15 January 2014
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Equisolon (EMEA/V/C/002382/0000)

International non-proprietary name: prednisolone

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

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Introduction

On 26 September 2012, the applicant Le Vet B.V. submitted an application for marketing authorisation to the European Medicines Agency (the Agency) for Equisolon, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 July 2010 as the applicant showed that the product would be in the interests of animal health at Community level (Article 3(2)(b) of Regulation (EC) No 726/2004). This decision took into account the equine condition, recurrent airway obstruction, to be treated and the advantages that this product formulation appears to offer, particularly in terms of ease of administration. The rapporteur appointed was C. Friis and co-rapporteur H. K. Ostensen.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

The applicant is registered as a small and medium-sized enterprise (SME) pursuant the definition set out in Commission Recommendation 2003/361/EC.

The active substance of Equisolon is prednisolone, a corticosteroid for systemic use which acts by expressing anti-inflammatory activity.

The product is intended for the alleviation of inflammatory and clinical parameters associated with RAO in horses, in combination with environmental control. The target species is horses. The route of administration is oral. The withdrawal period is 10 days for meat and offal.

On 15 January 2014, the CVMP adopted a positive opinion and assessment report, recommending the granting of a marketing authorisation for the veterinary medicinal product Equisolon oral powder for horses (33 mg/g; 100 mg, 300 mg and 600 mg).

On 12 March 2014, the European Commission adopted a Commission Decision granting a marketing authorisation for this product.

Scientific advice

The applicant received scientific advice from the CVMP on 17 September 2008 (SA/046/08) and 9 December 2010 with further clarification on 10 February 2011 (SA/082/10). The first scientific advice (SA/046/08) pertained to the establishment of the MRL for prednisolone and to conduct a target animal safety study in combination with a clinical efficacy trial. The second scientific advice (SA/082/10) was on residue data and their use in setting MRLs.

With regard to the advice on residue issues, the applicant has followed this advice. However with regard to the combined tolerance and efficacy study, the applicant has not followed the advice of a study of parallel design including more horses, or a prolonged observation period with additional 2 weeks. The applicant has justified these deviations, which CVMP has accepted.

MUMS status

The applicant requested classification for minor use minor species (MUMS)/limited market status this product by the CVMP. The CVMP confirmed at their September 2010 meeting that, where appropriate, the CVMP guidelines on data requirements for veterinary medicinal products intended for minor use

minor species were applied when assessing the application. MUMS status was granted as horses are considered a minor species.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the system of pharmacovigilance, which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the European Union (EU) or in a third country.

Manufacturing authorisations and inspection status

The active substance (prednisolone) is manufactured outside the EEA.

The manufacturer of the finished product and batch release is located at Lely Pharma B.V., Lelystad, The Netherlands.

All relevant sites have valid manufacturing authorisations or valid good manufacturing practice (GMP) certificates as appropriate. Hence, no GMP inspections were deemed necessary at this stage within the scope of this application procedure.

A qualified person declaration is provided for all sites involved in the manufacture of the active substance.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

The oral powder contains prednisolone (33 mg/g) as the active substance.

The formulation is a simple oral powder containing two commonly used excipients and a flavouring agent. The excipients are lactose monohydrate (as the filler/diluent), silica colloidal hydrated (as a glidant) and anise aroma powder (as a flavouring agent).

Container

The oral powder is filled either into single dose sachets containing 3 g, 9 g or 18 g powder (containing 100 mg, 300 mg and 600 mg of prednisolone, respectively) or in multi-dose high-density polyethylene (HDPE) jars containing 504 g powder. Sachets are presented in packs of 10 sachets (or multiples of this), in line with treatment recommendations (10 days).

Sachet material is composed of 5 layers: polyethylene terephthalate (PET) foil/ polyethylene (PE) white/aluminium/PE plus PE film (LD-LLDPE) and are heat-sealed.

