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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Aservo EquiHaler (EMEA/V/C/004991/0000)

INN: ciclesonide

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant Boehringer Ingelheim Vetmedica GmbH submitted on 31 August 2018 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Aservo EquiHaler, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 March 2018 as Aservo EquiHaler contains a new active substance (ciclesonide), which was not authorised in the Community on the date of entry into force of the Regulation.

Aservo EquiHaler, 343 micrograms per actuation, inhalation solution for horses is presented as an inhaler with a polyurethane nostril adapter. The inhaler contains a pre-inserted cartridge containing 4.3 ml of the inhalation solution (30 mg/ml) providing for 140 treatment actuations and with additional actuations to cover potential losses during administration.

The applicant applied for the following indication: "For the treatment of horses with moderate to severe clinical signs of equine asthma."

Ciclesonide is novel in veterinary medicines and is a pro-drug which following inhalation is converted into the active metabolite, desisobutyryl-ciclesonide (*des*-CIC), in the airways. *Des*-ciclesonide has anti-inflammatory properties which are exerted through a wide range of inhibitory activities.

The product is administered over 10 days, with the same dose for all horses independent of their body weight. The initial (days 1 to 5) dose is 8 actuations (corresponding to 2744 µg ciclesonide) administered twice daily approximately 12 h apart; followed (days 6-10) by 12 actuations (corresponding to 4116 µg ciclesonide) administered once daily approximately 24 h apart.

The proposed withdrawal period (meat and offal) is 18 days based on the CVMP approved maximum residue limits (MRL) and acceptable daily intake (ADI) (see European public MRL assessment report - EPMAR for ciclesonide (EMA/CVMP/808134/2018)). The product is not intended to be used in horses producing milk for human consumption.

The rapporteur appointed is Keith Baptiste and the co-rapporteur is Tonje Høy.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

On 7 November 2019, the CVMP adopted an opinion and CVMP assessment report.

On 28 January 2020, the European Commission adopted a Commission Decision granting the marketing authorisation for Aservo EquiHaler.

Scientific advice

Not applicable.

MUMS/limited market status

The applicant requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted as the target species (horse) is considered a minor species.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (DDPS) from Boehringer Ingelheim Animal Health. This version of the DDPS was approved by EMA on 17 July 2019 for several centrally authorised products for which Boehringer Ingelheim Vetmedica GmbH is the marketing authorisation holder the provided DDPS is considered acceptable.

Manufacturing authorisations and inspection status

Manufacture of the dosage form takes place at:

Fareva Amboise
Zone Industrielle
29 route des Industries
37530 Poce-sur-Cisse
FRANCE

The site's Manufacturing Authorisation was issued on 22 January 2016 by ANSES, France.

GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of sterile veterinary medicinal products and solid oral dosage forms for veterinary use has been presented.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release; the declaration has an audit date which is not more than three years ago.

Overall conclusions on administrative particulars

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

The detailed description of the pharmacovigilance system from Boehringer Ingelheim Animal Health was considered in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a clear, colourless to yellowish ethanolic solution of ciclesonide (30mg/ml, 343 µg/actuation) which contains hydrochloric acid for pH adjustment. The solution is intended for inhalation use in horses via the nostril.

The product is a multidose, non-pressurised, metered dose preparation providing an aerosolised mist delivered by an inhaler.

Each actuation delivers 343 µg of the active substance ciclesonide. One dose consists of 8 actuations, each delivering 343 micrograms of ciclesonide (= 2744 micrograms of ciclesonide), or 12 actuations (= 4116 micrograms of ciclesonide).

One treatment course consists of 140 actuations, corresponding to 10 days treatment plus an

additional amount covering priming and potential losses during administration.

Containers

The primary packaging material is a non-pressurised cartridge consisting of a polyethylene/polypropylene container closed with a polypropylene plastic cap with integrated sealing ring which represents the reservoir. The reservoir is crimped into an aluminium cylinder to form the cartridge. The cartridge is fitted with a metering dose mechanism providing an aerosolised mist of the inhalation solution for delivery to the horse's lung. The inhaler is delivered with the pre-inserted cartridge and a polyurethane nostril adapter. The cartridge cannot be removed from the Aservo EquiHaler.

The primary packaging material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system is supported by stability data and is considered adequate for the intended use of the product.

The inhaler is packed in an outer carton and each carton contains one inhaler.

The manufacture and control of the inhaler has been described and is the most critical part of the drug-inhaler combination.

Development pharmaceutics

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

The composition of the inhalation solution used during clinical studies is the same as that intended for marketing.

The container closure system has been described and extractable and leachable studies have been performed on container closure components in contact with the inhalation solution, concluding that there are no safety or stability concerns with respect to the nature and amounts found.

Inhaler:
The equine inhaler was developed in two stages: (1) pilot inhaler used in clinical studies and (2) final inhaler used in a pivotal study and for market supply. The development of the one-hand operated inhaler has been sufficiently described.

It is stated that one-time studies showed that neither the delivered dose nor the aerodynamic particle size distribution of the emitted aerosol changed when going from the pilot inhaler to the final equine inhaler.

Performance and characterisation studies on the final inhaler, performed according to guidance for requirements to human inhalation products, have been used to demonstrate the suitability of the inhaler for its intended use. The delivered dose as well as fine particle mass are critical parameters for inhalation products in order to ensure that a consistent dose of the active substance reaches the lungs and are both included in the specifications.

Robustness of the inhaler has been demonstrated with the results from a drop test on the strengthened inhaler. The chosen design is the best-balanced solution, considering ciclesonide's solubility and the technical challenges related to the formation of a large volume aerosol with each actuation.

Method of manufacture

The manufacture of the inhaler consists of manufacture of the filled bulk cartridge and then assembly of the bulk cartridge, the inhaler, nostril adapter and piercing element into the finished product.

Manufacture of the inhalation solution consists of the dissolution of the active ingredient, filtration of the solution, filling it into the plastic container and the final crimping into the aluminium container. The empty inhaler, nostril adapter and piercing element are supplied to the manufacturer of the cartridge who performs the assembly into the finished product. The release specifications used by the manufacturer of the inhaler, piercing element and nostril adapter are identical to those used by the finished product manufacturer upon receipt of the inhaler parts and are acceptable.

The batches used in performance and characterisation studies are all 20 L pilot batches manufactured by Boehringer Ingelheim Vetmedica GmbH, Ingelheim, Germany and not by the proposed manufacturer, Fareva Amboise, France. Manufacture of metered dose inhalation products is a non-standard manufacturing process. Manufacture of the inhalation solution and filling into the cartridge was considered a standard process; however, the assembly and control of the inhaler is critical for performance of the final product. Batch analysis data from a batch manufactured by the finished product manufacturer were provided, demonstrating compliance with the specifications. In addition, details about the manufacture and control of the different functional parts of the inhaler were provided to demonstrate that the process is adequately controlled. The provided data are considered sufficient.

Control of starting materials

Active substance

There is a monograph for ciclesonide in the Ph. Eur., and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for ciclesonide, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph, and additional specifications for residual solvents have been specified in annex II of the CEP.

Batch analysis data from 3 three batches analysed by both the applicant and active substance manufacturer were provided. Results are comparable and comply with Ph.Eur.

Stability data on three batches of active substance from the supplier stored for 36 months under long term conditions at 30 °C/65% RH are enclosed. The parameters tested are: appearance, ID, water content, related substances (impurities A,B,C, unspecified, total unspecified and total impurities) and assay.

All tested parameters were within the specification. No trends were observed during the storage period. A re-test period of 3 years when stored below 30 °C, is accepted.

Excipients

All the excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC. A certificate of analysis has been presented for each of the excipients: ethanol, purified water and dilute hydrochloric acid.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The active ingredient and the excipients are derived from vegetable source or chemical origin only, thus there is no TSE risk.

According to section A.4 on development pharmaceutics, materials of animal origin are used in the manufacture of some container closure components. It is stated, that the rigorous processing methods used for manufacture will render the materials non-infectious. Certificates from the suppliers of the materials of animal origin were provided to demonstrate compliance with Ph. Eur. 5.2.8/ EMEA/410/01 Rev. 3, *Note for guidance on minimizing risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*.

Control tests on the finished product

The specifications proposed for use at release and at the end of shelf-life are appropriate to control the quality of the finished product.

The fine particle fraction and fine particle mass are used to control the fine particle dose with particle size ≤ 5 µm.

The analytical methods used have been adequately described and appropriately validated in accordance with the EU/VICH guidelines. Satisfactory information regarding the reference standards used for assay, identity, delivered dose uniformity and degradation products has been presented. The reference standards are Ph. Eur. Chemical Reference Substances (CRS).

Batch analysis results are provided for three pilot scale (20 L) and one commercial scale batch (100 L) confirming the consistency of the manufacturing process and its ability to manufacture a uniform product complying with the proposed specification.

Stability

Stability data for one laboratory scale batch of the cartridge (2 L), three pilot scale (20 L) and one commercial scale batch (100 L) of finished product are included in stability studies. The pilot scale batches have been stored under long term conditions for 36 months at 30 °C/65% RH, the lab scale batch for 36 months at 25 ºC/60% RH and all five batches for 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines. For the commercial batch, 9 months data at 30 °C/65% RH are available. The batches are identical to those proposed for marketing (except the laboratory scale batch for which only the cartridge has been tested) and they were packed in the primary packaging proposed for marketing.

Parameters investigated included: appearance of the cartridge and the inhaler, colour and clarity of solution, assay, degradation products (impurity B, unspecified impurities, total impurities), microbial purity (initially and every year), aerodynamic particle size distribution (APSD), pump delivery, delivered dose uniformity, fine particle fraction (FPF), and number of actuations. Photostability studies were performed in accordance with VICH GL 5.

In-use stability testing covering 12 days of use has been performed. No significant changes were observed and the in-use shelf life is set at 12 days.

Based on the available stability data, the following shelf life/storage conditions can be accepted:

3 years: this veterinary medicinal product does not require any special conditions for storage.

Overall conclusions on quality

The medicinal product is a clear, colourless to yellowish ethanolic solution of the active substance ciclesonide intended for inhalation use in horses via the left nostril.

Hydrochloric acid is used for pH adjustment and is complaint with the Ph. Eur.

Satisfactory information on the development, manufacture and control of the finished product has been presented.

The manufacturing process for metered dose inhalation products is considered as a non-standard manufacturing process. Additional batch data from the proposed finished product manufacturer as well as detailed information on the manufacture and control of the inhaler parts has been provided and is considered sufficient to demonstrate that a consistent quality is obtained.

A copy of the Ph. Eur. CEP was provided for the active substance and a re-test period of 3 years is accepted.

Based on the provided data a 3 year shelf life with no special storage conditions is accepted. In use shelf life is 12 days.

The applicant has committed to place the first 3 batches produced for commercial release in a stability study.

Part 3 – Safety

The application for the veterinary medicinal product, Aservo EquiHaler, comes with a newly developed inhaler to be inserted into the left nostril of horses. The active substance of Aservo EquiHaler, ciclesonide, is a glucocorticoid, and a new active substance not previously authorised for a veterinary medicinal product in the EU. A full safety file in accordance with Article 12(3)(j) has been provided.

Maximum residues limits for ciclesonide in horses have been recommended by the CVMP.

