ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Equinixin 25mg/g Granules for Horses (UK, CZ)
Flunixin 25mg/g Granules for Horses
Flunixine Granules 25 mg/g for Horses (FR)
Flunixin vet 25 mg/g Granules for Horses (FI)
Flunimeg 250mg Granules for Horses (DK)
Flunixin N-vet 25 mg/g Granules for Horses (SE)

PuAR correct as of 20/11/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0374/001/MR
Name, strength and pharmaceutical form	Equinixin 25mg/g Granules for Horses (UK, CZ) Flunixin 25mg/g Granules for Horses Flunixine Granules 25 mg/g for Horses (FR) Flunixin vet 25 mg/g Granules for Horses (FI) Flunimeg 250mg Granules for Horses (DK) Flunixin N-vet 25 mg/g Granules for Horses (SE)
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP Northern Ireland
Active substance(s)	Flunixin (as flunixin meglumine)
ATC Vetcode	QM01AG90
Target species	Horses
Indication for use	For the alleviation of inflammation and pain associated with musculo-skeletal disorders.

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	Application in accordance with Article 32 (1) of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original mutual recognition procedure	27 October 2010
Date product first authorised in the Reference Member State	09 March 2006
Concerned Member States for original procedure	Austria Czech Republic Denmark Finland France Germany Greece Ireland Norway Romania Slovakia Sweden

I. SCIENTIFIC OVERVIEW

Equinixin 25 mg/g granules for horses is authorised for use in horses for the alleviation of inflammation and pain associated with musculo-skeletal disorders. The product is intended for oral administration only and contains flunixin (as flunixin meglumine) 250 mg per 10 g sachet. The product is supplied in cartons of 10 laminated foil sachets (C1S/LDPE/Alu/SP) each containing 10 g granules. The recommended dosage rate is 1.1 mg flunixin per kg bodyweight i.e. one 10 g sachet per 227 kg (500 lb) bodyweight once daily for up to 5 consecutive days according to clinical response. The product is administered by sprinkling on a small amount of food.

This application for the mutual recognition of a UK marketing authorisation was submitted in accordance with Article 32 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The product was authorised in the UK on 9th March 2006. Bioequivalence is claimed with the reference product Finadyne Granules, which has been approved in the UK since 1987.

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.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance flunixin (as flunixin meglumine) and excipients povidone K30, crospovidone, pregelatinised starch (maize), lactose monohydrate, sucrose, peppermint flavour and cellulose microcrystalline.

The product is presented in cartons of 10 laminated foil sachets (C1S/LDPE/Alu/SP) each containing 10 g granules.

The choice of formulation is justified.

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

[1] Summary of Product Characteristics

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance, flunixin meglumine, is an established active substance and supporting data have been provided in the form of a Certificate of Suitability. It is considered that the manufacturing process is adequately controlled and the active substance specifications have been suitably justified.

All excipients, with the exception of peppermint flavour, are the subject of monographs in the European Pharmacopoeia. Compliance with the requirements of the pharmacopoeia is therefore applied as the specification for each of these ingredients. In the case of peppermint flavour, an appropriate specification has been developed that identifies the material by its physical properties, and limits heavy metal and microbiological contaminants in accordance with normal requirements for a flavour used in food.

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

Lactose used in the manufacture of the granules is the sole ingredient obtained from materials of ruminant animal origin. It is obtained, using calf rennet, from milk fit for human consumption. All components of the product have been demonstrated to comply with relevant guidelines on minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicines.

E. Control on intermediate products

There are no intermediate products.

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.

G. Stability

Active substance:
Data have been provided which indicate that the active substance is stable when stored in the appropriate container under appropriate conditions. The retest period of three years is justified.

Finished product:
Data have been provided which indicate that the finished product is stable for 2 years when stored at a temperature below 25° C.
The product should be used immediately after addition to feed.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Special precautions for storage:

- Do not store above 25°C.
- Keep the sachet in the outer carton

Shelf-life:

- Shelf life of the veterinary medicinal product as packaged for sale: 2 years
- Shelf-life after addition to feed: Use immediately

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

The application was submitted in accordance with Article 13.1 of Directive 2001/82/EC, as amended, and bioequivalence with the reference product, Finadyne Granules, has been demonstrated. Therefore, results of pharmacological, toxicological and clinical trials are not required.

User Safety

Due to the nature of the product, the most likely routes of accidental exposure are dermal, ocular and oral. The dermal and ocular exposures are highly likely during administration of the product, whereas oral exposure is less likely. As the product is for horses and to be administered by vets and farmers, the risk of accidental exposure to children is considered to be very low.