The HDPE jars are white and are closed with a white low-density polyethylene (LDPE) lid fitted with a sealing ring. A measuring device for 4.6 g powder is delivered with the jar.

Development pharmaceutics

The description of the pharmaceutical development justifies the choice of formulation as well as for the selected quality of the constituents. The excipients are well-known and the manufacture consists of mixing the dry powders to obtain a homogeneous blend. The particle sizes of prednisolone and the main excipient lactose monohydrate are justified. The pharmaceutical formulation as an oral powder is considered acceptable on the basis of the data demonstrating homogeneity of the powder after blending and during filling. Simulation of transportation and in-use studies did not show segregation of the oral powder stored in the jar. The appropriateness of the sachets, jar and measuring device are demonstrated.

Method of manufacture

The manufacture of the finished product, by mixing the dry powders and then filling the powder into sachets or jars is described adequately and the in-process controls ensure a reproducible process. Process validation comprises homogeneity results of only one batch of the powder blend. The process validation scheme presented will ensure an appropriate process validation prior to marketing of the proposed product.

Control of starting materials

Active substance

The active substance master file procedure has been used to provide details of the manufacture and control of prednisolone.

The supplier of the active substance (micronised prednisolone) in China has obtained a Certificate of Suitability (CEP) to the monographs of the European Pharmacopoeia (Ph. Eur.). This shows a re-test period for the active substance of 3 years, when stored at a temperature not exceeding 30 °C, in double polyethylene bags placed in an airtight tin container.

The finished product manufacturer controls the active substance according to a specification which complies with the current Ph. Eur. monograph, and with additional requirements for dimethylformamide and particle size.

The prednisolone sourced from the supplier of the active substance is the stable polymorphic form I.

Excipients

Silica colloidal hydrated and lactose monohydrate comply with the relevant current Ph. Eur. monographs; the lactose monohydrate with additional requirements for particle size.

The anise powder is the subject of an in-house specification and complies with Regulation (EC) No 1334/2008, amending Directive 2000/13/EC, regarding flavouring requirements. The composition of the anise powder used is described.

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

None of the starting materials used for the active substance, prednisolone or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

Control tests during production

The weights of the individual ingredients are controlled during the production. The appearance of the powder blend is controlled prior to filling and net weight and closure of sachets are controlled after filling.

Control tests on the finished product

The description of the methods used for the control of the finished product and the specifications are provided.

The specifications at release and at the end of shelf life comply with the requirements to the general dosage form oral powders and to control the quality of the finished product.

The results of three batches (two pilot scale batches of 40 kg powder blend and one production scale batch of powder blend) demonstrated compliance with the proposed specification and demonstrate the consistency of the production.

Stability

The proposed shelf life is 3 years (36 months) for the sachets and the multi-dose jar. The proposed in-use shelf life of the multi-dose container is 4 weeks.

The stability studies provide data from three batches of the powder blend filled into sachets (3 g, 9 g and 18 g) and also into jars (504 g). All the batches were stored at long term conditions (25 °C/60% relative humidity (RH)) for 36 months and at accelerated conditions (40 °C/75% RH) for 6 months. Reduced stability testing (by a matrix design of the time points) was performed for batches stored under both the long term and accelerated conditions. The matrix design is however not justified, but the applicant has confirmed that an additional stability study will be performed on the first two commercial scale batches. The in-use shelf life (4 weeks) of the 504 g jar is acceptable. The stability results justify the proposed shelf life, i.e. 3 years is considered acceptable for sachets and jar.

Overall conclusions on quality

In general, the documentation is adequate to ensure a reproducible quality of the product considering the commitment to perform process validation on the first two commercial batches.

The development data support the choice of formulation and container closure system. The manufacture of the finished product by mixing the four ingredients is described adequately and it is controlled by in-process controls. The applicant has confirmed to perform process validation on three consecutive production scale batches prior to marketing which will ensure a consistent product quality.