Safety documentation

Pharmacodynamics

Studies in several animal species have revealed that ciclesonide is a non-halogenated ester parent compound that is converted in the lung and liver by esterases to form the active metabolite desisobutyryl-ciclesonide (*des*-CIC), through cleavage of C21-ester bond. The metabolite, *des*-CIC, has potent local anti-inflammatory activity within the lung, and has been shown in some species to be conjugated with fatty acids to prolong its anti-inflammatory activity within the lung; in the systemic circulation there is high protein-binding as well as a rapid elimination from the body.

A total of eight *in vivo* studies were qualified as pharmacodynamics studies. No pharmacodynamics studies were performed using horses. Animal species used in the studies included guinea pigs, rats, dogs and cats in line with the guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market species (EMA/CVMP/EWP/117899/2004–Rev.1).

Pulmonary studies:

In the laboratory animal studies, ciclesonide was given either orally or via the intra-tracheal route. In a rat ovalbumin (OVA)-induced asthma model, there was no major difference in the anti-inflammatory activity between ciclesonide and other well-known corticosteroids (budesonide, fluticasone and

mometasone), with respect to the duration of action on allergen-induced influx of eosinophils from bronchoalveolar lavages (BALF), as well as the same maximal efficacy in inhibiting the influx of eosinophils into the BALF. In a guinea-pig acetylcholine-induced bronchoconstriction model, ciclesonide demonstrated slight broncho-protection of 20 to 30% within the first three hours after its oral administration in anesthetised guinea pigs.

Systemic studies:

In the laboratory animal studies ciclesonide was given intravenously. In cats and dogs intravenous ciclesonide did not induce any cardiovascular or respiratory effects. In female rats and mice, neither 20 mg/kg bw ciclesonide intravenous nor the solvent had any effect on the behaviour. After repeated oral administration for 28 days in rats beside involution of the adrenals, effects on the thymus and decrease in gain of body weight were seen as indicators of systemic glucocorticoid action.

The pharmacological ADI assessment was based on rats and the measurement of tyrosine aminotransferase activity (see EPMAR (EMEA/CVMP/808134/2018) for more detail). Steroids with glucocorticoid activity enhance the induction of tyrosine aminotransferase activity by dibutyryl cyclic AMP. Ciclesonide administered via the oral route induced a statistically significant increase in tyrosine aminotransferase activity at the top dose of 540 µg/kg bw. Ciclesonide did not induce any statistically significant changes in corticosterone level, whatever the dose tested. No changes were seen in liver weight.

Pharmacokinetics

Several *in vitro* and *in vivo* studies were submitted. In the laboratory animal studies (mice, rabbits, rats, dogs), ciclesonide was given via different routes of administration, different doses as well as different formulations compared to the applicant's product. Thus, these studies provide some information about the basic pharmacokinetics characteristics of ciclesonide *in vivo*.

Several *in vivo* studies submitted demonstrated that ciclesonide and its main metabolite, *des*-CIC, demonstrate predictable pharmacokinetics when given intravenously or orally in rats and dogs. Exposure of the mouse to ciclesonide during the oral carcinogenicity study, as assessed by the serum concentration of *des*-CIC, a major metabolite of ciclesonide, was approximately in proportion to the dose and did not change with the frequency of dosing.

Inhalation doses in horses demonstrate less predictable pharmacokinetics. Plasma exposure for ciclesonide and *des*-CIC in terms of C_{max} and AUC_{last} increased with the dose. In one study this increase was not proportional between the 2700 µg and 4050 µg per horse doses. A trend towards an increase of plasma exposure higher than the dose proportionality was observed. In another study, no clear dose proportionality was shown between the doses. A trend towards an increase of plasma exposure higher than the dose in terms of C_{max} and AUC was observed between the doses of 2744 µg and 4116 µg per horse while it decreased between the 4116 µg and the 5488 µg doses. Dose proportionality was roughly observed when considering only the low dose of 2744 µg and the high dose of 5488 µg.

Absorption

In vivo studies:

Radioactive [^{14}C]-ciclesonide was well absorbed in the dog following oral administration of 1 mg/kg bw. Based on serum AUC data of total radioactivity, a mean of 66% of the oral administered dose was absorbed. Further oral dosing studies in dogs revealed that mean oral bioavailability was low and rose proportionally to increased concentrations in oral doses (0.68%, 1.03% and 2.08% at 0.1, 0.3 and 0.9 mg/kg bw, respectively).

In rats, following intravenous administration, radioactive [^{14}C]-ciclesonide demonstrated C_{max} concentrations of radioactivity in lungs were 7.45 times higher than the corresponding plasma concentrations. Following oral administration, a similar distribution of radioactivity was observed, but at a distinctly lower level, indicating low bioavailability of the radio-labelled compound (24%). Following intratracheal administration, [^{14}C]-ciclesonide demonstrated a high affinity for thyroid and lungs, with C_{max} 445 times higher in thyroid and 69 times higher in lungs than in plasma.

In horses two studies revealed that ciclesonide was rapidly absorbed after the inhalation administrations with a median T_{max} occurring 5 min after the last actuation, and rapidly converted to its active metabolite *des*-CIC, as demonstrated by concentrations found already at the first sampling time (after 5 minutes). Absolute systemic bioavailability of ciclesonide was low and was not higher than 5% at 2700 µg/horse and not higher than 17% for 4050 µg/horse. The apparent systemic bioavailability of the active metabolite based on data following intravenous administration of ciclesonide was 33.8% at 2700 µg and 59.0% at 4050 µg/horse. A higher tendency in favour of the 4050 µg dose was observed for the mean residence time of ciclesonide, almost 2-fold longer at 4050 µg than at 2700 µg/horse.

Plasma/Tissue Distribution

Protein binding *in vitro* studies were done using rats, humans and dog samples. Serum protein binding of ciclesonide was high and similar among species with slightly lower protein binding in the rat. The extent of protein binding was in the following order: rat (98.6-98.9%), human (98.9-99.4%), dog (99.5-99.6%). No apparent saturation of protein binding was observed in any species in the concentration range of 10 to 10000 ng/ml of ciclesonide. No protein-binding studies were done using horse samples.

In rats, following intravenous administration, radioactive [^{14}C]-ciclesonide was widely distributed throughout the tissues and organs, highest concentrations being observed in lungs (10.06 *µg* equiv./g), heart (7.12 *µg* equiv./g) and thyroid (3.68 *µg* equiv./g). High concentrations were also found in liver (4.93 *µg* equiv./g) and kidneys (3.063 *µg* equiv./g). Following intratracheal administration, [^{14}C]-ciclesonide showed a high affinity for thyroid and lungs.

Oral dosing studies in dogs revealed secondary elevations in blood profiles between 4 and 8 hours post dose, indicating possible enterohepatic recirculation. A favourable distribution from blood into tissues following intravenous dose (volume of distribution 9.95 l/kg) was observed.

In horses, a single-dose inhalation study revealed that pharmacokinetic profiles and parameters for ciclesonide and its active metabolite *des*-CIC were similar between the subgroups sex and body weight classes/species (i.e. ponies vs. horses). However, in another repeat dose study, ciclesonide and *des*-CIC accumulated more in female horses and male ponies. For example, at twice daily repeated administration of the dose at 2744 µg/horse over 5 days, the mean accumulation ratio for ciclesonide ranged from 1.33 (males 500-700 kg bw) to 2.55 (females 500-700 kg bw). Ratios higher than 3 were observed for female 979748/16 (200-400 kg bw), male 655174/9 (200-400 kg bw) and female 170992/7 (500-700 kg bw) with a ratio of 3.16, 5.68 and 5.19, respectively. The mean accumulation ratio range for *des*-CIC was from 1.24 (males 200- 400 kg bw) to 1.72 (females 500-700 kg bw). With twice daily repeated administration of the dose at 2744 µg over 5 days, followed by 5 days of once daily administration at 4116 µg, the mean accumulation ratio for ciclesonide ranged from 0.812 (males 500-700 kg bw) to 1.28 (males 200-400 kg bw). The mean accumulation ratio range for *des*-CIC was from 0.670 (males 500-700 kg bw) to 1.18 (females 200-400 kg bw).

Metabolism

In vitro studies:

In vitro studies showed that ciclesonide is very rapidly bio-transformed in the liver of rats and dogs producing several active and inactive metabolites. In rat liver there is a marked sex difference in the formation of the main metabolite. 22S-ciclesonide was bio-transformed more rapidly in rat liver, dog liver and mouse skin. For ciclesonide and its metabolite, a direct phase II reaction occurred following cleavage by esterase(s). *In vitro* metabolism of ciclesonide in the presence of rat, dog and human liver microsomes showed no gross interspecies differences with the formation of at least 3 metabolites, the major one being formed by de-esterification of ciclesonide. M2, the 6-hydroxy derivative of M1, and M3, the 23 or 24 hydroxy derivative of M1, were detected in all three species, while M7 was formed only with rat and human microsomes. Metabolite M5 was produced only with human microsomes.

An *in vitro* study using radio-labelled ciclesonide, found the distribution of the radioactivity differed markedly between human lung and liver tissue slices, with approximately 7.2 fold more radioactivity present at the end of the experiment within the lung tissue compared to the liver tissue on dry weight basis. Ciclesonide was hydrolysed into the active principle, *des*-CIC, in precision-cut lung slices. Further steps of biotransformation occurred within the lung, resulting in formation of more lipophilic metabolites, of the M4 family representing more than 45% of total metabolite formation. The oleate of *des*-CIC was the major metabolite of the M4-family. Furthermore, an *in vitro* metabolism study of ciclesonide in the rat lung using precision-cut lung slices showed that ciclesonide is reversibly conjugated at its C21-hydroxyl group with fatty acids. In the liver, ciclesonide is metabolised to inactive polar compounds.

From *in vitro* studies on horse liver slices, 33 different metabolites were detected. The three major metabolites were identified by LC-MS/MS as *des*-CIC and two isomers of hydroxycyclohexane *des*-CIC. Three minor metabolites were also identified as: Dihydroxycyclohexane *des*-CIC Isomer of hydroxycyclohexane *des*-CIC,Hydroxysteroid *des*-CIC.

These metabolites are comparable to those identified in other animal species. With the exception of studies reported under 'Depletion of residues', no studies were performed on horse samples to investigate lung characteristics of ciclesonide (*e.g.* retention within lung tissue, or biotransformation of ciclesonide in lung tissue).

Excretion

A radioactive [^{14}C]-ciclesonide study in dogs demonstrated that elimination of total radioactivity was characterized by a biphasic decline with a mean terminal half-life of 17 hours following intravenous administration of 0.1 mg/kg bw, and 14 hours following oral administration of 1 mg/kg bw. Faecal excretion accounted for 86% after intravenous dosing and 80% after oral dosing. Systemic clearance following intravenous administration was comparable to hepatic blood flow. Where calculable, mean elimination half-lives were typically approximately 3 hours and remained consistent with increasing dose levels.

In rats, following administration, radioactive [^{14}C]-ciclesonide high levels in kidneys were found and low recoveries via urine suggested a tubular reabsorption of radioactivity. High concentrations of radioactivity in liver after intravenous administration reflected a pronounced biliary excretion of compound-related material. The disappearance of radioactivity from rat blood was slower than that from plasma, indicating an association of radioactivity with red blood cells.

