ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Butagran Equi 200 mg/g Oral Powder for Horses

PuAR correct as of 04/10/2018 when RMS was transferred to BE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0394/001/DC
Name, strength and pharmaceutical form	Butagran Equi 200 mg/g Oral Powder for Horses
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer, The Netherlands
Active substance	Phenylbutazone
ATC Vetcode	QM01AA01
Target species	Horses
Indication for use	The product is indicated for the treatment of musculo-skeletal conditions where relief from pain and a reduction in the associated inflammation is required e.g. in lameness associated with osteoarthritic conditions, bursitis, laminitis and soft tissue inflammation, particularly where continued mobility is considered desirable. It is also of value in limiting post-surgical inflammation, myositis and other soft tissue inflammation. The product can be used as an anti-pyretic where this is considered advisable e.g. in viral respiratory infections.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	21st November 2012
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Denmark, Estonia, Germany, Italy, Latvia, Lithuania, Poland, Romania, Spain

I. SCIENTIFIC OVERVIEW

This was a generic application submitted under Article 13 (1) of Directive 2001/82/EC as amended, for Butagran Equi 200 mg/g Oral Powder for horses. The reference product was Pro-Dynam Oral Powder, marketed in the UK for over ten years.

The product is intended for use in horses for the treatment of musculo-skeletal conditions in which pain relief and reduction of swelling is required. The product may also be used to limit post-surgical inflammation, soft tissue inflammation and myositis. Additionally, it may be used as an anti-pyretic, when this is considered appropriate.

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, the slight reactions observed are indicated in the SPC[1]. The product is safe for the user, the consumer of foodstuffs from treated animals 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 benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains phenylbutazone and the excipients glucose monohydrate, hypromellose and butter vanilla flavour.

The container/closure system consists of a heat-sealed PET/LDPE/aluminium foil/LDPE laminated sachet of 5 grams of product, or a heat-sealed aluminium foil/LDPE/paper/LDPE laminated sachet of 5 grams of product. Sachets are packed in a cardboard box containing 100 sachets for single use. The particulars of the containers and controls performed are provided and conform to the regulation.

The products are of established pharmaceutical form and development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the products have been presented in accordance with the relevant European guidelines. A wet granulation process is used, using a simple step-progression process during which the product is periodically analysed.

C. Control of Starting Materials

The active substance phenlybutazone, an established active substance described in the European Pharmacopoeia. A certificate of suitability was provided. 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. Batch analytical data demonstrating compliance with this specification have been provided. The excipients glucose monohydrate and methylhydroxypropylcellulose are monographed in the Ph. Eur. The excipient butter vanilla flavour is not described in a pharmacopeia but is a well-known excipient and the specification is provided.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

Not applicable.

F. 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. Tests include those for appearance, dissolution, identification, phenylbutazone-related substances, purity and microbiological quality.

G. Stability

Stability data on the active substance were provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A re-test period of three years was agreed. Appropriate data for stability tests performed on the finished product were provided.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 36 months.
Shelf life after first opening the immediate packaging: use immediately after opening.

Do not store above 25°C

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been successfully claimed, results of pharmacological and toxicological tests are not required. Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

User Safety

The applicant provided a user risk assessment stating that the product contained the same ingredients as the reference product, and that the user safety data would therefore be comparable for the two products. Warnings and precautions

as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was 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

The product is intended for use in horses which will not be used for human consumption, and will therefore not enter the food chain.

Withdrawal Periods

- Not for use in horses intended for human consumption.
- Treated horses may never be slaughtered for human consumption.
- The horse must have been declared as not intended for human consumption under national horse passport legislation.

IV CLINICAL ASSESSMENT (EFFICACY)

This was a generic application according to Article 13, and bioequivalence with a reference product was successfully claimed. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacodynamics

Phenylbutazone is an acidic lipophilic non-steroidal anti-inflammatory active substance (NSAID), acting via inhibition of the cyclo-oxygenase system, demonstrating analgesic and anti-inflammatory ability.

Pharmacokinetics

The liver is the main organ of metabolism of phenlybutazone in the horse, with metabolites produced being gamma-hydroxybutazone and oxyphenbutazone. Hepatic metabolism predominantly dictates the plasma half-life and termination of action.

A suitable GLP[2] study provided evidence that product and reference product were bioequivalent.

A two-period, two sequence cross-over study using a 4.4 mg/kg dose of product or reference product was performed on eight target animals, five female and three male. Plasma samples were taken at suitable time points, (measuring the concentration of phenylbutazone), with a washout period between treatments of seven days. Suitable statistical analyses were used to define ANOVA[3], AUC_{last}[4] and C_{max}[5]. All data were acceptable.

IV.I.B Tolerance in the Target Species

As this is a generic application according to Article 13, and bioequivalence with a reference product was successfully claimed, tolerance studies were not required.

IV.I.C Resistance

As this is a generic application according to Article 13, and bioequivalence with a reference product was successfully claimed, resistance studies were not required.

IV.B Clinical Studies

This was a generic application according to Article 13, and bioequivalence with a reference product was successfully claimed. Further clinical studies were not required.

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

[2] GLP – Good Laboratory Practice.
[3] ANOVA – Analysis of variance.
[4] AUC – Area under the curve.
[5] C_{max} – Point at which active substance is at maximum concentration.

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)