Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
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(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PRASCEND

Date: rev. 18 June 2012

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0130/001/DC
Name, strength and pharmaceutical form	PRASCEND, 1mg, Tablet
Applicant	Boehringer Ingelheim Vetmedica GmbH Binger Str. 173 D-55218 Ingelheim Germany
Active substance(s)	Pergolide mesylate
ATC Vetcode	QN04BC02
Target species	Horses (Non food producing)
Indication for use	Horses not intended for human consumption: Symptomatic treatment of clinical signs associated with Pituitary Pars Intermedia Dysfunction (PPID) (Equine Cushing's Disease).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	29 July 2009
Concerned Member States for original procedure	IE, IT, UK (Second Wave: AT, BE, DK, FI, FR, IS, LU, NL, NO, SE)

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; adverse reactions reported are indicated in the SPC.
The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

Prascend is a scored immediate release tablet for use in horses containing 1 mg pergolide as pergolide mesylate and the excipients Lactose monohydrate,

Croscarmellose sodium, Povidone, Magnesium stearate, Ferric oxide (Iron oxide red, E 172).

The container/closure system is a blister package. The forming material of the blisters is nylon/aluminium foil/PVC and the lidding material is aluminium foil with a vinyl heat seal coating.

Except for the tablet imprint Prascend 1 mg tablets for horses are identical to the human medicinal product Parkotil 1.0 (Zul.-Nr.: 27276.02.00) that has been marketed in Germany since 1993.

The applicant has confirmed that the quality documentation provided in support of this application represents the full quality dossier of the human product as approved by the German Human Regulatory Authority (BfArM) until now. Therefore, the assessment of the core quality data has not been repeated by the Veterinary Regulatory Authority according to the Guideline on quality data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/QWP/128710/2004).

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

See IV.A.

Toxicological Studies

The applicant has provided bibliographical data which show that the active substance pergolide mesylate is acute highly toxic. However, the safety factor for the oral route in horses was at least 3000 as measured by the most sensitive species.
Predominant findings in subchronic and chronic toxicity studies were seen in female rats, namely inhibition of lysis of corpora lutea caused by a pharmacologically induced inhibition of prolactin release, the luteotropic hormone in rodents. The mouse has been shown to be physiologically more tolerant to the prolactin inhibition. Changes in locomotor activity in laboratory animals and emesis in dogs can also be attributed to the pharmacological activity of the compound.
There was no evidence of any teratogenic potential of pergolide in mice and rabbits. In rabbits, no effects on reproduction or fetal development were seen. All findings observed in mice including the impact on fertility, fetal weights and survival rate of

the offspring were attributed to the pharmacological inhibition of prolactin secretion resulting in lactation failure.
Pergolide mesylate does not possess an intrinsic genotoxic activity.
In carcinogenicity studies, the increase in uterine tumors was considered to be most likely due to the pharmacological action of pergolide throughout the lifespan of rodents and was considered to be not relevant for horses and humans.

Observations in Humans

The applicant has provided data on pergolide observed in clinical trials as well during pre- and postmarketing that show that adverse effects in humans were mainly seen in the nervous, gastrointestinal, cardiovascular and respiratory systems and on skin and appendages.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. The administration of Prascend tablets is not expected to present an undue hazard to the user under normal conditions of use in accordance with the adequate proposed warning phrases in the SPC. The packaging material is considered adequate to minimize the high risk for children due to accidental ingestion. Additionally, a warning phrase to prevent accidental misuse by children has been included.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that Prascend will be used for non food animals and only a small number of animals in a flock or herd will be treated. No phase II assessment and risk mitigation measures are therefore required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

This is an application making use of Article 6 of the Directive 2001/82/EC as amended. Therefore no residue documentation has been submitted.

IV. CLINICAL ASSESSMENT (EFFICACY)

Introduction

Pergolide is indicated for a “minor” use in a “minor” species justifying implementation of the requirements of the “Guideline on Efficacy and Target Animal Safety Data Requirements for Veterinary Medicinal Products Intended for Minor Uses or Minor Species” (EMEA/CVMP/EWP/117899/2004).