In horses, two studies revealed that ciclesonide demonstrated the t_{half} of ciclesonide was approximately 1.4 h and 2.6 h following inhalation doses of 2700 µg/horse and 4050 µg/horse, respectively, whereas

des-CIC had a slightly longer elimination phase ranging from 1.92 hour to 3.18 hour, respectively. In another study, an increase of the elimination phase was observed for ciclesonide after the repeated dose administration with a longer half-life that represented about 2-fold the half-life of the single dose. The same trend of the increase of half-life with the repeated dose administration was observed for *des*-CIC, but, was lower than ciclesonide. Following intravenous administration, the elimination phase was almost similar between ciclesonide and *des*-CIC, with an absolute harmonic mean of 11 hours. Urine concentrations of ciclesonide and its active metabolite *des*-CIC were below the LLOQ (20 and 50 pg/ml, respectively) 24 hours and 48 hours after repeated daily dosing at 2744 µg/horse twice a day for five days followed by repeated daily dosing at 4116 µg/horse once a day for five days.

Toxicological studies

The safety of ciclesonide is covered by several studies. Ciclesonide was orally dosed repeatedly in four studies involving rats and dogs ranging in dosing length from four weeks to 12 months.

Four inhalation studies were provided that were performed in rats and dogs dosed for either two weeks or four weeks.

A target animal safety study was provided based on dosing horses via inhalation for 30 days.

Reproduction studies conducted in rats and rabbits dosed orally were provided.

Both *in vitro* and *in vivo* genotoxicity studies were provided.

The carcinogenicity of ciclesonide was explored in a two year oral dosing study in mice as well as a two year inhalation rat study.

The active substance, ciclesonide, has been assessed by the CVMP in the context of the establishment of MRLs for horses.

Single dose toxicity

No single dose studies were conducted by the applicant.

Single dose toxicity information is gained from studies conducted in connection to the application for a human medicinal product, containing the same active substance. Studies are reported in mice and rats with oral and intraperitoneal administration. A minimum lethal dose could only be determined for the intraperitoneal administration; 200 mg/kg bw. Maximum doses given orally were 2000 mg/kg bw and the findings included atrophy of the thymus, spleen and adrenal glands. This suggests that ciclesonide possesses low acute toxicity.

Furthermore, the inhalation route offers low systemic exposure. In addition, the dosing characteristics of the inhaler prevents the target animal and user from accidentally receiving an acute overdose.

Repeat dose toxicity

4-week oral repeat-dose study in rats

In a GLP compliant study involving 20 Sprague-Dawley rats (equal numbers of both genders) were dosed (ciclesonide in a polyethylene glycol 400 solution) via gavage once daily (control, 0.1, 0.45, 2.0 mg/kg bw/day) for four weeks. Major findings were related to the high-dose group, including reduced food intake, blood cell count/biochemistry changes, reduced oestrus events, atrophy of adrenal cortex, thymus and skin, depletion of lymphocytes in the mesenteric lymph nodes, bone marrow suppression and venous wall thickening of the heart. Mammary gland tissue activation in males and tibial hyperostosis in females were also noted.

All findings were reversed after four weeks except the mammary gland tissue activation and skin atrophy in males. Ophthalmoscopy, electrocardiogram, and urinalysis revealed no substance-related findings. The NOAEL was set at the lowest dosing 0.1 mg/kg bw/day noting that increased red blood cells, haemoglobin, haematocrit and reduced reticulocytes were statistically significant in the female group.

6-month oral repeat-dose study in rats

In a GLP study involving Sprague-Dawley rats (20 males and 20 females for each dose level, except the control group and 1.6 mg/kg bw/day group were eight males and eight females) were dosed via gavage once daily (controls, 0.08, 0.36, 1.6 mg/kg bw/day) for six months with a recovery period of four weeks. Major findings were related to the high-dose group, including reduced food intake, haematology/biochemistry changes, as well as atrophy of thymus and adrenal cortex. These were not fully recovered in the males after 4 weeks recovery, except the blood changes. The NOAEL was set at the lowest dosed group 0.08 mg/kg bw/day, perceiving the following events as being of no biological relevance: reversible decreased weight of spleen and adrenal glands, transient increase of alanine aminotransferase in the female group and transient reduced water consumption and mean corpuscular volume in the male group.

4-week oral repeat-dose study in dogs

This was a GLP study in which six dogs (3 females, 3 males) at every dose level were dosed via capsules once daily (control, 0.01, 0.04, 0.4 mg/kg bw/day) for four weeks with a recovery period of another four weeks for two male and two female dogs in the high dose group. The major findings were related to the high-dose group, including weight loss, dose-dependent serum cortisol suppression, moderate atrophy of the adrenal cortex, thymus and lymph node depletion, and mild lymphocytic interstitial infiltration and inflammatory reaction in the lungs. Behaviour, clinical observations, physical examination, ophthalmoscopy, and electrocardiogram revealed no substance-related findings. Haematology and clinical chemistry revealed no statistically significant or biologically relevant changes as compared to controls. The NOAEL was set at the lowest dosed group 0.01 mg/kg bw/day.

12-month oral repeat-dose study in dogs

This was a GLP study involving ten dogs (5 females, 5 males) at every dose level dosed with capsules once daily (control, 0.005, 0.03, 0.2 mg/kg bw/day) for 12 months and with a recovery period of four weeks for four animals in the high dose group. Major findings were associated with the high dose group, including mean body weight reduction, moderate cortisol suppression, cortical atrophy of the adrenal cortex, dose-dependent thymus atrophy with cysts, spermiogenic disturbances and epididymides oligospermia, atrophy of the ovaries, and keratinization of the vaginal epithelium.

The LOAEL was established at 0.005 mg/kg bw/day with one male in this group showing slight thymus atrophy.

2-week inhalation dose range finding study in rats

This was a non-GLP study involving groups of six male and six female rats dosed via nose-only inhalation once daily for 60 min (vehicle 1, vehicle 2, vehicle 3, 0.5, 1.7, 5.3 mg/kg bw/day). Ciclesonide was dosed in an ethanolic solution. Major findings were dose-related body weight reduction in the male high dose group and all female groups. All ciclesonide groups dosed demonstrated reduced food intake. Dose-dependent increase in red blood cells, haemoglobin, haematocrit, neutrophils, monocytes and decrease in lymphocytes. Dose-related decrease in organ weights of the thymus, spleen and adrenal glands. Dose-dependent lymphoid depletion in the thymus, spleen and mesenteric lymph nodes. No treatment-related changes were observed in animals of the three different ethanolic vehicle-control groups.

4-week inhalation repeat-dose study in rats

This was a GLP study involving groups of 15 male and 15 female Wistar rats dosed via nose-only inhalation once daily for 60 min (control, 0.049, 0.26, 1.6 mg/kg bw/day) with a recovery period of two weeks for 20 animals from the control and 20 from the high dose group (evenly divided by sex). The major findings were seen in the high and mid dose groups including decreased corticosterone serum concentration and increased urine volume, atrophy of thymus, lymphoid depletion of spleen, mesenteric lymph node, and lymphatic tissue of the nasal cavity, corneal epithelium, reduced endochondral ossification of the growth plate of the knee and cellular depletion of haematopoietic cells in the bone marrow. They were completely or incompletely reversible during the recovery period. Metaplasia and hyperplasia of squamous cells at the inner surface of arytenoid cartilage and at the ventral and transitional epithelium of epiglottis, and foam cell accumulation of lungs were noted.

The NOAEL was set at the lowest dose 0.049 mg/kg bw/day.

2-week inhalation repeat-dose study in dogs

This was a non-GLP study involving groups of two female and two male Beagle dogs dosed via inhalation (jet nozzles) once daily for 10 min (vehicle control, 0.19, 0.5, 1.1, 2.3 mg/kg bw/day). Ciclesonide was dosed in an ethanolic solution. High systemic exposure ciclesonide and *des*-CIC was demonstrated. Main findings included salivation during exposure was seen in all groups, including the control. A tendency to reduced body weight gain or reduced body weight was observed in all groups exposed to ciclesonide. Increased glycogen storage in the liver and increase in lipolysis resulted in increased vacuolisation in the adrenal glands. Atrophy of the zona reticularis and a trend towards decreased absolute and relative organ weights of adrenals, spleen, and thymus. No ophthalmoscopic or cardiovascular changes observations.

4-week inhalation repeat-dose study in dogs

This was a GLP study involving groups of three male and three female dogs dosed via inhalation once daily for 10 min (vehicle control, 0.15, 0.48, 1.8 mg/kg bw/day) with a recovery period of three weeks for two male and two female dogs from the control and from the high dose group. Ciclesonide was dosed in an ethanolic solution. The main findings included a dose dependent decrease in body weight and body weight gain, but no test item-related effects on food consumption. Dose dependent decrease in cortisol base level concentration in all dose groups and a dose dependently reduced increase in blood cortisol following ACTH stimulation. Both effects were partially reversible during the recovery period. Atrophy of the adrenal glands and thymus in a dose dependent manner in the mid- and high dose groups. Findings were partly reversible.

The systemic NOAEL was considered to be 0.15 mg/kg bw/day and the local NOAEL (respiratory organ) 1.8 mg/kg bw/day.

Conclusions, repeated toxicity studies

The potential toxic effects of ciclesonide after repeated oral and inhalation administration were assessed in several studies in rats and dogs.

All pivotal studies were conducted by GLP certified institutions under full GLP compliance and in line with respective OECD guidelines, where applicable.

The most common effects seen after repeated administration of ciclesonide were glucocorticosteroid effects on lymphatic organs, haematology parameters, adrenal gland and suppression of serum cortisol. Furthermore, body weight loss/reduced body weight gain was observed often in conjunction with decreased food intake. In addition, increased development of alveolar structures in the mammary

gland were noted in the rats. Hence, target organs have been identified and the toxicological profile of ciclesonide after oral and inhalation administration was comparable in rats and dogs.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

In a GLP fertility study, 28 male and 28 female rats were dosed once daily by gavage with ciclesonide in a polyethylene glycol 400 solution. Male rats were dosed four weeks and the females two weeks prior to mating and during mating time (up to three weeks). Dose levels were control, 0.1, 0.3, 0.9 mg/kg bw/day. Pre-coital interval, copulation rate, and fertility rate were not different between groups. The number of live foetuses as well as the pre- and post-implantive losses, were not influenced by treatment. Sperm characteristics and weight of testes were not influenced during the treatment period.

The NOEL for fertility and early embryo-foetal development was set at the highest dose 0.9 mg/kg bw/day. The NOEL for maternal (female toxicity) was set at 0.3 mg/kg bw/day due to reduced body weight gain. For males, no NOEL was defined since food consumption was significantly reduced also in low dose animals during week 2 and 3.

Study of developmental toxicity

Pre- and postnatal development oral study in rats

In a GLP study, pregnant/lactating rats (F0) were dosed from day 6 *post coitum* until day 20 *post partum*. The dose levels were control, 0.1, 0.3, 0.9 mg/kg bw/day with 24 female rats in each group. In total, 24 male pups and 24 female pups (F1) were kept and reared to maturity and paired for assessment of fertility of the F1 generation. During gestation, food consumption was reduced in the high dose group and body weight gain was significantly reduced in the mid- and high dose group. There were no indications of test article-related effects on the maternal reproduction parameters and performance.

The F1 pups experienced significant reductions in mean body weights in the high dose group. All other parameters of the pups - external examination after parturition, gender ratio, developmental indices, behavioural tests, abnormal findings during the lactation and rearing periods, necropsy findings or organ weights - gave no indication of test article-related effects. The F2 foetuses were not affected on gender ratio, body weights or external parameters due to dosing of the F0 dams.

The NOAEL for the F0 and F1 was 0.1 mg/kg bw/day based on reduced body weights. The NOAEL for the reproduction parameters of the F1 was 0.9 mg/kg bw/day.

