ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pyroflam 50mg/ml Solution for Injection for Cattle, Horses and Pigs
Flunixin Solution Injectable 50 mg/ml Bayer (France)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0231/002/DC
Name, strength and pharmaceutical form	Pyroflam 50 mg/ml Solution for Injection for Cattle, Horses and Pigs
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry County Down BT35 6JP Northern Ireland
Active substance(s)	Flunixin Meglumine
ATC Vetcode	QM01AG90
Target species	Cattle, Horses and Pigs
Indication for use	In horses: • alleviation of inflammation and pain associated with musculo-skeletal disorders. • alleviation of visceral pain associated with colic. • adjunctive therapy in the treatment of endotoxaemia and septic shock. In cattle: • reduction of acute inflammation associated with respiratory disease. • adjunctive therapy in the treatment of acute mastitis. In Pigs: • Adjunctive therapy in the treatment of swine respiratory diseases.

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**).

PuAR correct as of 19/11/2018 when RMS was transferred to FR.

Please contact the RMS for future updates.

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 13.1 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	03 December 2009
Concerned Member States for original procedure	France

I. SCIENTIFIC OVERVIEW

Pyroflam 50 mg/ml Solution for Injection for Cattle, Horses and Pigs contains the active substance flunixin (as flunixin meglumine). The product is authorised to be used in cattle, horses and pigs. The product is used in the treatment of alleviation of inflammation and pain associated with musculo-skeletal disorders, alleviation of visceral pain associated with colic and adjunctive therapy in the treatment of endotoxaemia and septic shock in horses, reduction of acute inflammation associated with respiratory disease, as an adjunctive therapy in the treatment of acute mastitis in cattle and as an adjunctive therapy in the treatment of swine respiratory diseases in pigs. The product is to be administered intravenously in cattle and horses and intramuscularly in pigs. For use in equine colic, the recommended dose rate is 1.1 mg flunixin/kg bodyweight equivalent to 1 ml per 45 kg bodyweight. The treatment may be repeated once or twice if colic recurs. For use in musculo-skeletal disorders, the recommended dose rate is 1.1 mg flunixin/kg bodyweight equivalent to 1 ml per 45 kg bodyweight, once daily for up to 5 days according to clinical response and 0.25 mg/kg (1 ml per 200 kg) every 6-8 hours for the treatment of endotoxaemia or septic shock associated with gastric torsion and with other conditions in which the circulation of blood to the gastrointestinal tract is compromised. In cattle, the recommended dose rate is 2.2 mg flunixin/kg bodyweight equivalent to 2 ml per 45 kg bodyweight. And in pigs, the recommended dose rate is 2 ml per 45 kg bodyweight (equivalent to 2.2 mg flunixin/kg) once by intramuscular injection, in the neck, in conjunction with appropriate antimicrobial therapy. The injection volume should be limited to a maximum of 5 ml per injection site.

The extension application to add pigs as a target species was approved in December 2009. The original application for Pyroflam solution for injection was supported by data demonstrating bioequivalence in cattle and horses with the reference product. However, the extension application relied upon waiver 4.b of the CVMP bioequivalence guideline "The product is to be parenterally or orally administered as a solution and contains the same active substance(s) and excipients in the same concentrations as the veterinary medicinal product currently approved for use in the target species which is the subject of the new application". The applicant has demonstrated that Pyroflam 50 mg/ml Solution for Injection for cattle, horses and pigs is identical in composition to the reference product.

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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains flunixin meglumine as an active substance and excipients propylene glycol, disodium edetate, sodium formaldehyde sulphoxylate dehydrate, diethanolamine, phenol, hydrochloric acid and water for injections.

The container/closure system consists of clear colourless glass (Type I) vials of nominal capacity 50, 100 or 250 ml, closed with bromobutyl rubber closures secured with aluminium overseals.

The choice of the formulation and presence of preservative is justified.

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

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 is flunixin meglumine, 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. Batch analytical data demonstrating compliance with this specification have been 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 this product.

[1] SPC = Summary of product characteristics

E. Control on intermediate products

A number of non-routine tests have been performed on the bulk product. These are considered acceptable.

