Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Danilon Equidos Gold 1.5 g Granules for Horses and Ponies

Date Created: November 2020

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Danilon Equidos Gold 1.5 g Granules for Horses and Ponies, Granules
Applicant	Ecuphar Veterinaria S.L.U., Avenida Río de Janeiro, , 60-66, Planta 13, Barcelona, 08016, Spain
Active substance	Suxibuzone
ATC Vetcode	QM01AA90
Target species	Horses
Indication for use	Treatment of pain and inflammation associated with musculo-skeletal conditions in the horse e.g. osteoarthritic conditions, bursitis, laminitis and soft tissue inflammation.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	An extension application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	10/09/2020

I. SCIENTIFIC OVERVIEW

The application is for an MA submitted in accordance with Article 12.3 of Directive 2001/82/EC, as amended by 2004/28/EC; a line extension to add a more potent formulation to the existing marketing authorisation of Danilon Equidos 1.5 g Granules for Top Dressing, which has been authorised Nationally in the UK since August 2001.

The existing product; Danilon Equidos 1.5 g Granules for Top Dressing contains suxibuzone at a concentration of 150 mg/g in 10 g sachets. The proposed product, Danilon Equidos NF 1.5 g Granules for Horses and Ponies contains suxibuzone at a concentration of 500 mg/g in a 3 g sachet. Both sachets contain the same dose of suxibuzone, i.e. 1.5 g.

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, any reactions observed are indicated in the SPC.[1] 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 [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains suxibuzone (microencapsulated) 1.500 mg and the excipients tarrazine (E-102), mannitol, sucrose, povidone K-30, sodium saccharin and ethyl cellulose.

The container/closure system consists of 3 g laminated opaline/aluminium polyethylene sachets, with outer cartons containing 18 or 60 sachets.
The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of preparation of binding solution, blending, granulation, drying, sieving, homogenisation and packaging.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is suxibuzone an established active substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Certificates of analysis were provided for three batches of the active substance demonstrating compliance with the applicant's specification. and a residues solvents declaration from the supplier was also provided.

The excipients are sucrose, mannitol, povidone K30, saccharin sodium, tartrazine (E102), ethyl cellulose, purified water and ethanol.

The packaging materials consist of heat sealed laminated opaline/aluminium polyethylene sachets, with secondary pack cartons containing 18 or 60 sachets.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for appearance, identification, assay, degradation and microbiological quality.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

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

Shelf life of the veterinary medicinal product as packaged for sale: 4 years

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological & Toxicological Studies

This is a line extension, submitted in accordance with Article 12.3 of Directive 2001/82/EC, as amended, of Danilon Equidos 1.5 g Granules for top dressing (Vm 46037/4000) which is currently presented in 10 g sachets. The original

authorisation was approved based on a full dossier. No new data have been provided.

Cross-reference was made to the safety and clinical data provided for Danilon Equidos 1.5 g Granules for top dressing, which has been authorised in the UK since August 2001 by the same Marketing Authorisation holder.

This product, Danilon Equidos Gold 1.5 g Granules for Horses and Ponies is a more potent formulation than the parent product, whereby the quantity of active substance per sachet remains the same as the existing marketing authorisation but is presented in 3 g sachets.

User Safety

A user risk assessment (URA), was provided in compliance with the relevant guideline which shows that the nature of the product administration, from the sachet straight on the feed, minimises user contact with the product. When administering the product, the user of the product (animal owner or veterinarian), would potentially contact the product only at the time of opening and administering each sachet by adding it to a portion of feed. Each sachet is opened prior to the administration of each individual dose and it is immediately added to a portion of feed. When administering the highest (loading) dose, the user will open two sachets twice daily in the first days of treatment.

Referring to the previously submitted data, skin irritation and sensitisation as well as ocular irritation were tested for Danilon Equidos 1.5 g Granules for top dressing, with negative results for all tests and therefore with minimal risk for the user.