13 week juvenile inhalation study in rats

GLP study involving 44 female and 44 male Wistar rats dosed with clean air, vehicle control, 8.5/5.5, 26.1/17.1, 73.7/48.9 µg/kg/day at day 10–35 / 35-98 post natum. Inhalation exposure was done oro-nasally for 1 hour/day, 7 days/week from day 10 to day 35 / 98 post natal. The main findings included decreased body weight gain in females from the mid to high dose group and decreased food intake in the high dose groups. RBCs were significantly reduced in all ciclesonide dosed groups as well as decreased plasma proteins (TP, ALB, GLB). High dose group demonstrated significantly increased mammary gland hypertrophy/hyperplasia as well as lymphoid depletion of the thymus.

The NOAEL was set at 5.5 µg/kg bw/day.

Maximum Tolerated Dose oral study in rabbits

Non-GLP study involving non-pregnant female rabbits dosed at 0.1 to 15 mg/kg bw/day in increasing doses over five days. The maximum tolerated dose was set at 15 mg/kg bw/day.

Embryo-foetal development oral study in rats

GLP compliant study involving 21-26 Sprague-Dawley female rats dosed once daily by gavage at dose levels including vehicle control, 0.1, 0.3, 0.9 mg/kg bw/day. Dosing period was from day 6 to 15, after mating. In conclusion, mild maternal toxic effects were seen at 0.3 and 0.9 mg/kg/day (reduction of body weight gain) resulting in a maternal NOEL of 0.1 mg/kg bw/day. No adverse effects on embryo-foetal development were seen corresponding to a foetal NOAEL of 0.9 mg/kg bw/day.

Dose range finding study for an embryo-foetal development oral study in pregnant rabbits

Non-GLP study involving 3 groups of 6 mated New Zealand White rabbits dosed once daily by gavage from gestation day (GD) 6 to 18 at dose levels of 0.3, 1.0, 5.0 mg/kg bw/day. The dosing period covers the time of organogenesis. In conclusion, no malformations and no clear effects were seen at an oral dose of 0.3 mg/kg bw/day which can be considered as the NOAEL for embryo-foetal development.

Embryo-foetal development oral study in pregnant rabbits

GLP study involving four groups of 19, 20, 17 and 18 pregnant New Zealand White rabbits were dosed once daily by gavage from gestation day (GD) 6 to 18 at four dose levels; control vehicle, 0.1, 0.3, 2.0 mg/kg bw/day. The dosing period covers the time of organogenesis.

There were 5, 24, 2 and 9 malformations observed in 2, 4, 2, and 4 litters in the control, 0.1, 0.3 and 2 mg/kg bw/day groups, respectively. Based on the total litter losses of two females, the slightly lower foetal body weights, and the finding of gall bladder absence observed at 2 mg/kg bw/day, the NOAEL for embryo-foetal development was considered to be 0.3 mg/kg bw/day.

Conclusion, reproductive toxicity including developmental toxicity

All pivotal studies were conducted by GLP certified institutions under full GLP compliance and in-line with respective OECD guidelines, where applicable.

The effects of ciclesonide on reproduction were tested in an oral fertility study in rats (Segment I) and an oral pre- and postnatal development study in rats (Segment III). These studies were conducted according to ICH guidelines for the development of ciclesonide as a human product.

Effects on juvenile animals were tested in an inhalation juvenile rat toxicity study.

The reproductive endpoints; pre-coital interval, copulation and fertility rate, number of implantations, pre- and post implantive loss, and number of live foetuses, sperm motility and sperm count were not affected. The NOEL for fertility and early embryo-foetal development was set at 0.9 mg/kg bw/day. The NOEL for maternal (female toxicity) was set at 0.3 mg/kg bw/day. For males, no NOEL was defined since food consumption was significantly reduced also in low dose animals during weeks 2 and 3.

In the oral pre- and postnatal development study in rats (Segment III) there were no indications of test article-related effects on the maternal reproduction parameters. A reduction of food consumption was noted in the F0 dams dosed at 0.9 mg/kg bw/day during the gestation period and during days of the lactation period. The body weight gain was reduced during the gestation period at 0.3 mg/kg bw/day and 0.9 mg/kg bw/day. In the F1 pups, reduced body weights were noted on all recorded days at 0.9 mg/kg bw/day. The NOAEL for the F0 dams and their F1 progeny was

0.1 mg/kg bw/day. With respect to the reproduction parameters of the F1 parent animals, the NOAEL was 0.9 mg/kg bw/day.

The juvenile study exposed rats to ciclesonide by inhalation from day 10 to 98 *post-natum*.

Decreases in body weight gain occurred in the mid-dose females and high dose animals of both genders. Slight changes in haematology were found in the mid and high dose groups in rats of either gender.

Thymus, adrenal gland, spleen, and kidney weights were decreased in the mid and high dose groups. Treatment-related histopathological findings were observed in high dose animals and consisted of minimal lymphoid depletion in the thymus and minimal increased glandular secretion or lobular hypertrophy/hyperplasia of the mammary glands.

The low dose should be considered as the NOAEL in this study, i.e. 8.5 µg/kg bw/day (day 10-35) and 5.5 µg/kg bw/day (day 35-98).

The findings in the juvenile animal toxicity study in rats described above are known corticosteroid effects regardless of whether juvenile or adult animals are used. In the repeated dose toxicity studies in adult rats, comparable findings occurred and the same target organs were identified.

Developmental toxicity was addressed in rats and rabbits (Segment II). In the rat study, the maternal NOAEL was set at of 0.1 mg/kg bw/day. No adverse effects on rat embryofoetal development were seen corresponding to a foetal NOAEL of 0.9 mg/kg bw/day. In rabbits, ciclesonide is known to be teratogenic. The NOAEL for maternal toxicity was considered to be 0.3 mg/kg bw/day, based on the slight effects on food consumption and on body weight change. The NOAEL for embryo-foetal development was considered to be 0.3 mg/kg bw/day based on the total litter losses of two females, the slightly lower foetal body weights, and the finding of gall bladder absence in the higher dose.

Genotoxicity

Five *in vitro* and four *in vivo* studies are provided. All genotoxicity studies were conducted by GLP certified institutions under full GLP compliance and in-line with respective OECD guidelines valid at the time the studies were conducted.

Ciclesonide was negative in gene mutation assays in bacteria (Ames test) and in mammalian cells. It was negative in an *in vitro* chromosomal aberration study and an *in vitro* micronucleus assay. In contrast to that, the *in vivo* micronucleus studies were positive which appears to be a class effect. Similar effects were obtained in a micronucleus *in vivo* study comparing ciclesonide, budesonide, and dexamethasone.

Ciclesonide was subsequently shown not to increase tumour incidence in mouse oral and rat inhalation carcinogenicity studies and from these data it was concluded that its effect on the mouse bone marrow was a consequence of glucocorticoid agonism and did not predict carcinogenic potential. This is supported by the lack of carcinogenic risk in man demonstrated by decades of clinical use of glucocorticoid receptor agonists.

Carcinogenicity

Carcinogenicity oral study in mice

GLP-study conducted to investigate carcinogenic potential of ciclesonide when administered orally by gavage to B6C3F1 mice over a period of 24 months. The test followed OECD GL 451 (valid at the time). Ciclesonide was administered as a solution in polyethylene glycol 400 at doses of untreated

control, vehicle control, 150, 450 and 900 µg/kg bw/day, respectively, to groups of 50 male and 50 female mice. No compound-related mortality was observed. Non-neoplastic findings concerned an increased incidence and/or degree of osteosclerosis (femur, tibia, and sternum) of females receiving 900 or 450 µg/kg/day. Adenoma of the stomach antrum in one male and three females receiving 900 µg/kg/day, and in one male receiving 450 µg/kg bw/day was observed. One male of the 150 µg/kg bw/day group was found to have an adenoma (borderline case to polypoid hyperplasia). The incidence of proliferative lesions in the antral stomach in the 150 µg/kg bw/day males and females were comparable to the controls suggesting a NOAEL of 150 µg/kg bw/day for a potential treatment-related incidence.

Carcinogenicity inhalation study in rats

GLP-study conducted to investigate the possible carcinogenic potential of ciclesonide when administered by inhalation. Five groups of Wistar rats each consisting of 54 males and 56 females were exposed by nose-only inhalation for a minimum period of 732 days (7 days/week, 1 hour/day). The dose levels were clean air (group A), or 14.0/16.2 µg/kg bw/day (group B), 34.9/40.4 µg/kg bw/day (group C), 89.3/103.6 µg/kg bw/day (group D) of ciclesonide (concentration is the mean dose calculated in males/females) and the vehicle (placebo, group E). The test followed ICH Guideline S1B, and the EPA Health Effects Testing Guideline "Oncogenicity". Histopathological evaluation revealed no statistically significant dose-related increases with respect to the number of tumour-bearing animals: The total number of tumours and the organ specific tumour rates in any treatment group as compared with the clean air control group revealed also no statistically significant dose-related increase.

Conclusion, carcinogenicity

Taken together and based on the results of the carcinogenicity studies in mice (oral administration) and rats (administration by inhalation), the high systemic exposure to *des*-CIC (active metabolite of ciclesonide) in the rat study and the lack of a genotoxic potential of ciclesonide, there is no concern in relation to genotoxic-carcinogenic potency of ciclesonide.

Studies of other effects

Skin irritation and skin sensitisation

Two GLP-studies were provided, conducted on guinea-pigs to test both the skin irritation and sensitization properties of ciclesonide dissolved in ethanol 96%. Ciclesonide caused no skin irritating effects. Also, ciclesonide did not show any sensitizing properties in the maximization test in guinea pigs.

A further two GLP-studies were provided to test the antigenic potential of ciclesonide in male guinea pigs. The results of these studies demonstrated that no antigenic potential and no active systemic anaphylactic symptoms were observed by challenge with ciclesonide in any animals sensitized.

No eye-irritation test was performed but human data indicates that adverse events located to the eyes are in relation to systemic exposure (cataract and glaucoma). Regarding the local effect of ethanol on the eye, the ECHA classifies pure ethanol as a medium hazard to the eyes.

Neurotoxicity

No evidence of a neurotoxic potential has been identified in safety pharmacology studies and in repeat-dose toxicity studies. Glucocorticoids do not possess a structural relationship to known neurotoxins. Therefore, no studies for neurotoxicity have been conducted with ciclesonide.

User safety

The applicant has presented a user safety risk assessment identifying hazards based on safety studies conducted in several species exposed to ciclesonide via inhalation, via per oral dosing and via dermal application.

The drug product is administered as an inhalation formulated as a vapour. It is a prescription-only medicine mainly to be administered by the horse owner according to the posology and instructions provided. The main potential route of accidental contact with the product is considered to be via inhalation, but dermal and ocular exposure cannot be ruled out. The estimated worst case exposure scenario is the maximum possible amount inhaled by the user in association with accidental actuations without the nostril adapter attached to the inhaler. Other exposure scenarios such as priming of the inhaler and accumulation during the length of the treatment period have been evaluated.

Accidental oral exposure is considered unlikely.

Information on hazards for the user as a result of ciclesonide exposure is derived from human data. The hazards identified are primarily systemic glucocorticosteroid effects dependent on dose and duration. The most frequently observed adverse reactions experienced in humans treated with ciclesonide are stated in the product information. Marketed human products are approved for children from the age of 12 years (oral inhalation) and from 6 years of age (nasal spray). Warnings concerning accidental exposure of children and potential assistants are addressed in the product information.