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.

G. 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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The claim of a 28 days stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at +25°C.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Storage conditions:
Do not store above 25°C.
Keep container in the outer carton to protect from light.
Following withdrawal of the first dose use the product within 28 days. Discard unused material.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.
The pharmacological aspects of this product are identical to the reference product.
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.

Toxicological Studies

As this is a generic application according to Article 13.1, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.
The toxicological aspects of this product are identical to the reference product.
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.

User Safety

The following operator warnings are included in the SPC and product literature:
Avoid eye contact and direct contact with skin
Wash hands after use. In the case of accidental contact with eyes, rinse immediately with plenty of water and seek medical advice.
Avoid accidental self-injection.
To avoid possible sensitisation reactions, avoid contact with the skin.
Gloves should be worn during application.
The product may cause reactions in sensitive individuals. If you have known hypersensitivity for non-steroidal anti-inflammatory products do not handle the product. Reactions may be serious.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

As the original application was submitted according to Article 13.1, of Directive 2001/82/EC, the ecotoxicity data was not required.

For the extension application, the environmental risk assessment was carried out in accordance with VICH Phase 1 guidelines and using the CVMP guidance in support of VICH guidelines. The product is indicated for use in pigs and is administered by parenteral injection. The residues of flunixin will reach the environment in the excreta of treated animals.

Pigs will be treated with the product when in housing. Residues will reach the environment when manure from the treated animals is spread onto land. As an injectable NSAID, it is accepted that treatment with the product will be of small numbers of animals resulting in low environmental exposure. Further indication of the low exposure comes from the PEC_{soil} value of 9.6 μg/kg. There are no other concerns regarding the product which require further assessment. The assessment of environmental safety can end at Phase I.

The environmental risk assessment has demonstrated that use of this product will not result in extensive environmental exposure. The environmental safety is considered acceptable.

III.B Residues documentation

Residue Studies

The application is made in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC and therefore data on residues depletion studies are not required.

MRLs

Flunixin is listed in Annex I of Council Regulation 2377/90

MRLs are listed below:

	Marker residue	Cattle	Horse	Pigs
Muscle	Flunixin	20 µg/kg	10 µg/kg	50 µg/kg
Liver	Flunixin	300 µg/kg	100 µg/kg	200 µg/kg
Kidney	Flunixin	100 µg/kg	200 µg/kg	30 µg/kg
Fat	Flunixin	30 µg/kg	20 µg/kg	10 µg/kg
Milk	5-Hydroxy Flunixin	40 µg/kg	-	-

Withdrawal Periods

Based on the data provided, the following withdrawal periods are included on the SPC:

Cattle: Meat and offal: 10 Days
Milk: 24 Hours

Horses: Meat and offal: 10 Days
Milk: The product is not authorised for use in lactating animals producing milk for human consumption.

Pigs: Meat and offal: 22 Days

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, this information is not required as it has already been presented for the reference product.

Bioequivalence

The applicant is claiming exemption from the need to conduct bioequivalence studies in accordance with exemption 4 b) of the guideline for the conduct of bioequivalence studies, EMEA/CVMP/016/00:

*"*The product is to be parenterally or orally administered as a solution and contains the same active substance(s) and excipients in the same concentrations as the veterinary medicinal product currently approved for use in the target species which is the subject of the new application"

Additionally, the applicant refers to section 5.1.6 (Parenteral Solutions) of the Note for Guidance on the investigation of bioavailability and bioequivalence, CPMP/EWP/QWP/1401/98:

“In the case of other parenteral routes, e.g. intramuscular or subcutaneous, if the product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same or comparable excipients as the medicinal products currently approved, then bioequivalence testing is not required.”

The applicant states that the product is identical in formulation to the veterinary medicinal product already approved for use in the target species. A comparison of the formulations is presented.

Tolerance in the Target Species of Animals

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, this information is not required as it has already been presented for the reference product.

IV.B Clinical Studies

Since the application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended by Directive 2004/28/EC, on the basis of being a generic of a reference medicinal product, this information is not required as it has already been presented for the reference product.

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)