Regarding inhalation toxicity, the granulometry of the new formulation has been homogenised and there are no particles of less than 50 µm. Particles of less than 10 µm are not considered to be inhaled and reach the nasopharyngeal level, therefore the risk to the user from inhalation of the product is negligible. Furthermore, most horses are fed in open air or well-ventilated areas, which further reduces the potential for user exposure.

The URA concluded that differing only in concentration of active substance but not in the daily dose administered, it is considered that the toxicology of the new 500 mg/g strength in 3 g sachets is equivalent to the existing 150 mg/g product formulation in 10 g sachets. Furthermore, taking into account the very limited potential for exposure to this product for the user, (for treatment of individual animals) and the special formulation, (dry granules packed in individual doses which greatly reduces the potential level of exposure for the user), the use of the proposed product, is considered overall to be safe to use by the person administering the product to the target animal, when the appropriate user warnings are followed

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

Tartrazine may cause allergic reactions
In case of known hypersensitivity to suxibuzone or any of the excipients, avoid contact with the product.
Wash hands after use.
Use in a well-ventilated area. To avoid exposure to the granules, part-sachets should not be used. Avoid inhaling any dust when opening sachet and mixing with feed. Avoid contact with skin, eyes and mucosa. In case of accidental contact, wash with plenty of clean water. In case of accidental ingestion, seek medical advice immediately and show this label to the physician.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The pattern of use of the new strength for a sporadic condition will be the same as for the current Danilon Equidos 1.5 g Granules for top dressing. Individual treatment is administered in a small portion of feed, which is normally given at the stable. The use of the product does not represent a risk for the environment and no special use measures need to be adopted.

The standard disposal advice in the SPC states 'Any unused veterinary medicinal product or waste material derived from such veterinary medicinal products should be disposed of in accordance with local requirements.'
This advice is considered satisfactory the product is not expected to pose a risk for the user when used as recommended.

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

The application is made in accordance with Article 12.3 of Directive 2001/82/EC as amended by 2004/28/EC, a line extension to add a more potent formulation to the existing marketing authorisation of Danilon Equidos 1.5 g Granules for Top Dressing, which has been authorised Nationally in the UK since August 2001.
No data have been submitted in this section of the dossier. As the quantity of active substance per sachet remains the same, cross-reference can be made to

the safety and clinical data of the existing product Danilon Equidos 1.5 g Granules for Top Dressing.

Pharmacology

No data have been submitted in this section of the dossier. The quantity of active substance per sachet remains the same, cross-reference can be made to the safety and clinical data of the existing product 'Danilon Equidos 1.5 g Granules for Top Dressing'

Tolerance in the Target Species

Tolerance studies were not required because the applicant has cross-referenced the safety and clinical data of the product 'Danilon Equidos 1.5 g Granules for top dressing' authorised in the UK on 2 August 2001.

IV.II. Clinical Documentation

Field Trials

The application has been submitted in accordance with article 12(3), a line extension of the full application Danilon Equidos 1.5 g Granules for Top Dressing to add a new product potency.

The applicant submitted an *in vivo* bioequivalence to compare the pharmacokinetics of the existing product, Danilon Equidos 1.5 g Granules for Top Dressing and the new product Danilon Equidos NF 1.5 g Granules for Horses and Ponies. The study was a single dose, two period, two sequence, cross-over study, with a wash-out period of 7 days, and conducted in accordance with Good Laboratory Practice (GLP). The study was conducted in 24 horses, which were considered adequately representative of the target population and adequately monitored throughout the study.