When comparing the estimated worst-case amount of drug product inhaled by the user to the lowest NOAEL, derived from a four week dog inhalation study, the margin-of-exposure is 16 which is below the trigger value of 100.

The lowest human therapeutic dose (inhaled orally) is 40 µg/person/day. In case the nostril adaptor is detached from the handle and an actuation takes place (worst case scenario), the amount of ciclesonide inhaled is up to 178 µg/person. To account for individual variations a MOE (margin of exposure) of 10 is deemed as a reasonable factor to apply. The adverse reactions related to glucocorticosteroids are dose and duration dependent and a single dose of 800 µg/person does not provoke any measurable effects; however, since the MOE is violated, the user is involuntarily exposed and does not benefit from the exposure, the risk must be mitigated by the user wearing an aerosol filtering mask during administration.

No adverse effects on embryo-foetal development in rats were seen corresponding to a foetal NOAEL of 900 µg/kg/day. Skeletal malformations and cleft palate were observed in foetuses of rabbits dosed 1000 and 5000 µg/kg/day with the active substance in a dose range finding study. The NOAEL for an embryo-foetal development study in rabbits was considered to be 300 µg/kg/day based on the total litter losses of two females, the slightly lower foetal body weights, and the absence of gall bladder observed at 2000 µg/kg/day.

Based on the margin of exposure being just above 100 (101) when applying the worst-case inhalation scenario (2.97 µg/kg/day) to the embryo-foetal NOAEL and the seriousness of the potential toxic effects on the foetus, pregnant women should not administer the product. Information for pregnant users based on the human product SPC is included in the product information.

The solvent used is ethanol which has been assessed by ECHA and a Derived-No-Effect-Level for the inhalation route has been established. The margin of exposure calculated for ethanol must be based on the most sensitive target organ. Hence, the Derived No Effect Level (DNEL) published by the German MAK commission on teratogenicity applies (380 mg/m³). The potential worst-case exposure to ethanol by inhalation does not represent a risk to pregnant women. Ethanol is classified as medium irritant to

the eyes and no dermal hazard is identified for acute or short-term exposure. Advice regarding what to do in the event of eye exposure is included in the product information.

Dermal sensitisation and irritation studies confirmed that the drug product does not cause any effects in the test animals used. It was considered likely that local effects will not occur as a result of dermal contact with the vapour.

Environmental risk assessment

According to the applicant and according to the decision tree in the VICH guideline GL 6 "Guideline on Environmental Impact Assessment (EIA) for Veterinary Medicinal Products - Phase I" (CVMP/VICH/592/98-FINAL) [1], the assessment for ciclesonide 30 mg/ml ends in Phase I. No risks to the environment were identified and consequently no precautionary measures are required.

It is agreed that in principle a Phase II ERA is not needed for this product since it is used for individual treatment of horses, being considered minor species within the European Union, which will lead to limited environmental exposure. This is further supported by the fact that the active substance, ciclesonide, and its active metabolite *des*-ciclesonide are excreted in very low quantity from treated animals, as the concentration in urine is below the lower limit of quantification and detection (20 and 50 pg/ml, respectively) already 24 hours post medication.

The cartridge contains considerably more of the formulation than needed for one course of treatment and the inhaler is intended for use as a single treatment course before being discarded. As significant amounts of ciclesonide solution will still be present in the inhaler after finishing the treatment course, it is stated in the product summary that this should be taken into account at disposal so the horse owner does not discard the used inhaler in the plastic waste system, which the owner could otherwise consider prudent for an empty plastic inhaler.

Residues documentation

MRLs

The Committee for Medicinal Products for Veterinary Use has recommended the inclusion of ciclesonide in Equidae in Table 1 (Allowed substances) of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Ciclesonide	The sum of ciclesonide and desisobutyryl-ciclesonide, measured as desisobutyryl-ciclesonide after hydrolysis of ciclesonide to desisobutyryl-ciclesonide	*Equidae*	0.6 µg/kg 4 µg/kg 0.6 µg/kg 0.6 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Corticoides / Glucocorticoides

The excipients listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are

considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Analytical method

Two methods were used for the determination of the marker residue in horse tissues. One method was used for the determination in muscle, liver, and kidney, while another method was used for the determination in fat. The methods were described in an internationally recognised format and validated in accordance with VICH Guideline 49. The limit of quantification for the marker residue was 0.3 µg/kg in all edible tissues.

The marker residue is the sum of ciclesonide and desisobutyryl-ciclesonide, measured as desisobutyryl-ciclesonide after hydrolysis of ciclesonide to desisobutyryl-ciclesonide and a validated analytical method is available indicating that residues in edible tissues can be adequately monitored.

The relevant European Reference Laboratory (EURL) has reviewed the analytical method and is in agreement with the above assessment.

Residue studies

See Pharmacokinetics section under Safety, above.

Depletion of residues

The applicant has performed a GLP study to establish residue depletion in the target species. Sixteen horses (8 males and 8 females, body weight 335 to 500 kg) were treated according to the SPC treatment plan. After the prescribed 10 days treatment period, groups of four horses were euthanized at 12 hours, 3 days, 6 days, and 9 days post final administration (group 1, 2, 3 and 4, respectively). Samples of liver, kidney, fat, loin muscle and lung were harvested and analysed for desisobutyryl-ciclesonide and the metabolites M3-2 and M3-4 using a MC-MS/MS method.

Results show that all 16 horses received exactly 140 actuations, but that in one instance in a single horse there was a slight drug loss during the first two actuations.

The dosing applied in the residue study is according to the proposed dosing schedules and is to be regarded as the worst-case scenario. The dosing is regardless of the body weight of the horse but depletion is according to residue data not correlated to the weight of the horse.

The total residues were determined in non-radiolabel studies and estimated on the basis of the sum of measured parent and metabolites. Considering the uncertainties in this estimation due to the limited number of metabolites measured, and the relatively high LOQ of the analytical method, a conservative approach was used to establish the ratio of marker to total residues. The ratio of marker to total residues was set to 0.5 for muscle and fat, 0.15 for liver, and 0.25 for kidney based on mean residue levels seen across the first three time points.

Residues of desisobutyryl-ciclesonide were below the LOQ in liver specimens from all 4 groups. Residues in kidney specimens from group 1 ranged from 0.35 – 0.77 µg/kg and were below the LOQ in kidney specimens from all other groups. Residues in muscle were <0.3 – 0.76 µg/kg for specimens from group 1, <0.3 – 0.38 µg/kg for specimens from group 2 and were below the LOQ in specimens from groups 3 and 4. Residues in fat were above the LOQ in 15 of 16 specimens analysed and ranged from <0.3 – 33.3 µg/kg. All samples were below the LOQ with regard to M3-2 and M3-4.

These results showed a rapid elimination of desisobutyryl-ciclesonide in liver, kidney, and muscle tissue. Quantifiable concentrations remained during the study period in fat tissue but the data showed a progressive decline in concentration with time.

Withdrawal periods

The MRL value and withdrawal period is based on the tissue residue study presented above.

A withdrawal period of 17.89 days was calculated using the EMA Software Applications for the calculation of the withdrawal period. Although some deviations from the test assumptions were seen, the resulting withdrawal period of 17.89 days is most likely the best conservative estimate. At the last sampling point, 9 days after end of treatment, all residue values were below the MRL.

The applicant proposed a withdrawal period of 18 days for meat and offal, which was accepted by the CVMP. The withdrawal period is based on the edible tissue with the slowest depletion i.e. fat. The product is not intended to be used in horses producing milk for human consumption.

Overall conclusions on the safety documentation

***Pharmacodynamics**:*

No pharmacodynamics studies conducted in horses were provided. In laboratory animals, it was shown that ciclesonide and its main metabolite, *des*-CIC, have potent local anti-inflammatory activity in the lung.

The pharmacological ADI assessment was based on rats and the measurement of tyrosine aminotransferase activity. Ciclesonide administered via the oral route induced a statistically significant increase in tyrosine aminotransferase activity at the top dose of 540 µg/kg bw.

Pharmacokinetics:

Inhalation doses in horses demonstrated less predictable pharmacokinetics than in other species. Plasma exposure for ciclesonide and *des*-CIC in terms of C_{max} and AUC_{last} increased with the dose.

Two horse studies showed that ciclesonide was rapidly absorbed after inhalation administration with a median T_{max} occurring 5 min after the last actuation and rapidly converted to its active metabolite *des*-CIC, as demonstrated by concentrations found already at the first sampling time. The absolute systemic bioavailability of ciclesonide was low and no higher than 17 % when dosed 4.116 µg (day 6-10 of treatment). Fat had the highest level of residues among all tissues.

In vitro studies showed metabolites in horse liver tissue comparable to those identified in other animal species. No studies were performed on horse samples to investigate lung characteristics of ciclesonide (e.g. retention within lung tissue, or biotransformation of ciclesonide in lung tissue).

In horses, two studies revealed the half-life of ciclesonide was approximately 1.4 hours and 2.6 hours following inhalation doses of 2700 µg and 4050 µg/horse, respectively, whereas *des*-CIC had a slightly longer elimination phase ranging from 1.92 hours to 3.18 hours, respectively. Following intravenous administration, the elimination phase was almost similar between ciclesonide and *des*-CIC.

Toxicity studies

The repeat dose studies consisted of oral studies ranging from four weeks to twelve months of dosing rats or dogs and inhalation studies with the duration of two or four weeks dosing rats and dogs.

The major findings in the toxicology studies can be summarized into local effects and systemic effects.

The systemic effects are general glucocorticosteroid effects such as atrophy of adrenal cortex, spleen and thymus, lymphoid depletion in the thymus, spleen and mesenteric lymph nodes, suppression of serum cortisol, atrophy of the skin, changes in erythrocytes, lymphocytes, neutrophils and differential blood cell counts.

The findings appear to be dose dependent as the atrophy of thymus, spleen and adrenal glands can be seen after a single very high doses (2000 mg/kg per oral, rat) but also time dependent since the same findings occur at 1.4 mg/kg, *per os*, in rats after six months of dosing.

The weight loss observed in all studies deviates from the weight gain typically observed in glucocorticosteroid treated individuals. Cataract, glaucoma, increased blood pressure and tachycardia, frequently observed when dosing glucocorticosteroids, was not identified.

The local effects when dosing the drug product as inhalation are atrophy of lymphatic tissue of the nasal cavity, epiphora, metaplasia and hyperplasia of squamous cells at the inner surface of arytenoid cartilage and at the ventral and transitional epithelium of epiglottis and foam cell accumulation of the lungs.

Ciclesonide is well tolerated in humans as inhalation doses of 800 µg/day for seven days (marketed therapeutic dose is 40-640 µg/day) or as a nasal spray dosing 200 µg/day.

The most sensitive parameters and hence those with relevance for setting the NOAELs appears to be based on weight reduction, cortisol suppression and atrophy of the adrenal cortex and thymus.

In *in vivo* mice studies ciclesonide produced micronucleus in erythrocytes in a dose and time dependent manner. A clastogenic potential but no mutagenic potential is indicated. This effect is explained as a class effect of glucocorticosteroids either because they enhance erythropoiesis or by unknown effects on cellular function.

A two year orally dosed mice carcinogenicity study and a two year inhalation rat carcinogenicity study did not indicate a carcinogenic potential of ciclesonide. However, treatment-related non-neoplastic findings in the antrum of the stomach seen in mouse, cannot be excluded as treatment-related.

