause rhinitis, nasal discomfort, nosebleed, upper respiratory tract infection and headache. An aerosol filtering mask must be worn during handling and administration. This prevents inadvertent inhalation in case of unintended release of actuations outside the nostril or without the nostril adapter.

The product can cause irritation to the eyes due to its ethanol content. Avoid contact with eyes. In case of accidental eye contact, rinse with large quantities of water.
In case of experiencing an adverse reaction due to accidental inhalation, and in case of eye irritation, seek medical advice and show the package leaflet or the label to the physician.

These precautions should be followed by the person administering the product and persons in close proximity to the horse's head during administration.

The safety of ciclesonide after inhalatory exposure has not been established in pregnant women. In animal studies ciclesonide has been shown to induce malformations in foetuses (cleft palate, skeletal malformations). Pregnant women should therefore not administer the product.

If the Aservo EquiHaler is visually damaged it should not be used any more.

It is essential to keep the product out of reach for children.

4.6 Adverse reactions (frequency and seriousness)

Mild nasal discharge was commonly observed during safety and clinical studies.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reactions)
- 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 the veterinary medicinal product has not been established during pregnancy or lactation. Use only according to the benefit/risk assessment by the responsible veterinarian.
The product was shown to be teratogenic following oral administration after high doses in rabbits but not in rats.

4.8 Interaction with other medicinal products and other forms of interaction

Concomitant use of clenbuterol in a field study in seven horses with severe equine asthma did not indicate any safety concerns.

4.9 Amounts to be administered and administration route

Inhalation use.

The number of actuations to be administered is the same for all horses. The total treatment duration is 10 days:
- Day 1 to 5:
  8 actuations (corresponding to 2,744 µg ciclesonide) administered twice daily approximately 12 h apart
- Day 6 to 10:
  12 actuations (corresponding to 4,116 µg ciclesonide) administered once daily approximately 24 h apart.

The onset of clinical improvement may take several days. The 10 days treatment schedule should normally be completed. In case of any concerns related to the treatment the responsible veterinarian should be consulted.

The Aservo EquiHaler contains sufficient inhalation solution for one horse for the entire treatment duration of the 10 days and an additional amount covering priming and potential losses during administration.

Treatment schedule for use:

Treatment days 1 to 5	**Treatment days 6 to 10**
8 actuations morning **and** evening approximately 12 h apart	12 actuations once daily approximately 24 h apart

The "**Instructions for handling and use of the Aservo EquiHaler**" is provided in section "Other information" of the package leaflet.

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

After administration of the veterinary medicinal product at up to the 3-fold recommended dose for 3 times the recommended treatment duration no relevant clinical signs were observed.

4.11 Withdrawal period(s)

Meat and offal: 18 days
Not authorised for use in horses producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Respiratory system, other drugs for obstructive airway diseases, inhalants
ATCvet code: QR03BA08

5.1 Pharmacodynamic properties

Ciclesonide is a prodrug which is enzymatically converted to the pharmacologically active metabolite desisobutyryl-ciclesonide (des-ciclesonide) following inhalation. The glucocorticoid-receptor affinity of des-ciclesonide was tested in rats and humans and demonstrated that the glucocorticoid-receptor affinity of des-ciclesonide is up to 120 times greater than the parent compound's affinity and 12 times greater than dexamethasone's affinity. Des-ciclesonide has anti-inflammatory properties which are exerted through a wide range of inhibitory activities.

In general, cortisol levels serve as a marker for suppression of the hypothalamic-pituitary-adrenal axis by systemic action of corticosteroids which could be associated with side effects.

No statistically significant suppression of cortisol levels was observed in horses with equine asthma at the recommended dosing regimen and in healthy horses with ciclesonide treatment up to three times the dose and three times the duration.

The pivotal field trial included horses (mean age 18.5 years) with severe equine asthma characterised by the following main criteria: clinical signs >14 days duration; horses that tolerated insertion of the nostril adapter; laboured breathing at rest; weighted clinical score ≥11/23. The weighted clinical score included the following parameters: coughing, nasal discharge, nasal flaring, laboured breathing at rest, respiratory rate, tracheal sounds and abnormal lung sounds. Clinical success was defined as an improvement of at least 30% in the weighted clinical score. In total, 73.4% of the ciclesonide group and 43.2% of the placebo group demonstrated treatment success, and the difference between the groups was statistically significant.

5.2 Pharmacokinetic particulars

Absorption
Ciclesonide was rapidly absorbed after inhalation with a median T_{max} of about 5 minutes after the last actuation and rapidly converted to its active metabolite des-ciclesonide as shown by concentrations at the first sampling time, i.e. 5 minutes after the last actuation.

Distribution
The volume of distribution in horses is 25.7 l/kg, indicating that ciclesonide is distributed readily into the tissues.
Following inhalative administration in horses, the absolute systemic bioavailability of ciclesonide was very low and was not higher than 5%-17%. The apparent systemic bioavailability of des-ciclesonide following administration of ciclesonide was in the range of 33.8%-59.0%. The plasma exposure for ciclesonide and des-ciclesonide in terms of C_{max} and AUC_{last} increased with the dose. A slight trend to an increase of plasma exposure higher than the dose proportionality was observed.
In-vitro protein binding of des -ciclesonide was tested in the plasma from mice, rats, rabbits, dogs and humans (mouse plasma 98.9% to 99.1%; rat plasma 97.5% to 98.0%; rabbit plasma 99.1% to 99.2%; dog plasma 97.9% to 98.0%; human plasma 98.5% to 98.8%).

Metabolism
Ciclesonide is a pro-drug that is rapidly metabolized to the major active metabolite (des-ciclesonide) after inhalation. In vitro, three metabolites were reported as major metabolites. In vivo, only des-ciclesonide occurred whereas the other two metabolites could not be confirmed.

Elimination
The mean apparent harmonic terminal half-life after single inhalation administration was approximately 3-5 hours for ciclesonide and approximately 4-5 hours for des-ciclesonide.
Elimination of ciclesonide and its active metabolite des-ciclesonide is principally via faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Hydrochloric acid
Water, purified

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first activation: 12 days.

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

One Aservo EquiHaler with a polyurethane nostril adapter contains a pre-inserted cartridge. The cartridge consists of a polyethylene/polypropylene plastic container closed with a polypropylene cap and crimped in an aluminium cylinder. The cartridge contains sufficient inhalation solution for the entire treatment duration (140 treatment actuations). The cartridge also contains an additional amount covering priming and potential losses during administration within the 10 day treatment duration. Additionally, there is residual solution which cannot be delivered with the required accuracy, and should therefore not be administered.
The cartridge cannot be removed from the Aservo EquiHaler.

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

Any used or unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
The cartridge contains residual amount of the product at the end of the course of administration. This should be taken into account at disposal of the used veterinary medicinal product.

7. MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Vetmedica GmbH
55216 Ingelheim am Rhein
GERMANY

8. MARKETING AUTHORISATION NUMBER(S)

Vm 04491/5003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.