The active substance prednisolone complies with the Ph. Eur. monograph and the manufacturer of the active substance has obtained a CEP. The manufacturer of the finished product controls the active substance according to the Ph. Eur. monograph and with additional requirements for residual solvents and particle size. The finished product is controlled by specifications at release and during shelf life which comply with general requirements to the dosage form.

A shelf life of 3 years (without special storage conditions) is acceptable for both sachets and jar. In-use shelf life for the jar is 4 weeks.

The applicant intends to start a new stability study including in-use testing on the first two commercial batches to confirm the proposed shelf life and storage conditions.

Recommendation(s)

A process validation on three consecutive production scale batches should be performed prior to marketing.

A stability study should be initiated including in-use testing on the first two commercial batches.

Part 3 – Safety

Toxicology data for prednisolone have previously been assessed by the CVMP and the toxicological profile is presented in the European Public MRL Assessment Report (EPMAR) of prednisolone (EMEA/MRL/629/99-FINAL, July 1999). No new data on prednisolone toxicity were provided in this application.

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

Toxicological studies

Single dose toxicity

The acute oral LD_{50} of prednisolone is 1,680 mg/kg in mice.

Repeat dose toxicity

Repeated dose toxicity studies have been carried out in rats, dogs, rabbits and guinea pigs. Myeloid depletion of the bone marrow is reported in rats at high doses (6 mg/kg bodyweight (bw)) and liver toxicity in rabbits at doses above 0.5 mg/kg bw subcutaneously.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

A reproduction study in the target species has not been performed, but foetal effects have been studied in rats and rabbits. In both species prednisolone induces a dose-related incidence of cleft palate and a reduction in the numbers of live foetuses and reduced foetal weights at doses above 5 mg/kg bw. Given the risk of foetal malformation demonstrated in animal experiments, the product should not be used in pregnant mares.

Mutagenicity/genotoxicity

Prednisolone was not genotoxic in a series of *in vitro* and *in vivo* tests and did not increase the incidence of tumours in a 18 month rat study.

Studies of other effects

The immunotoxicity of prednisolone has been tested in Beagle dogs. At the lowest dose (1 mg/kg bw) prednisolone induced inhibition of peripheral blood lymphocyte-phytomitogen responses, but did not interfere with the normal immunogenic response to challenge with virulent canine distemper virus.

User safety

The applicant has performed a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1. The non-professional user can be exposed to the product before, during and after administration of the product. Exposure routes include skin contact with the powder, inhalation of dust and accidental ingestion by a child.

In relation to inhalation of dust, it was considered that a worst case scenario would consist of a user inhaling 0.1% of the contents of a 504 g jar as a result of the jar being seriously disturbed. This would correspond to inhalation of 16.5 mg prednisolone. A margin of exposure (MOE) was derived by comparing this value with the no observable effect level (NOEL) of 20 µg/kg bw/day established for increased tyrosine aminotransferase activity in rats. The MOE was calculated to be 0.07 based on this worst case scenario. Based on this a warning to avoid dust production has been added to the summary of product characteristics (SPC) for all product sizes.

In the absence of severe disturbance of the product, inhalation of significant quantities of dust is not expected.

During a standard 10-day treatment, the worst exposure scenario for skin contact has been calculated to 1 mg prednisolone, which results in a MOE of approximately 1.

Accidental ingestion of the product by a child is expected to be limited to a maximum of 2 g (i.e. about 60 mg of active substance) as the powder is not palatable. Therapeutic prednisolone doses for 2-year-old children range from 1.25 to 12.5 mg per day and consequently it is concluded that accidental exposure may be orders of magnitude above the therapeutic dose and may cause adverse effects. A warning has been included in the SPC addressing this.

The excipients used in Equisolon oral powder formulation are widely used in approved veterinary and human marketed pharmaceutical products and none are anticipated to represent a human user safety concern.