Four reproduction studies covering fertility, pre- and postnatal development and embryo-foetal development concluded that ciclesonide is teratogenic in rabbits.

The solvent ethanol, which constitutes 96% of the formulation, is classified as a medium eye irritant when pure and it might cause the squamous metaplasia of the laryngeal epithelium, foamy cell accumulation and granuloma in the lungs and nasal discharge, since these findings are observed across all dose groups.

Overview of toxicity findings:

Results of pivotal toxicity studies			
Study type	**Tested species/test system**	**Result**	**Comments**
Single toxicity	Mouse/i.p. Rat/i.p. Rat/i.p.	Mortalities were only observed when ciclesonide was given by the i.p. route. Oral doses of 2000 mg/kg were not lethal in mice or rats. The major findings were atrophy of thymus, spleen, and adrenal gland.	
Repeat dose toxicity	Rat/inh. Dog/inh.	NOAEL 0.049 µg/kg bw/day NOAEL 0.15 µg/kg/ bw/day	4 weeks dosing

Results of pivotal toxicity studies			
Reproduction toxicity	Rat/p.o. fertility and pre- and post natal	NOAEL 0.9 µg/kg bw/day	
Developmental toxicity	Rabbit/p.o. embryo-foetal	NOAEL 0.3 µg/kg bw/day	Teratogenic at higher doses
Genotoxicity	Mouse/p.o.	Increased micronuclei	Regarded as glucocorticosteroid class effect. Clastogenic not mutagenic potential
Carcinogenicity	Mouse/p.o. Rat/inh.	NOAEL 150 µg/kg bw/day No carcinogenicity indicated	Adenomas in antrum, drug relation cannot be excluded 2 years dosing both studies
Other effects			

User safety

To estimate the amount the user could be accidentally exposed to, a laboratory study on the amount of molecules inhaled in two different scenarios has been conducted. The estimated total exposure of the user compared to the lowest NOAEL is below a MOE of 100. As a risk mitigation measure an aerosol protective mask must be worn by the user during administration. The hazards of drug exposure have been identified in animal studies and from human data. A possible risk for pregnant users was identified, and advice for pregnant women is included in the product information.

Residues

A GLP compliant tissue residue study was performed. The study showed a fast elimination in liver, kidney and muscle, whereas the elimination in fat was slower.

A withdrawal period of 18 days for meat and offal is recommended.

Environmental risk assessment

It is accepted that the Environmental Risk Assessment could end in Phase I. With regard to potential contamination from residual unused contents, the product summary states that this should be taken into account at disposal.

Part 4 – Efficacy

Pharmacodynamics

See part 3.

Pharmacokinetics

See part 3.

Dose justification

The proposed dose is 16 actuations per day (administered as 8 actuations twice daily, approximately 12 hours apart) for 5 days, followed by 12 actuations once daily over another 5 days. These doses correspond to approximately 2 x 2744 µg (5488 µg) and 1 x 4116 µg ciclesonide, respectively.

For the equine doses proposed by the applicant, there is no dedicated investigation of a dose-response relationship according to body weight. The equine pharmacokinetic studies provided showed a trend towards increased plasma exposure, above the dose proportionality observed. Body weight was not investigated as an explanatory variable for this trend.

Clinical studies showed an improvement of clinical respiratory symptoms in horses administered ciclesonide with the highest proposed doses.

Three non-GLP exploratory efficacy studies using mouldy hay challenge equine experimental models on horses with Recurrent Airway Obstructions (RAO) were conducted, investigating doses up to 2700 µg per inhalation twice daily (BID) and 3712,5 µug once daily (SID), and for 14 days (n=8). Treatments were compared against a positive control (oral dexamethasone) or a negative control (inhalation of the vehicle only). The results from the studies are summarised below (under dose finding studies). However, due to limitations in the disease model and study design, the studies are considered as proof-of-concept only. The proposed dosing regimen was further investigated in both a pilot and a pivotal clinical field trial.

Dose finding studies

The effect of ciclesonide administered by inhalation (covering a dose range from 450 µg to 2700 µg BID) on indices of lung function (transpulmonary pressure (ΔPL), lung resistance (RL) and lung elasticity (EL)) and on clinical score (breathing effort score or weighted clinical scoring system previously adopted by Tesarowski et al.) was investigated in two studies conducted in horses following a mouldy hay challenge. In addition, the effect of a once daily dose of 3712.5 µg inhaled ciclesonide on lung function variables and weighted clinical score was compared to 2700 µg and placebo BID in one study. Systemic effects were assessed by monitoring haematological parameters such as Complete blood counts (CBC's) and serum cortisol concentrations.

Administration of ciclesonide by inhalation at doses of 450 µg and 900 µg failed to significantly alter lung function indices over time. An inhaled dose of ciclesonide 1800 µg BID significantly improved both ΔPL and EL but not RL on days 7 and 14 of treatment, compared to baseline. The positive control oral dexamethasone significantly altered ΔPL, RL and EL values at all assessment time points compared to baseline. At day 14, dexamethasone-treated horses had significantly lower values of RL than horses treated with 1800 µg ciclesonide. Inhalation doses of 2700 µg ciclesonide BID using the pilot inhaler with nozzle B (The relevant difference between nozzle A and B is the duration of aerosol generation per actuation (A: 1.5 sec/actuation vs. B:1.0 sec/actuation)) had an equivalent efficacy to oral dexamethasone in reducing clinical scores on D7, 14 and 21 as compared to baseline.

The administration of 2700 µg ciclesonide BID (5400 µg/day) resulted in improvements of lung function variables and weighted clinical score within the first 7 days, with no further pronounced improvement throughout the second week of administration. According to the applicant, reducing the overall daily ciclesonide dose throughout the second treatment week by switching from twice (BID) to once daily (SID) administration (from 5400 µg/day to 3712.5 µg/day) showed benefits with respect to owner compliance while improvement of clinical scores were still seen.

Serum cortisol concentrations were not significantly altered in the groups receiving any of the ciclesonide doses. In contrast, dexamethasone treatment significantly reduced serum cortisol values compared to both day 0 and ciclesonide at equivalent time points ($p<0.0001$). Compared with day

0, dexamethasone also resulted in a significant (p=0.002) reduction in lymphocyte counts at day 14 of treatment. Systemic effects of inhaled ciclesonide was significantly less pronounced, as compared to oral dexamethasone (based on systemic cortisol values and CBC/serum chemistry results).

Conclusion on dose justification and dose finding:

Three non-GLP exploratory efficacy studies were conducted involving mouldy hay challenged equine experimental models of Recurrent Airway Obstructions (RAO), investigating doses of 450 µg, 900 µg, 1687.5 µg, 1800 µg and 2700 µg per inhalation BID, as well as 3712.5 µg per inhalation SID for 14 days (n=8). Treatments were compared against a positive control (oral dexamethasone) or a negative control (inhalation of the vehicle only). The results of these studies lead to a proposed dosing schedule of 5 days BID, followed by 5 days at a higher dose SID; this dosing regimen was taken further to be confirmed under field conditions.

Inhaler

For all dose characterization studies detailed above, study medication (with the exception of dexamethasone) was always administered with a pilot inhaler (non-pressurized metered dose inhaler). The formulation of the ciclesonide inhalation solution used in the pilot inhaler was identical to the formulation of the final product intended for marketing. The performance of this pilot inhaler was compared with the final inhaler (used in the pivotal studies) by means of a bridging study. This study demonstrated equivalence of performance data derived from both, the pilot and final inhaler.

Target animal tolerance

One pivotal GLP-compliant study was performed to evaluate the systemic and local tolerance of ciclesonide delivered per inhalation via the specific equine inhaler. The study was a blinded, randomized, placebo-controlled laboratory study with a parallel group design. Twenty-four horses (12 male,12 female) with a maximum body weight of 550 kg, and eight horses (4 male, 4 female) with a maximum body weight of 300 kg were enrolled into one of four treatment groups for inhalation treatment with either a placebo/vehicle or 1x, 2x and 3x the recommended therapeutic dose (RTD) for 30 days (1xRTD: 5488 µg Day 0-14, 4116 µg Day 15-29; 2xRTD: 10976 µg Day 0-14, 8232 µg Day 15-29; 3xRTD: 16464 µg Day 0-14, 12348 µg Day 15-29).

The study was not conducted in full compliance with the Guideline on target animal safety for veterinary pharmaceutical products (EMEA/CVMP/VICH/393388/2006, VICH Topic GL43) as the doses deviated from the recommended 1x, 3x and 5x RTD schedule. The reason for omitting the 5x dose was that it was difficult to ensure compliance when dosing the horses with the inhaler due to the high number of required actuations for a 5x dosing. This is acceptable since overdosing is not impending due to the administration form.

Administration of the 2x RTD once daily (SID) dose and the twice daily (BID) 3x RTD dose required a total of 24 actuations, and the 3x RTD (SID) dose required a total administration of 36 actuations. A "split dosing" approach was necessary in light of the predetermined limit of 16 actuations per dosing period, in order to maintain tolerance by the horses towards the inhaler. Administration of these doses was therefore split over two (2x RTD, SID), four (3x RTD, BID) and three (3x RTD, SID) occasions per day. In the majority of cases, the interval between the first and the last actuation did not exceed 1-2 hours.

Overall, inhaled ciclesonide administered via a specific equine inhaler up to 3x RTD for 30 consecutive days was well-tolerated. However, some minor and questionable findings were reported. A trend towards decreasing cortisol levels compared to baseline was seen in the highest dose group, although not statistically significant. Some haematology findings consistent with a typical glucocorticoid-

mediated response that results in neutrophilia, lymphopenia and an overall increase in leucocyte numbers were reported but remained within reference range and were dose independent. Due to the lack of significance, these findings are not mentioned in the SPC.

Moreover, weight loss (although not statistically significant and clinically relevant) was reported in all treated groups compared to the control group when comparing body weight at D29 to baseline. This did not seem to be correlated to decreased food consumption, as in the rat and dog studies in which body weight loss was one of the main findings. Similar weight losses were recorded in the pilot field trial, where 12 horses in the group treated with ciclesonide lost weight during the trial period (>10 kg, from 11-53 kg, mean = 24 kg). The body weight measurement was estimated and not confirmed by a calibrated weigh scale hence, the findings are subject to uncertainty. Due to the lack of significance, these findings are not mentioned in the SPC.

Regarding local tolerance, low-grade epithelial changes of the epiglottis were findings from endoscopy and are possibly related to aerosol inhalation and not the active substance. However, these findings were minor and not considered to be clinically relevant. Epiphora was observed in a dose-finding study in association with inhalation of the product but is not reported in any other clinical study.

In addition, abnormal nasal discharge seems to have increased following ciclesonide treatment as compared to placebo/vehicle. Cultivation of nasal swabs revealed that treatment may have altered nasal fungal colonization compared to the vehicle control group, but not compared to pre-treatment values. Nasal discharge is listed as an adverse reaction in section 4.6 of the SPC.

In summary, based on the results of this study, it appears that inhaled ciclesonide administered via a specific equine inhaler up to three times the maximum recommended dose for 30 consecutive days is well tolerated.

Clinical studies

Clinical field trials

One GCP pilot field study and one pivotal GCP-compliant field study were performed to demonstrate the clinical efficacy and safety of ciclesonide administered via inhalation according to the applied dosing regimen in horses suffering from Recurrent Airway Obstruction (RAO) and/or Summer Pasture-Associated Recurrent Airway Obstruction (SPAOPD), under field conditions.