Pergolide – authorised and used in the EU for decades in human medicines to treat Parkinson’s disease - is a novel substance in veterinary medicines. However, according to the literature submitted extra-label use of pergolide in equids is practice for at least 26 years.

Therefore, literature data was accepted to prove efficacy and target animal safety of Prascend.

IV.A Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical data that demonstrates that pergolide is a synthetic ergot derivative and a potent, long-acting dopamine receptor agonist. Both in vitro and in vivo pharmacological studies demonstrate the activity of pergolide as a selective dopamine agonist with little or no effect on norepinephrine, epinephrine or serotonin pathways at therapeutic doses. Pergolide inhibits the binding of dopamine in a non-competitive manner and spiperone, an antipsychotic substance and ligand to both 5HT- and dopamine receptors, in a competitive manner. A pharmacological study in the target species horse demonstrate reductions in pituitary gland/pars intermedia ACTH, cortisol, and in particular pars intermedia pro-opiolipomelanocortin peptides for 24 hours following a single dose of pergolide. Considering these pharmacodynamic properties, and the pathophysiology of Pars Intermedia Dysfunction (PPID)/Equine Cushing’s Disease (ECD) that comes along with loss of dopaminergic inhibition of the pars intermedia there is a good rationale for the use of pergolide in PPID/ECD.

As with other dopamine agonists, pergolide inhibits the release of prolactin. A warning regarding this property of pergolide is adequately included in the SPC.

The potential of pergolide to induce fibrosis, i.e. the formation of fibrotic tissues in some body structures followed by cardiac valvulopathy, which led to a restricted use of pergolide in humans, has so far been reported after prolonged administration of the substance at elevated doses to humans only and has not been observed in horses.

Trials on pharmacokinetics in horses following single oral administration of pergolide mesylate demonstrate that pergolide is rapidly absorbed with a short time to peak concentration. Plasma concentrations were variable. Pergolide mesylate is approximately 90% associated with plasma proteins in humans and laboratory animals. Thus caution should be exercised if it is co-administered with other drugs

known to affect protein binding. Dopamine antagonists ordinarily should not be administered concurrently with pergolide mesylate; these agents may diminish the effectiveness of pergolide mesylate. Warnings regarding these properties of pergolide are adequately included in the SPC.

Tolerance in the Target Species of Animals

Information on the safety of pergolide (mesylate) in horses was derived from literature, according to which adverse reactions are not mentioned frequently. Dose rates of up to 10 µg/kg bw have been used. At higher dose rates, especially in horses starting therapy with a high dose rate, adverse reactions at least possibly causally related to treatment were (transient) anorexia, sweating, dyspnoea, dizziness, colic, prolonged gestation and failing to lactate. Adverse reactions seem to be dose-related in that low doses like the recommended (starting) dose of 2 µg/kg bw can be expected to be well tolerated. When adverse reactions were reported they were not severe and resulted in the (transient) reduction of the dose. Initiating treatment with low doses, which can be gradually increased until an optimal dose is found, help to prevent adverse reactions. The SPC provides detailed advice to ensure safe use of Prascend.

IV.B Clinical Studies

The presented literature data cover the past 26 years of off-label use of pergolide (mesylate). It reports unanimously on orally administered pergolide (mesylate) being efficacious in treating (clinical) signs in horses suffering from PPID/ECD that needs pharmacological treatment. Treatment with pergolide resulted in a benefit in the vast majority of cases. Improvement of clinical signs of PPID/ECD (in particularly hirsutism, hyperhidrosis, weight loss/muscle wasting, abnormal fat distribution, lethargy, (chronic), polyuria, polydipsia, chronic infections, neurological signs), is described frequently as being impressive. Horses in poor clinical condition improved to normal or at least near normal. Despite clinical improvement or resolution, change of laboratory parameters is reported frequently being inconsistent and laboratory parameters may remain abnormal. For safety reasons low-dose pergolide therapy was advocated as the best treatment compared with high-dose therapy. Thus the average (starting) dose of 2 µg pergolide/kg bw recommended by the SPC reflects an efficacious dose, which requires individual titration. The detailed recommendations of the SPC on dosing, dose-titration and monitoring of treatment result reflect the clinical literature.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for

the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Safety and efficacy

1.
After marketing authorisation had been granted, the marketing authorisation holder applied for editorial text changes of the product literature. With this variation application two new studies - a target animal safety study conducted according to Good Laboratory Practice and a clinical field study conducted according to Good Clinical Practice - were provided.