The applicant has measured the plasma concentration of suxibuzone and the active metabolites; phenylbutazone and oxyphenbutazone. The plasma concentration of suxibuzone, was demonstrated to be below the lower limit of quantification at each time point throughout the study, thereby demonstrating the rapid conversion of suxibuzone to the active metabolites phenylbutazone and oxyphenbutazone. In accordance with section 5.11 of the guideline (EMEA/CVMP/16/2000-Rev.2), for pro-drugs which have low plasma concentrations and are quickly eliminated, it is acceptable to demonstrate bioequivalence for the main active metabolite. Therefore, it is considered acceptable for bioequivalence to be demonstrated by plasma levels of phenylbutazone.

Study title	The Bioequivalence Study of Suxibuzone in Horses after Oral Administration.
Objectives	The aim of this study was to demonstrate bioequivalence between the approved veterinary medicinal product Danilon Equidos 1.5 g Granules for Top Dressing and Danilon Equidos Granules 500 mg/g after oral administration.
Test site	Single EU site
Compliance with Regulatory guidelines	GLP and quality assurance statement provided
Test Product	Danilon Equidos Granules 500 mg/g
Control product/placebo	Danilon Equidos 1.5 g Granules for Top Dressing
Animals	24 Horses Breed: Czech Warmblood, x12 male and x 12 female Age 2-14 years, not treated with any drugs for at least 28 days before the start of the study. All clinically healthy.
Randomisation	Animals were ranked randomly according to their sex and body weight on D-7 into two groups (Group A or Group B: 12 animals/group). To ensure an even distribution of animals into two homogeneous groups with respect to their sex and body weight, a randomisation scheme for 24 animals using a block size of two was used. Animals of each block were allocated by lot to one of the two groups.
Blinding	The personnel performing analyses of the plasma samples for suxibuzone, phenylbutazone and oxyphenbutazone determination were blinded regarding allocation of animals to treatment regimen.
Method	The concentration of suxibuzone (SUX), phenylbutazone (PBZ) and oxyphenbutazone (OPBZ) in equine plasma was determined and evaluated following the validated LC-MS/MS method, and applying the relevant SOP. The analytical method involved SPE extraction from plasma, clean up by SPE extraction and LC-MS/MS analysis. The evaluation of the SUX, PBZ and OPBZ concentration was carried out using the internal standard method. The plasma samples were stored until processing at -25 ± 5ºC.

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Statistical method	For statistical evaluation, the EquivTest/PK software was used. The PBZ plasma concentrations at each sampling point were considered for calculation of pivotal parameters (AUC and C_{max}) in order to demonstrate bioequivalence. Analysis of variance was performed using ln-transformed AUC, C_{max}, C_{max}/dose and AUC/dose parameters. The ANOVA model with estimation of the error variance contained formulation, sequence, period and animal within sequence. Bioequivalence was concluded if the 90% confidence interval for the ratio of the means for AUC_t and AUC_i is included within the interval 80 - 125% and if the 90% confidence interval for the ratio of the means for C_{max} is included within the interval 70 - 143%.
RESULTS	**Baseline data:** <u>Group A</u> Number 12 Age mean 4.3 (2-14) years Sex 6 males/6 females Bodyweight D -7 522.9 kg (480 - 608 kg) D +9 523.5 kg (474 - 600 kg) Actual dose administered: Period 1 (test item) mean 6.305 mg/kg (5.016 – 7.819 mg/kg) Period 2 (reference item) mean 6.291 mg/kg (5.033 – 7.84 mg/kg) <u>Group B</u> Number 12 Age mean 3.8 (2-11) years Sex 6 males/6 females Bodyweight D -7 519.6 kg (427 - 642.0 kg) D +9 519.4 kg (417 - 630 kg) Actual dose administered Period 1 (reference item) mean 6.260 mg/kg (6.250 - 6.274 mg/kg) Period 2 (test item) mean 6.287 (6.250 - 6.331 mg/kg) The groups are considered homogenous and comparable between study groups A and B, with respect to age, weight and sex which is in line with the Guideline on the conduct of bioequivalence

	studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2).
Participant flow	All 24 horses completed the study.
Adverse events	None
DISCUSSION	The 90% confidence intervals l for the ratio of the means (test/reference) for AUC and C_{max} fell within the pre-set acceptance boundaries of 80 - 125% and 70 - 143%, respectively. Therefore, the test item and reference product can be claimed bioequivalent.