Given the risk of foetal malformation demonstrated in animal experiments, the product should not be handled by pregnant women. An appropriate warning is included in the SPC.

Environmental risk assessment (ERA)

A Phase I assessment of environmental exposure based on the characteristics and use pattern of the product was submitted in accordance with VICH GL6.

Based on the data provided, the ERA can stop at Phase I, and no Phase II assessment is required because the product is indicated for use in individual animals only.

Equisolon is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The pharmacological profile of the substance is addressed in part 4, and the toxicological profile of prednisolone has been previously assessed by the CVMP during the MRL assessment procedure and is considered to be acceptable.

Equisolon powder may give rise to exposure of users via skin contact, inhalation of dust or ingestion. A warning not to shake the product has been included in the SPC to prevent dust formation. As accidental ingestion by a child may cause adverse effects, a warning is included in the SPC addressing this.

Given the risk of foetal malformation, the product should not be handled by pregnant women, or used in pregnant mares. Appropriate warnings are included in the SPC.

Equisolon is indicated for use in individual animals and therefore is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Identification of the product concerned

The product used in the residue depletion studies is identical to the final formulation.

Residue studies

Pharmacokinetics

See Part 4.

Depletion of residues

The applicant followed the CVMP's scientific advice on depletion studies. Two studies in horses were provided. The first was a combined pharmacokinetic and depletion study where 12 animals were orally dosed with 1 mg prednisolone/kg bw daily for 14 days and animals were slaughtered 7, 14 and 28 days after the last administration. The second study followed the same protocol but included only 8 animals and two slaughter times of 1 and 3 days after the last dose. The two studies were combined and residue profiles were determined for liver, kidney, muscle and fat. One animal showed a very high residue level in liver at day 28, which CVMP considered an outlier.

Quantification of prednisolone in tissues was performed by means of validated LC-MS/MS (liquid chromatography-tandem mass spectrometry) methods.

MRLs

The active substance in Equisolon is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Prednisolone	Prednisolone	Equidae	4 µg/kg 8 µg/kg 6 µg/kg 15 µg/kg	Muscle Fat Liver Kidney	NO ENTRY	Corticoids/ glucocorticoids

The excipients contained in the product 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 veterinary medicinal product.

Withdrawal periods

The statistical approach could not be applied for the liver or fat tissue. Since concentrations of prednisolone were below the MRLs for kidney and fat at 3 days and for liver and muscle at 7 days, the alternative approach was chosen, and a withdrawal period for Equisolon of 10 days is considered acceptable for meat and offal (7 days plus 30% safety span). No MRL has been established for horse milk; therefore, Equisolon is not authorised for use in mares producing milk for human consumption.

Overall conclusions on the residues documentation

Prednisolone is excreted rapidly from tissues after daily oral dosing of 1 mg/kg bw for 14 days. Prednisolone concentrations in muscle, fat, liver and kidney are below the MRL after 7 days. With a safety span of 30%, a withdrawal period of 10 days is considered acceptable for horses. No MRL has been established for horse milk; therefore, Equisolon is not authorised for use in mares producing milk for human consumption.

Part 4 - Efficacy

No specific pharmacological studies were provided. Reference was made to bibliographic data. In view of the well described use in published literature of corticosteroids including prednisolone in the (minor

species) horses affected by recurrent airway obstruction (RAO, also known as heaves), this was considered acceptable by the CVMP.

Pharmacodynamics

Prednisolone is a synthetic glucocorticoid with anti-inflammatory and immunosuppressant properties, and has about four times the anti-inflammatory activity of cortisol (hydrocortisone). It possesses only slight mineralocorticoid activity, and has approximately 0.8 times the sodium-retaining effect of cortisol. Prednisolone has a medium duration of activity.

Corticosteroids suppress the immunologic response by inhibition of dilatation of capillaries, migration and function of leucocytes and phagocytosis. Glucocorticoids have an effect on metabolism by increasing gluconeogenesis.

