



**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**

Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs

**PuAR correct as of 23/01/2019 when RMS was transferred to DE.
Please contact the RMS for future updates.**

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0329/001/E/001
Name, strength and pharmaceutical form	Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs
Applicant	Norbrook Laboratories Ltd. Station Works Camlough Road NEWRY Co. Down, BT35 6JP Northern Ireland
Active substance(s)	Flunixin (as flunixin meglumine)
ATC Vetcode	QM01AG90
Target species	Cattle, Horses and Pigs
Indication for use	<p>In horses, indicated for the alleviation of inflammation and pain associated with musculo-skeletal disorders and for the alleviation of visceral pain associated with colic, also indicated for the treatment of endotoxaemia or septic shock associated with gastric torsion and for other conditions in which the circulation of the blood to the gastrointestinal tract is compromised.</p> <p>In cattle, indicated for the control of acute inflammation associated with respiratory disease. It may also be used as adjunctive therapy in the treatment of acute mastitis.</p> <p>In pigs, the product is indicated for use as an adjunctive therapy in the treatment of swine respiratory diseases.</p>

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	Essential similarity application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	29 October 2008
Date product first authorised in the Reference Member State (MRP only)	26 November 1998
Concerned Member States for original procedure	Germany Iceland The Netherlands Portugal Sweden

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; the slight reactions observed are indicated in the SPC.

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 reference product is Finadyne Solution, marketed by Schering-Plough Animal Health. The reference product has been authorised in the UK for use in cattle and horses since August 1987. Pigs were added as a target species in November 2003.

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

II. QUALITY ASPECTS

A. Composition

The product contains 50 mg/ml flunixin as flunixin meglumine and excipients sodium formaldehyde sulphonylate, disodium edetate, phenol, propylene glycol, diethanolamine, hydrochloric acid and water for injections.

This product is supplied in 50 ml, 100 ml and 250 ml clear colourless glass vials, complete with bromobutyl bungs and aluminium caps.

The product is also presented in packs of 5, 10 and 12 vials for the 50 ml and 100 ml and packs of 5 vials for the 250 ml, each vial is provided in an individual carton which is packed into a plain brown outer cardboard containing the specified number of vials.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are 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 as 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

A TSE declaration that the product contains no materials of animal origin falling within the scope of the guideline was provided. An assurance has been given that any ingredients that could be of animal origin will be obtained only from non-animal sources.

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 sites 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 28 day stability after broaching is based on the demonstration of stability for a batch broached and stored for 28 days at 25°C/60%RH.

H. Genetically Modified Organisms

None

J. Other Information

Shelf-Life:

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

Following withdrawal of the first dose use the product within 28 days. Discard unused product.

Special Precautions for Storage:

Store below 25°C. Keep the vial in the outer carton to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

The pharmacological aspects of this product are identical to the reference product Finadyne Solution.

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, consumers and the environment.

III.A Safety Testing

Pharmacological Studies

The authorisation is in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC and therefore data on pharmacological tests are not required.

The applicant has submitted two pharmacokinetic studies in cattle and horses. These studies are reported in Part IV of this report.

Toxicological Studies

The authorisation is in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC and therefore data on toxicological tests are not required.

The applicant has submitted two tolerance studies in cattle and horses. These studies are reported in detail in Part IV of this report.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which addresses the different routes of exposure and justifies the user warnings. The main routes of exposure are from accidental contact with skin and eyes during administration or by accidental self-injection. The product is a prescription only medicine and will be administered by veterinary surgeons or farmers and therefore accidental exposure to children is not expected.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Avoid eye contact and direct contact with skin.
- 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.
- Wash hands after use.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that exposure will not be extensive and that there are no concerns for the environment which require further assessment.

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

Residue Studies

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

Pharmacokinetics

The authorisation is in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC and therefore data on pharmacological tests are not required. The applicant has submitted pharmacokinetic studies in cattle and horses, these studies are reported in Part IV of this report.

MRLs

Flunixin is listed in Annex I of Council Regulation 2377/90. The marker substance is flunixin in all target species and 5-hydroxyflunixin in milk from cattle. MRLs are listed below:

	Porcine	Equine	Bovine
Muscle	50 µg/kg	10 µg/kg	20 µg/kg
Liver	200 µg/kg	100 µg/kg	300 µg/kg
Kidney	30 µg/kg	200 µg/kg	100 µg/kg
Fat / skin	10 µg/kg	20 µg/kg	30 µg/kg
Milk	-	-	40 µg/kg

The excipient, meglumine is not pharmacologically active in the formulation and is listed in the CVMP publication "Substances considered as not falling within the scope of Council Regulation 2377/90" [EMEA/CVMP/046/00-Rev4 18 November 2002] at doses up to 1.5mg/kg bw.

Withdrawal Periods

Flunixin 50 mg/ml solution for injection has the same withdrawal periods as the reference product as follows:

- Cattle: Meat 7 days
 Milk 36 hours
- Horses: Meat 7 days
- Pigs: Meat 22 days

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

This is an application for a generic product made on the basis of 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. Consequently, no pharmacodynamic data have been provided, the information in Section 5.1 of the SPC is based on the established characteristics of flunixin and is considered accurate.

Pharmacokinetics

In order to substantiate the essential similarity claim, the applicant conducted bioequivalence studies in both cattle and horses to compare the plasma concentrations of flunixin achieved with the two formulations.

The study in cattle involved six animals being treated with 2.2 mg flunixin per kg bodyweight, the recommended dose rate for cattle. The calculated dose was intravenously administered into the jugular vein on a single occasion. Blood samples were taken from each animal for assay of the flunixin content at the following time points: 0, 10, 15, 30, 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 32 and 48 hours after administration. The study demonstrated bioavailability of the active ingredient for up to the dosing interval of 24 hours.

The study in horses was of a cross-over design with two treatment periods. Following acclimatisation for 6 days, six horses were randomly allocated to 2 groups based on bodyweight involved. During the first period group A was treated with Flunixin Injection and group B with the reference product. After a 7 day washout period, group A was treated with the reference product and group B with Flunixin Injection. Blood samples were taken at the following timepoints: 10, 15, 30 and 45 minutes, then 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 32 hours after administration. The results from the two treatments were compared. This study demonstrated bioequivalence of the test product, Flunixin Injection, with the pioneer product, Finadyne Solution.

No bioequivalence study in pigs was presented. In line with exemption 4b of the bioequivalence guidelines, this study is not required. The product has also been shown to be equivalent to the reference product in both cattle and horses, therefore the lack of the study is satisfactory. The information given in Section 5.2 of the SPC is suitable.

Tolerance in the Target Species of Animals

The study in cattle involved 18 cattle being split into three groups. The first group was given the recommended dose rate of 2.2 mg flunixin/kg bodyweight (2 ml/45 kg), the second group was given 2 x recommended dose rate, 4.4 mg flunixin/kg bodyweight (4ml/45kg) and the third group were left untreated as the control group. The test article was administered once daily, by slow intravenous

injection, for 5 consecutive days. The study demonstrated that up to 2x the recommended dose rate was well tolerated when administered by slow intravenous injection for 5 days.

The study in horses involved six horses which were identically treated at 2 x recommended dose rate, once daily by slow intravenous injection for 5 consecutive days. The study demonstrated the lack of adverse effects of administering 2x the dose rate intravenously for 5 days

IV.B Clinical Studies

The authorisation is in accordance with Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC and therefore data on pharmacological and toxicological tests are not required. As bioequivalence with the pioneer product has been demonstrated, clinical efficacy is likely to be the same for the two products.

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 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