Pilot clinical field study

The pilot clinical field study was a GCP-compliant prospective, placebo-controlled, randomised, double-blind, multi-site field study, investigating the efficacy and safety of ciclesonide in horses suffering from RAO and/or SPAOPD, under field conditions, over a period of 10 (±1) days.

The study was conducted in Germany, and involved 70 horses (ITT), both not pre-treated and pre- and concomitantly treated with clenbuterol, (ITT-population:) 33 female, 37 male; mean age: 17.4 years, median weight: 459 kg, various breeds. The per protocol population (PPS) comprised 60 horses. The ratio of IVP to CP was approximately 1:1 with respect to those horses which did not (n=25 vs. n=22) and those which did (n=7 vs. n=6) receive pre- and concomitant treatment with clenbuterol.

Ciclesonide or placebo were administered via the equine inhaler (pilot inhaler with nozzle B). From Day 1 to Day 5, 8 actuations (2744 µg ciclesonide in the IVP or 0 µg ciclesonide in the CP) were administered twice daily. From Day 6 to Day 10 (±1), 12 actuations (4116 µg ciclesonide in the IVP or 0 µg ciclesonide in the CP) were administered once daily in the evening. Clinical examination at Day 1, 5 and 10 (±1) included physical examination, assessment of weighted clinical score (modified from Tesarowski et al, 1996), upper airway endoscopy, Obel lameness score, haematology and

biochemistry, owner assessment (general health, inhaler acceptance), and sampling swabs from upper airway mucosa for detection of fungi and yeast. Due to the exploratory nature of this non-pivotal study, primary and secondary variables were not defined. Animals were considered as treatment failures if the weighted clinical score reduction was less than 20% of the weighted clinical score at the start of the respective time interval. Incidence, severity and causal relationship of adverse events was tabulated and summarized descriptively in the ITT dataset.

No severe adverse event occurred. Seven AEs (IVP/CP – 3/4) related to the mucosa of the left nasal cavity including swab sampling and analysis for fungal/yeast infection. Two AEs (IVP/CP – 1/1) related to bronchi and lung (1 severe dyspnoea, 1 abnormal nasal discharge and mucus in trachea). Two AEs (IVP – 2) related to increase/decrease in blood cortisol levels, and three horses in the CP group showed limb swelling and lameness. Reviewing the body size/estimated body weights of the horses, it was noted that 12 horses in the IVP group lost weight during the trial period (>10 kg, from 11-53 kg, mean =24 kg). This was not seen in any of the horses in the CP group. The body weight measurement was estimated and not confirmed by a calibrated weigh scale hence, the findings are subject to uncertainty. Due to the lack of significance, these findings are not mentioned in the SPC.

Ciclesonide treatment did improve clinical scores, but similar changes were seen in the placebo group as well and differences were not statistically significant. In horses with acute clinical symptoms (<14 days) there was no statistically significant difference in efficacy between the ciclesonide (n=6) and placebo (n=8) groups. Overall, there was no difference between the IVP and CP groups with respect to frequency and types of adverse reactions, apart from weight loss that occurred in 12 horses in the IVP group. The administration of ciclesonide via inhalation according to the applied dosing regimen was generally well tolerated. In conclusion, the results of this study were only supportive of the clinical efficacy and safety of ciclesonide administered via inhalation according to the applied dosing regimen in horses suffering from RAO and/or SPAOPD.

Pivotal clinical field study

The pivotal European GCP-compliant clinical field study was a randomized, double-blinded study of parallel group design including a placebo control group.

The objective and methodology of the pivotal study were similar to that of the pilot clinical field efficacy study, although with the following notable clinical differences:

1. the target population was defined as horses with "moderate to severe clinical symptoms of equine asthma" (weighted clinical scores of 11 or higher) and a duration of the current episode of more than 14 days.
2. modification of one parameter in the weighted clinical score: abdominal lift was re-classified using different descriptors to avoid varying interpretations of "heave line".
3. the exclusion of horses pre- or co-administered clenbuterol.
4. Daily owner journals were not requested detailing comments on the practical use of the final inhaler.

The objective of the pivotal field study was to evaluate the efficacy and safety of ciclesonide in comparison to placebo administered as an inhalation solution in RAO and/or SPAOPD horses under field conditions over a period of 10 (± 1) days. The study was conducted in twenty-four sites located in Germany (16), France (3) and Switzerland (5).

The test product consisted of the final inhaler and formulation: 30 mg/ml ciclesonide for inhalation. The treatment was administered for ten days, with the same dose for all horses independent of their body weight: D 1-5: eight actuations (corresponding to 2744 µg ciclesonide) administered twice daily approximately 12 h apart; D 6-10: 12 actuations (corresponding to 4116 µg ciclesonide) administered once daily approximately 24 h apart.

Two hundred and twenty-four horses (n=224) of various breeds, >200 kg, 83 female & 137 male, mean age = 18.5 years were included in the study.

The inclusion criteria included:

1. Diagnosis of RAO and/or SPAOPD based on
    a) laboured breathing at rest and abdominal lift present;
    b) duration of current episode (e.g. history of coughing, nasal discharge) >14 days;
    c) a medical history of chronicity (chronicity as defined by frequent recurrence, at least two episodes in the past);
    d) an improvement in clinical signs of one of the last episodes following the administration of a bronchodilator, glucocorticoid, and/or change in environment;
    e) age ≥4 years;
2. Body weight >200 kg;
3. Weighted clinical score of ≥11.

The exclusion criteria included:

1. pregnant or lactating mares;
2. suspected systemic infectious diseases (e.g. pneumonia);
3. known upper respiratory tract functional disorders, which interfere with respiration at rest;
4. unable to use the equine inhaler or impetuous temperament of the horse precluding proper administration of the IVP or CP with the equine inhaler.

The primary efficacy variable was the treatment response, assessed using a weighted clinical score (modified from Tesarowski et al, 1996). The treatment response was defined as a reduction in weighted clinical score by at least 30% between D0 and D10 (±1).

The following secondary variables were defined:

1. treatment response defined as a reduction in weighted clinical score by ≥40% between D0 and D10 (±1);
2. treatment response defined as a reduction in weighted clinical score by ≥50% between D0 and D10 (±1);
3. difference in weighted clinical score between D0 and D10 (±1);
4. difference in individual score parameters of weighted clinical score between D0 and D10±1;
5. difference in owner assessment between D0 and D10 (± 1), "Quality of life".

Statistical method for primary analysis: the primary efficacy assessment of the study was to show superiority of the IVP to CP. The null hypothesis was tested for the FAS population using a two-sided Chi square test with alpha=0.05. Risk ratios and risk differences together with 95% confidence intervals were used to quantify the treatment response for the comparison of ciclesonide against placebo. The confirmatory analysis was repeated for the PPS population as sensitivity analyses. Secondary analysis: all secondary variables were compared by treatment group and study visits using appropriate descriptive and graphical statistical analysis methods.

Results

Outcomes for endpoints: for the primary efficacy analysis, a Full Analysis Set (n=220) was used (IVP: n=109, CP: n=111).

A reduction in weighted clinical score of ≥30% between Day 0 and Day 10 was observed in 73.4% of horses treated with ciclesonide vs. 43.2% of placebo treated horses ($p<0.0001$).

Analysis of secondary efficacy variables yielded the following results:

1. re-defining successful treatment response to 40% or 50% improvement in weighted clinical scores still showed a statistically better outcome of ciclesonide treatment vs placebo (p-values: 0.0002 for 40% and 0.0017 for 50%);
2. the mean reduction of the total weighted clinical score from D0-10 was significantly greater in the IVP group than in the CP group (-7.2 vs -3.8, respectively, p<0.0001 (95% CI [-4.3—2.3]);
3. differences in individual score parameters of weighted clinical score and owner assessment of the "improvement in quality of life (QOL)" support the above results.

With regard to the adverse events and protocol deviations, safety analysis was based on the safety data set, including 223 valid cases (IVP n= 110; CP n=113). The systemic and local safety profile of inhaled ciclesonide observed in previous studies was confirmed in this study. No serious adverse event occurred and 24 non-serious adverse events were reported (10.8%). Adverse events were equally distributed amongst the two groups (IVP=11, CP=13). No relevant hematologic effects could be observed.

The total number of adverse events / total number of horses was 11/5 (IVP) and 13/8 (CP):

- twelve AEs (IVP/CP – 7/5) related to blood and lymphatic system. All events in this class were changes in the leucocytes except for two anaemia cases in placebo treated horses;
- three AEs (IVP/CP – 1/2) related to digestive tract, including one case of stomatitis (IVP treated);
- one AE (CP – 1) related to endocrine system;
- one AE (CP – 1) related to eye;
- two AEs (IVP/CP – 1/1) related to musculoskeletal system;
- three AEs (CP – 3) related to respiratory tract;
- two AEs (IVP -2) related to systemic disorders.

Relation to study treatment was always regarded as low or unknown except for cough and tachypnea in two placebo cases.

If major entry criteria were not met, this was classified as major deviation (N=3). Deviations regarding drug administration were classified as major if less than 80% of the total dose was administered according to the fill indicator taking into account the day of last administration of study drug (N=10). Less than eight days treatment time was regarded as major deviation (N=6). Most minor deviations (N=113) affected minor discrepancies (≤20%) of the administered dose according to the fill indicator of the inhaler; most of these were caused by owner non-compliance or difficult attitude of the horse.

Discussion/conclusions

This study demonstrated the improvement of clinical signs following monotherapy with ciclesonide-administered via the final inhaler (relative to both baseline weighted clinical score measurements and placebo), using the intended dosing regimen and final formulation under field conditions. As with the pilot clinical field efficacy study, there was an improvement in weighted clinical score (and QOL score) in the placebo group. Unlike the pilot clinical field efficacy study, this effect could not be attributed to pre - and /or co-administration of clenbuterol. However, it is considered that there is a potential for spontaneous clinical improvements, resulting for instance from temporal alterations in the concentration of airborne antigens.

The safety of inhaled ciclesonide was demonstrated in this study. Out of the 24 reported adverse events, 11 occurred in the ciclesonide treated group; none were considered serious or definitively attributable to the administered drug per se.

In conclusion, the results of this pivotal study support the clinical safety and efficacy of ciclesonide administered via inhalation according to the applied dosing regimen for the alleviation of clinical signs of horses suffering from severe equine asthma (RAO and/or SPAOPD).

Inhaler

Regarding the use of the pilot inhaler, several comments from investigators were noted.

In the pilot field study (using the pilot inhaler), the personnel were exposed to the product while administering it due to leakage from the pilot Equine Inhaler. The leakage originated from the junction between the nasal piece and the chamber, or less commonly, from behind the flag. A second person was always needed to restrain the horse so that the person administering the drug was able to cock the pilot inhaler, which required both hands, between applications. Occasionally, between the morning and the evening treatment, some of the pieces of the pilot inhaler remained wet. This caused problems when administrating the next treatment because the flag remained stuck inside the wall of the air chamber preventing the normal administration of the drug. Due to the issues found with using the pilot inhaler, then the inhaler was re-designed into the final inhaler. There is not an equivalent study design to confirm the practical issues with using the inhaler were resolved with the final inhaler design. In the pivotal field study, horses were selected for compliance by inserting the nostril adapter into the nostril. At the end of the study, the product was collected to assess the total amount of delivered inhaled dose according to the fill indicator and ranked into three categories (100% or more of total dosing regimen; 80-100%; less than 80%). This demonstrated similar number of horses in the ciclesonide (86, 13, 10) and placebo (79, 15, 17) groups for each the three categories, respectively. In conclusion, the final inhaler appeared to deliver 100% or more of the dosing regimen to the majority of horses in the pivotal field study.