RAO is a commonly occurring respiratory disease in mature horses. Affected horses are susceptible to inhaled antigens and other pro-inflammatory agents, including fungal spores and dust-derived endotoxin. It is recognised that the use of corticosteroids (tablets or injections) for the treatment of RAO in horses is well-known in equine medicine.

Pharmacokinetics

The pharmacokinetics of Equisolon were determined in 12 horses after oral administration of 1 mg prednisolone/kg bw once daily during 14 days. Pharmacokinetic parameters were calculated at Day 1, 7 and 14.

Prednisolone was absorbed rapidly achieving a peak concentration of approximately 200 ng/ml in blood plasma after 2–3 hours. Plasma elimination half-life was approximately 3 hours. Bioavailability after oral administration is about 60%. Partial metabolism of prednisolone to the biologically inert substance prednisone takes place. Equal amounts of prednisolone, prednisone, 20β-dihydroprednisolone and 20β-dihydroprednisone are found in urine. Excretion of prednisolone is complete within 3 days.

The pharmacokinetics did not differ markedly during treatment, i.e. multiple dosing did not result in plasma accumulation of prednisolone, and the pharmacokinetic findings are in line with those reported in public literature.

Dose determination/justification

No separate dose determination/justification study was provided. However, the applicant provided a bibliographic review demonstrating the clinical benefits in horses affected by RAO, when given daily oral doses of 1 mg prednisolone/kg bw over 10 days. Most of the studies were done in combination with environmental control in order to eliminate or reduce antigen exposure. In addition to the bibliographic data, the applicant also provided a small scale field study combining dose titration, tolerance and efficacy data for the treatment of heaves in horses (see "Clinical trial(s)").

The CVMP agreed that the anti-inflammatory effect of prednisolone is well-known, and in horses prednisolone at a dose between 1 and 2 mg/kg has been a part of the treatment strategy for RAO for many years, and is also part of a standard treatment recommendation for this condition. Given the well-known use of the active substance in the proposed indication and posology, the MUMS status of the application, and the absence of medicines authorised for this indication in the target species, the CVMP considered the data acceptable to conclude that a dose of 1 mg prednisolone/kg bw over 10

days, in combination with environmental control would be effective to alleviate inflammatory and clinical parameters associated with RAO in horses, in combination with environmental control.

Clinical trial(s)

Prior to submission of the dossier, the applicant had asked for scientific advice, i.e. if a target animal safety study could be combined with a clinical efficacy study with a study protocol including 8 horses in a cross-over design, receiving 0, 1, 2 and 5 mg prednisolone/kg bw.

In principle, the CVMP accepted a combined tolerance and efficacy study taking into consideration the MUMS status of this application. However, the CVMP recommended a study with a different (parallel) design, including a larger number of horses in order to prevent carry-over effect from one treatment group to another. Furthermore, concern was expressed that the severity of the diseases could be influenced by challenging the same horse 4 times. The proposed protocol of 5 day challenge followed by 10 days treatment and 15 days observation period was in principle also accepted, although it was advised that the study would be strengthened with an additional 2 weeks observation period.

The study protocol (see below) followed in principle the CVMP scientific advice. Although the applicant did not follow the advice of a parallel design including a higher number of horses, or the prolonged observation period with an additional 2 weeks, the CVMP accepted this, because the applicant demonstrated that the blood cortisol level before each challenge was the same for all treatment groups, and that no carry-over effect was seen.

Target animal tolerance

The protocol for the combined dose titration, tolerance and efficacy study for treatment of heaves is described below (see "Field trials").

No clinical adverse reactions were detected related to prednisolone at 1, 3 or 5 mg prednisolone/kg bw.

A large battery of haematological and blood chemical parameters have been measured. A reduction was detected on leucocytes and lymphocytes counts. Furthermore, changes in blood parameters including a reduction in cortisol aspartate aminotransferase (AST) and albumin and an increase in alkaline phosphatase, lactate dehydrogenase (LDH) and triglycerides could be related to the test item. The observed changes are all associated with glucocorticoid treatment and are well described in the literature. Reference to these effects is included in the SPC.