The following precautions are listed on the SPC and product literature:

- The product may cause hypersensitivity (allergy) in sensitive individuals. Reactions may be serious. People with known hypersensitivity to substances belonging to the non-steroidal anti-inflammatory group should avoid contact with the product.
- To avoid possible sensitisation reactions, avoid contact with the skin. Impermeable gloves should be worn during application. In case of skin contact, wash exposed area with plenty of water and soap. If symptoms persist seek medical advice.
- Avoid eye contact. Wear approved safety glasses when handling this product. In the case of accidental contact with eyes, rinse immediately with plenty of water and seek medical advice.
- Avoid inhalation. Wear either a disposable half-mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143 when handling the product. In case of inhalation, seek medical advice.
- Wash hands after use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guidelines. The PEC^{2}_{soil} values derived from several studies were acceptable and in accordance with VICH guidelines. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[2] Predicted Environmental Concentration

III.B Residues documentation

The application was submitted in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC and Directive 2009/9/EC, on the basis that the product has been demonstrated to be a generic and therefore results of residues studies are not required.

Withdrawal Periods

Meat and offal: 15 Days
Milk: Not permitted for use in lactating mares producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13.1 of Directive 2001/82/EC, as amended, and bioequivalence with the reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics:
Flunixin meglumine is a relatively potent non-narcotic, non-steroidal analgesic with anti-inflammatory and anti-pyretic properties.

Flunixin meglumine acts as a reversible non-selective inhibitor of cyclo-oxygenase (both COX 1 and COX 2 forms), an important enzyme in the arachidonic acid cascade pathway which is responsible for converting arachidonic acid to cyclic endoperoxides. Consequently, synthesis of eicosanoids, important mediators of the inflammatory process involved in central pyresis, pain perception and tissue inflammation, is inhibited. Through its effects on the arachidonic acid cascade, flunixin also inhibits the production of thromboxane, a potent platelet pro-aggregator and vasoconstrictor which is released during blood clotting. Flunixin exerts its antipyretic effect by inhibiting prostaglandin E2 synthesis in the hypothalamus. Although flunixin has no direct effect on endotoxins after they have been produced, it reduces prostaglandin production and hence reduces the many effects of the prostaglandin cascade. Prostaglandins are part of the complex processes involved in the development of endotoxic shock.

Pharmacokinetics:
The application was based on essential similarity of Equinixin 25 mg/g Granules for horses to the established product Finadyne Granules. The applicant demonstrated that the products were essentially similar by submitting the report of a bioequivalence study. This study compared the two products in terms of

how much of the active ingredient, flunixin, was absorbed into the bloodstream when the products were given as recommended, i.e. by mouth.

The study utilised a well-accepted study design known as a "crossover", and involved two groups of horses. The first group received a single dose of Equinixin Granules. After a suitable delay to allow all the flunixin to disappear from their systems, the animals received a similar dose of Finadyne Granules. The second group of animals were treated in the same way except that they received Finadyne first and Equinixin second, hence the term "crossover". Blood samples were collected from all the horses at intervals throughout the study and the amount of flunixin in these samples was measured using a validated method. AUC[3] was used to demonstrate bioequivalence in accordance with the bioequivalence guidelines. Confidence intervals from Cmax[4] and AUC were within the stipulated range of 80-125%, bioequivalence was therefore established.

Tolerance in the Target Species of Animals

The applicant conducted a target animal safety study in horses following the oral administration of Equinixin 25 mg/g granules for horses. The study was conducted in accordance with the principles of Good Laboratory Practice. In this study, a suitable number of horses were divided into different groups. The horses were given six daily doses of the product at either the recommended dose or three times the recommended dose. Blood and faeces samples were collected at predetermined intervals up to 14 days from the first dose. A comprehensive range of tests were carried out on the blood samples to check the blood cells themselves, the levels of various enzymes and other substances in the blood and the clotting ability of the blood. The faeces samples were checked for the presence of blood. The tests included were chosen because of the known effects of NSAIDs on the gastrointestinal tract, kidneys, blood cells and clotting mechanisms. No significant adverse effects were noted in the group of animals which received the recommended dose of Equinixin Granules six times. At the higher dose rate, some changes were observed, likely indicating minor toxicological effects of flunixin on the kidneys, the white blood cells and possibly the gastro-intestinal tract. These findings are typical of the effects of NSAIDs. All the changes had reversed by the end of the study, 14 days after the first treatment.

IV.B Clinical Studies

As the application was made on the basis of essential similarity with an established product marketed in the EU for at least 10 years, there is no requirement to provide results of toxicological or pharmacological tests and clinical trials. As bioequivalence with the reference product has been demonstrated, clinical efficacy is likely to be similar for the two products.

[3] Area under the curve
[4] Maximum plasma concentration

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.

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)