As Aservo EquiHaler consists of a novel delivery system, for a new active substance (ciclesonide), and clinical studies undertaken under GCP conditions might not reflect all "real life" situations, the applicant will provide augmented pharmacovigilance reporting in a representative number of horses with severe asthma.

- Veterinarians and horses' owners/users will be surveyed to record their experiences in using the product to complete the 10 day course of dosing. Data collected will include, but is not limited to, the age of horses treated, number of successful daily actuations administered, acceptance/tolerance of the horse for the final inhaler and any other compliance issues. The results of these surveys will be compiled, analysed and submitted together with the 6 month PSUR report. At this point a decision will be taken regarding continuing the augmented pharmacovigilance reporting for further PSUR cycles. Any major or significant findings will be reported in line with timelines for reporting serious adverse reactions.
- All PV investigations will be thorough. Following the report of any adverse reactions, the owners and veterinarians will be contacted. Data collected will include, the history of the case, dose and timing of Aservo EquiHaler, clinical observations, other medications, description and timing of the adverse reactions, any interventions, and outcome/s will be compiled and documented.

The CVMP notes the applicant's proposal to provide educational material to explain the use of the product and enable/encourage veterinarians and horse owners to report experience with administration of the product. The applicant has stated that there will be regular updates to the educational material according to feedback from the field. This was endorsed by the CVMP.

The applicant confirmed that there is additional clinical data being generated to support an application in another territory. The study report will be provided, when available, with the next PSUR submission.

Overall conclusion on efficacy

Tolerance

Ciclesonide was generally well-tolerated systemically at up to the three-fold recommended treatment dose and for up to three times the intended treatment period (30 days in total). The most common adverse reaction seen was nasal discharge, which is mentioned in the SPC.

Although not statistically significant, a trend towards decreasing cortisol levels compared to baseline was seen in the highest dose group in the TAS study. Some of the haematology findings were consistent with a typical glucocorticoid-mediated response that results in neutrophilia, lymphopenia, and an overall increase in leucocyte numbers, but CBC results were within reference limits. Moreover, it appears that some degree of weight loss was seen in all ciclesonide-treated groups at D29 when compared to pre-treatment, and thus a systemic effect of ciclesonide cannot be entirely dismissed.

No fatalities were observed in any of the studies. It was concluded that no severe clinical symptoms in healthy horses occur at dose rates up to three times the recommended dose. Due to practical limitations (acceptance from the horse) with the inhaler, a 5x dose study was not conducted.

Dose justification

For the equine doses proposed by the applicant, there are no dose adjustments according to body weight. Efficacy was assessed by quantitative and semi-quantitative methods (indices of lung function, including transpulmonary pressure (ΔPL), lung resistance (RL) and lung elasticity (EL)) as well as a weighted clinical score adopted from Tesarowski et al. 1996), respectively). Improvement of respiratory signs in ciclesonide treated horses was shown with the highest proposed doses. The studies are considered as proof-of-concept only.

Dose determination

Three non-GLP exploratory efficacy studies in a mouldy hay challenge equine experimental models of Recurrent Airway Obstructions (RAO) were conducted, investigating doses of 450 µg, 900 µg, 1800 µg and 2700 µg per inhalation BID, as well as 3712.5 µg per inhalation SID for 14 days (n=8). Treatments were compared against a positive control (oral dexamethasone) or a negative control (inhalation of the vehicle only). The results of these studies lead to the final proposed dosing schedule that was further investigated in a pilot and pivotal clinical field trials.

The final proposed dose is 16 actuations per day (administered as 8 actuations twice daily, approximately 12 hours apart) for 5 days, followed by 12 actuations once daily over another 5 days. These doses correspond to approximately 2 x 2744 µg (5488 µg) and 1 x 4116 µg ciclesonide, respectively.

Clinical studies

One GCP pilot field study and one pivotal GCP-compliant field study investigated the clinical efficacy and safety of ciclesonide administered via inhalation according to the applied dosing regimen in horses suffering from RAO and/or SPAOPD.

Results from the pivotal clinical field trial showed a higher rate of treatment success in terms of improvement of clinical signs in horses with RAO and SPAOPD treated with ciclesonide at the proposed daily dose (2744 µg BID for 5 days per inhalation followed by 4116 µg ciclesonide SID for another 5 days), when compared to horses treated with placebo. This conclusion is based on the inclusion/exclusion criteria employed in the pivotal clinical trial.

No follow-up data are available from the field studies. The results from the dose finding studies (studies no. 2012053 and 2013074), in which an assessment of the clinical signs and lung function

parameters was performed 7 days after discontinuation of the treatment, may indicate that the duration of effect is limited.

Inhaler

Major practical problems were encountered in the pilot clinical study, related to the pilot inhaler.

Despite "non-tolerance" or "difficult temperament of the horse" being a criterion for exclusion in all studies, problems with compliance of the final inhaler were noted. The final inhaler was not tested in an equivalent study design as the pilot inhaler.

Part 5 – Benefit-risk assessment

Introduction

Aservo EquiHaler, 343 microgram/actuation, is an inhalation solution for horses, containing the active substance ciclesonide. It is presented in one pack size, an inhaler with a pre-inserted cartridge. The cartridge consists of a polyethylene/polypropylene container crimped in an aluminium cylinder.
The cartridge contains sufficient inhalation solution for one treatment course consisting of 140 actuations, corresponding to 10 days treatment plus an additional amount covering priming and potential losses during administration. The inhaler delivers 343 micrograms of ciclesonide per actuation.
The active substance of Aservo EquiHaler, ciclesonide, is novel in veterinary medicine, and is a pro-drug, which following inhalation is converted into the active metabolite, desisobutyryl-ciclesonide (*des*-ciclesonide). *Des*-ciclesonide has anti-inflammatory properties which are exerted through a wide range of inhibitory activities.

The applicant originally applied for the following indication: "For the treatment of horses with moderate to severe clinical signs of equine asthma." The indication approved is "For the alleviation of clinical signs, associated with severe equine asthma (formerly known as Recurrent Airway Obstruction (RAO), and Summer Pasture-Associated Recurrent Airway Obstruction (SPA-RAO))".

Ciclesonide is administered over 10 days, with the same dose for all horses independent of their body weight. The initial (days 1 to 5) dose is 8 actuations (corresponding to 2744 µg ciclesonide) administered twice daily approximately 12 h apart, followed (days 6-10) by 12 actuations (corresponding to 4116 µg ciclesonide) administered once daily approximately 24 h apart.

The proposed withdrawal period (meat and offal) is 18 days. The product is not intended to be used in horses producing milk for human consumption.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

Benefit assessment

Direct therapeutic benefit

The benefit of the Aservo EquiHaler is its efficacy for the alleviation of clinical signs of severe equine asthma (formerly known as Recurrent Airway Obstruction (RAO), and Summer Pasture-Associated Recurrent Airway Obstruction (SPA-RAO)), which was investigated in both laboratory and field studies. Dose finding/determination laboratory studies were non-GLP and the study design of the two GCP field studies did not reflect all types of field conditions. This is reflected in the product literature.

The clinical trials conducted in accordance with GCP demonstrated that the product is efficacious in alleviating clinical signs associated with severe equine asthma.

Additional benefits

The Aservo EquiHaler increases the range of available glucocorticoid treatment possibilities for the reduction of clinical signs associated with severe equine asthma and would thus provide a new treatment possibility for a minor species.

The use of the product in accordance with the proposed dosing regimen appears to be well-tolerated without inducing the systemic effects typically associated with glucocorticoid treatment.

Risk assessment

Quality:

Satisfactory information on development, manufacture and control of the active substance and finished product has been presented.

The results of tests carried out on the finished product indicate consistency and uniformity of important product quality characteristics.

Safety:

Measures to manage the risks identified below are addressed in the risk management section.

Risks for the target animal:

Administration of ciclesonide in accordance with SPC recommendations is generally well-tolerated. Mild and transient adverse effects, such as nasal discharge, were commonly observed.

The safety of ciclesonide in horses was confirmed in a target animal safety study. Systemic changes were observed in some animals administered ciclesonide at 3x the maximum recommended treatment dose, and systemic effects at the recommended dose of inhaled ciclesonide in horses cannot be entirely ruled out based on the results of this study. A trend towards decreasing cortisol levels compared to baseline was seen in the highest dose group. Some of the haematology findings are consistent with a typical glucocorticoid-mediated response that results in neutrophilia, lymphopenia and an overall increase in leucocyte numbers, but remained within normal reference ranges. In addition, a trend towards weight loss was seen in all dose groups, a finding which was significant only in rat and dog studies, regardless of dose. Due to the lack of significance, these findings are not mentioned in the SPC. Ciclesonide is teratogenic to rabbits.

Risk for the user:

The user safety assessment has been conducted in accordance with the relevant CVMP guidance. Accidental inhalation poses a potential risk of systemic and developmental effects that requires users to wear an aerosol protective mask and administer the product in well-ventilated surroundings to mitigate the risks. Other possible harmful effects identified are related to eyes, nasal mucosa and upper respiratory tract and are also addressed with appropriate risk management measures. Therefore, Aservo Equihaler active substance is not expected to pose a risk for the user when used according to the SPC.

Risk for the environment:

Aservo EquiHaler is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Consumer risks:

The consumer safety assessment has been conducted in accordance with the relevant CVMP guidance. Based on the information provided, the CVMP concluded that consumer safety, due to potential exposure of the active substance, for this product is acceptable when used according to the SPC recommendations. A withdrawal period of 18 days is established. The product is not authorised for use in animals producing milk for human consumption.

Special risks (Inhaler):

Concerns have been raised for horses that do not tolerate the inhaler. The final inhaler was not tested in an equivalent study design as the pilot inhaler, and non-tolerant horses were excluded in the pivotal clinical trial.

Risk management or mitigation measures

Information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user and consumer, and to provide advice on how to reduce these risks.

Evaluation of the benefit-risk balance

The applicant applied for the following indication "For the treatment of horses with moderate to severe clinical signs of equine asthma". The product has been shown to be efficacious for the alleviation of clinical signs associated with one type of equine asthma condition, and the CVMP agreed to the following indication(s*):* 'For the alleviation of clinical signs of severe equine asthma (formerly known as Recurrent Airway Obstruction (RAO), and Summer Pasture-Associated Recurrent Airway Obstruction (SPA-RAO))'.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product has a satisfactory safety and efficacy in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Precautionary measures, including a withdrawal period, have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is considered positive for the product and the indication agreed upon. There remain concerns about the final inhaler that is essential for dosing horses. The concerns are whether product information and educational material can result in the selection of appropriate candidates with severe asthmatic horses that can be dosed reliably, according to the SPC, for 10 days, and safely by the person administering the product.

Conclusion on benefit-risk balance

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Aservo EquiHaler is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC.

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned veterinary medicinal product.

In addition, the CVMP has recommended conditions for marketing authorisation and product information.

This product is a new active substance administered via an integrated novel inhaler. To address some remaining concerns regarding the acceptance of the inhaler and the compliance of both horse owners and horses in using the final inhaler, the applicant has committed to provide augmented pharmacovigilance reporting in a representative number of horses from the target population.