Given the risk of foetal malformation observed in other animal species, and the lack of data in horses, the use of prednisolone during pregnancy is contraindicated.

Based on the data from the field study and bibliographic references, the CVMP concluded that Equisolon is well tolerated in horses over a treatment period of 10 days when used as recommended. However, although Equisolon was well tolerated in the clinical study, in view of the limited data available, reference to the known clinical adverse effects of prednisolone in horses, such as development of laminitis, has been made in the SPC.

Field trials

The pivotal field study was a good clinical practice (GCP)-compliant field study conducted in 2011 in the Netherlands. The protocol for the combined dose titration, tolerance and efficacy study for

treatment of heaves included 8 heaves-affected horses developing RAO after challenge (2 female, 6 male/castrated) with a mean age of approximately 16 years (7–23 years) and mean weight of 487 kg (370–653 kg). Horses receiving any medication or with any clinical condition adversely interfering with the purpose or conduct of the study were excluded from the trial. Animals were randomly assigned to the 4 groups: 1) no treatment, 2) the recommended therapeutic dose (RTD) of 1 mg/kg prednisolone per os (p.o.), 3) 2 mg/kg prednisolone p.o. (2x RTD), and 4) 5 mg/kg p.o. (5x RTD) in a cross-over design. All groups were exposed to hay for 5 days, and then treated for 10 days followed by a washout period of 20 days before the next exposure and treatment. The study was performed in 4 periods (35 days each) and each period contained the same 4 stages described above.

The efficacy was evaluated by clinical examination, tracheobronchial exudate by bronchoscopy, lung air pressure and fraction of neutrophilic granulocytes in bronchoalveolar lavage. All were done blinded. Efficacy and tolerance parameters were determined within 24 hours prior to each challenge stage, after completion of each challenge stage, after each treatment stage and after the completion of the recovery and washout stage of the 4th period.

After challenge by exposure to hay, all treatment groups showed a comparable increase in the clinical score, lung air pressure, and degree of exudate and percentage of neutrophils in bronchoalveolar lavage.

Using an analysis of variance (ANOVA) test, an effect of prednisolone could be demonstrated for the endpoint "tracheobronchial exudate" for the 1 mg/kg dose. For the endpoint "fraction of neutrophilic granulocytes in bronchoalveolar lavage" a significant statistical effect was demonstrated for the 2 mg/kg and the 5 mg/kg dose. For the endpoint "clinical score" and "lung air pressure" no significant statistical effect could be demonstrated for any of the tested doses. However, an additional post-study evaluation using non-parametric logistic analysis showed a significant improvement in clinical score compared to the negative control group. The applicant explained that the ANOVA analysis is less suitable for "clinical scored" parameters with only 3 levels (0, 1 and 2) of scores, and that for such cases a logistic analysis should be applied, as analysis is based here on the frequency of scores.

Based on the results of the study, the CVMP concluded that treatment (p.o.) with 1 mg prednisolone/kg bw over 10 days in combination with environmental control resulted in significant improvements in parameters associated with RAO and inflammation in heaves-affected horses.

Overall conclusion on efficacy and target animal safety

Recurrent airway obstructions (RAO) have a well-known pathogenesis involving complex interactions with the immune system and environment.

The CVMP considered the well-known use of the active substance, prednisolone, in the proposed indication and posology, the MUMS status of the application (as horses are considered a minor species), and the absence of medicines authorised for this indication in the target species. Although only a small scale clinical study had been conducted by the applicant, the CVMP agreed that the data from this study together with the bibliographic data provided, would allow conclusions that a dose of 1 mg prednisolone/kg bw over 10 days in combination with environmental control would be effective to alleviate inflammatory and clinical parameters associated with RAO in horses.