As palatability can potentially be affected by a more concentrated product (thereby affecting efficacy) the applicant conducted a field study to demonstrate the palatability of the new product.

Twenty-five healthy animals were included in the study which were considered representative of the target population and met the required number of animals as stated in the Guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011). The palatability of the new product was assessed when given in 500 g of concentrate feed and determined over the first 5 days of treatment, with dose levels administered in accordance with the SPC. In addition, 5 days is considered to be of adequate duration for the purposes of the study. The voluntary acceptance times of the medicated feed were similar in the individual animal when compared to consumption of blank feed.

The overall palatability score was 75.8%, which meets the requirement in the guideline (EMA/CVMP/EWP/206024/2011) of greater than 70%.

Study title	Palatability assessment of a new formulation of Danilon Equidos
Objectives	The aim of the present study was to assess the palatability (voluntary acceptance) in horses of a new formulation of Danilon Equidos mixed with food.
Test site	Single EU site
Compliance with Regulatory guidelines	GLP and quality assurance statement provided
Test Product	Danilon Equidos Granules 500 mg/g
Control product/placebo	Danilon Equidos 1.5 g Granules for Top Dressing
Animals	25 healthy horses; of different breeds, 17 castrated males and 8 females, 3 - 20 years, weight 343 -

<table>
<tr><td></td><td>554 kg. All animals were identified individually with their unique name and identification number. Each animal had its own passport in accordance with EU regulations.</td></tr>
<tr><td>Randomisation</td><td>Different breeds and age ranges</td></tr>
<tr><td>Blinding</td><td>Not blinded. This was considered acceptable for this study.</td></tr>
<tr><td>Method</td><td>Acceptance was defined as voluntary full consumption of medicated feed within a maximum offering time of 15 minutes, and non-acceptance (failure) was defined by a partial intake or a refusal of the medicated feed within the offering time.</td></tr>
<tr><td>Statistical method</td><td></td></tr>
<tr><td>RESULTS</td><td>Acceptance was defined as voluntary full consumption of medicated feed within a maximum offering time of 15 minutes, and non-acceptance (failure) was defined by a partial intake or a refusal of the medicated feed within the offering time.
<table>
<tr><th>Parameter</th><th>Value</th></tr>
<tr><td>Total No. of Administrations</td><td>250</td></tr>
<tr><td>No. of valid administrations*</td><td>248</td></tr>
<tr><td>Total No. of successful administrations</td><td>188</td></tr>
<tr><td>Total No. of failures</td><td>60</td></tr>
<tr><td>No. of partial intakes</td><td>57</td></tr>
<tr><td>No of refusals</td><td>3</td></tr>
</table></td></tr>
<tr><td>Participant flow</td><td>All 25 horses completed the study</td></tr>
<tr><td>Adverse events</td><td>Animal No.4 had a thick whitish nasal discharge on day 1, no other clinical signs were noted, and no treatment required. Animal No.2, during day 5 was found with signs of discomfort . No other symptoms were noted, no treatment was required.</td></tr>
<tr><td>DISCUSSION</td><td>Based on the results, it can be concluded that palatability of the new more concentrated veterinary product was demonstrated as defined in the guideline EMA/CVMP/EWP/206024/2011 and the product is palatable when mixed with a portion of feed. The product was voluntarily taken by 75.8% of the studied horses.
The proposed wording in Section 4.9 of the SPC; ‘When added to a portion of feed the product will be</td></tr>
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	accepted by most horses', and Section 5.1 of the SPC 'When mixed with concentrate feed, the product was shown to be palatable to horses'. This wording is the same as for the existing product and considered acceptable.

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 benefit/risk profile of the productis favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)