In the target animal safety study tolerance towards pergolide was investigated over 6 months in young horses at doses of 4, 6 and 8µg/kg, which lie within the recommended therapeutic dose range of 2 – 10µg/kg body weight (bw). The maximum treatment dose of 10µg/kg bw was, however, not subject of the safety examination nor have overdoses been examined. Horses were subjected to common physical and laboratory investigations. Cardiac function was examined in addition. During treatment several adverse events were recorded in horses some of which were classified as serious. However, none was attributed to treatment. Changes noted at physical, laboratory and post-mortem examination were judged as not clinically relevant or incidental in nature. Adverse reactions reported in horses suffering from Cushing's Disease and listed in the product literature (inappetence, transient anorexia, lethargy, depression, ataxia, diarrhoea, colic) were not reported during the study.

Efficacy of pergolide mesylate tablets (formulation identical to Prascend) for the control of clinical signs associated with pituitary pars intermedia dysfunction was investigated by an US multi-centre, open-label study under clinical conditions involving treated horses in a single treatment group receiving pergolide mesylate tablets, in which each animal served as its own control. Tablets were administered at nominal 2 µg pergolide/kg bw once daily. If diagnostic clinical improvement was evident on study day 90, treatment was to be continued for another 3 months at the same dose once daily. Otherwise the dose was to be doubled to a nominal 4 µg/kg

bw given once daily for the next 3 months. Additionally, if the dosage was not well tolerated, dose adjustment was determined on a case-by-case basis. The majority of horses (60%) maintained the starting dose. 2.5% of the horses required a transient dose reduction. The remaining horses needed a dose increase. Assessment of efficacy was based on the results of endocrinology testing and/or specified clinical signs related to Cushing's Disease. According to these pre-defined efficacy criteria 76% of cases were analysed as treatment successes.

As regards safety, the field study confirms the known spectrum of adverse reactions.

Conclusion:

The editorial amendments of the product literature were considered useful. Although the clinical study demonstrated efficacy after using a dose titration scheme, which was less complex compared to that recommended by the authorized product literature of Prascend, the detailed recommendations for dose titration were maintained. They definitely warrant a well adapted treatment. Adverse reactions reported during the clinical study confirm information of the authorized product literature in this regard. Thus, the overall conclusion and benefit-risk assessment mentioned remain valid.

2.
After initial authorization and variation, the marketing authorisation holder applied for authorization in additional Member States. Second Wave CMS were AT, BE, DK, FI, FR, IS, LU, NL, NO, and SE. With this repeat use procedure application the bibliographical data and the two studies (one clinical and one target animal safety study) mentioned above were provided. The repeat use procedure resulted in amendments of the product literature agreed by all Member States involved to update and state more precisely several paragraphs of the product literature.

3.
Following the repeat use procedure the MAH applies for a type II variation to implement the text changes of the product literature resulting from the repeat use procedure. The documentation submitted by the MAH comprises the product literature agreed at day 90 of the repeat use procedure. Finally it was concluded that the variation and with it the product literature provided is approvable subject to further amendments.

Conclusion:

The amendments of the product literature were considered useful and have been agreed. The overall conclusion and benefit-risk assessment remain valid.

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Change of MAH	Module 1	9 October 2010
Change or addition of imprints on tablets DE/V/0130/001/IA/002	Module 3	22 April 2010

Safety/efficacy changes

Summary of change **(Type; application number)**	**Section updated in Module 3**	**Approval date**
Variation procedure (DE/V/0130/II/005/G) to update scientific data and to amend the product literature	Module 4, point 1	14 June 2011
Repeat use procedure (DE/V/0130/001/E/001) for authorisation in additional Member States	Module 4, point 2	21 December 2011
Variation procedure (DE/V/0130/001/II/006) for harmonisation of the product literature between original and new Concerned Member States after repeat use procedure (DE/V/0130/001/E/001)	Module 4, point 3	15 May 2012