In the limited number of horses included in this study, no adverse clinical events were observed following treatment with prednisolone. Some changes were noted to a number of haematological and blood chemical parameters, which all were expected when treating with a glucocorticoid. Although Equisolon was well tolerated in this study, it was agreed that in view of the limited data available, the well-known clinical adverse effects of prednisolone in horses should also be included in the SPC.

Part 5 – Benefit-risk assessment

Introduction

Equisolon oral powder contains prednisolone as active substance and is presented in single-dose sachets containing 3, 6 and 18 g oral powder, or in a multi-use HDPE jar containing 504 g oral powder. The product is indicated for the alleviation of inflammatory and clinical parameters associated with recurrent airway obstruction (RAO) in horses, in combination with environmental control. The route of administration is oral use. The proposed withdrawal period is 10 days for meat and offal. The product will not be authorised in mares producing milk for human consumption.

The product has been classified as MUMS/limited market and therefore specific data requirements apply that have been considered in the assessment.

Benefit assessment

Direct therapeutic benefit

Based on bibliographic and limited clinical data, a beneficial effect of prednisolone administration in horses recovering from symptoms attributable to respiratory airway obstruction (RAO, heaves) in the presence of environmental control has been shown. A beneficial effect was seen on the alleviation of a limited number of inflammatory and clinical parameters associated with RAO, in combination with environmental control.

A small clinical study including 8 horses together with the bibliographic data confirmed that a dose of 1 mg prednisolone/kg bw over 10 days in combination with environmental control is effective to alleviate inflammatory and clinical parameters associated with RAO in horses.

Additional benefits

Equisolon provides a new veterinary medicinal product for a minor species (MUMS indication).

Risk assessment

Main potential risks have been identified as follows:

Quality: The applicant is recommended to provide data on validation of the manufacturing process post authorisation.

For the target species: The product was well tolerated in the target species with no serious clinical adverse reactions during a 10-day treatment period in a clinical study with a limited number of animals. Although no serious adverse effects were observed during the limited clinical trial (8 horses), it is expected that known side effects of prednisolone would also occur following treatment with Equisolon.

For the user: On the basis of a user safety assessment, dust could potentially expose users to significant levels of prednisolone, and consequently a warning is included in the SPC to avoid dust formation by not shaking the product shortly before opening.

There is a risk of foetal malformation resulting from prednisolone exposure, so the product should not be handled by pregnant women, or used in pregnant mares.

For the environment: The environmental risk assessment was performed according to the relevant guidelines. Based on the data provided, Equisolon is not expected to pose a risk for the environment when used according to the SPC.

For the consumer: A withdrawal period of 10 days has been established for meat and offal. As no MRL has been established for prednisolone in milk, the product should not be used in animals producing milk for human consumption.

Risk management or mitigation measures

Warnings and risk management measures have been included in the SPC to manage possible risks to target animal, other animal species, the user and the environment.

Evaluation of the benefit-risk balance

The formulation and manufacture of the product are well described, and the specifications set will ensure that a product of an appropriate and consistent quality will be produced.

Clinical efficacy is mainly based on bibliographic data, supported by a small scale clinical study undertaken by the applicant. Considering the well-known use of the active substance in the proposed indication, the MUMS status of the application (horses are minor species), and the absence of medicines authorised for this indication in the target species, the CVMP agreed that the limited data provided allow conclusions that a dose of 1 mg prednisolone/kg bw over 10 days in combination with environmental control is effective to alleviate inflammatory and clinical parameters associated with RAO in horses.

Equisolon is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended.

A sufficient withdrawal period has been set.

The product has been shown to have a positive benefit-risk balance.

Conclusion on the overall benefit-risk balance

The overall benefit-risk evaluation of the product is deemed positive with a sufficiently clear and complete SPC and other product information.

Conclusion

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of Equisolon were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy the CVMP recommends the granting of the marketing authorisation for Equisolon.