Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs (DE, IS, UK)

Norixin 50mg/ml Solution for Injection for Cattle, Horses and Pigs (NL)

Flunixin 3E 50mg/ml Solution for Injection for Cattle, Horses and Pigs (PT)

Flunixin N-Vet for Cattle, Horses and Pigs (SE)

Date: 16 April 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0325/001/MR
Name, strength and pharmaceutical form	Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs (DE, IS, UK) Norixin 50mg/ml Solution for Injection for Cattle, Horses and Pigs (NL) Flunixin 3E 50mg/ml Solution for Injection for Cattle, Horses and Pigs (PT) Flunixin N-Vet for Cattle, Horses and Pigs (SE)
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Active substance(s)	Flunixin (as flunixin meglumine)
ATC Vetcode	QM01AG90
Target species	Cattle, Horses and Pigs
Indication for use	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. 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. In pigs, the product is indicated for use as an 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 Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	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 UK (MRP only)	26 November 1998
Concerned Member States for original procedure	IS, NL, PT, SE and UK (former RMS)

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 sulphoxylate, disodium edetate, phenol, propylene glycol, sodium hydroxide, 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 (PHARMACO-TOXICOLOGICAL)

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:

The veterinary medicinal product can cause skin and eye irritation. Avoid contact with skin and eyes. In case of accidental skin exposure, wash the affected area immediately with plenty of water. In case of accidental eye contact, rinse immediately with plenty of water. If skin and/or eye irritation persists, seek medical advice immediately and show the package leaflet or the label to the physician.

The veterinary medicinal product can cause hypersensitivity (allergy) reactions. People with known hypersensitivity to non-steroidal anti-inflammatory drugs should avoid contact with the veterinary medicinal product. Adverse reactions can be serious. Gloves should be worn during application.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

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.

MRLs

Flunixin is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:.

Pharmacologically active Substance	***Marker residue***	***Animal Species***	***MRL***	***Target Tissues***
Flunixin	Flunixin	Bovine	20 µg/kg 30 µg/kg 300 µg/kg 100 µg/kg	Muscle Fat Liver Kidney
		Porcine	50 µg/kg 10 µg/kg 200 µg/kg 30 µg/kg	Muscle Fat Liver Kidney
		Equidae	10 µg/kg 20 µg/kg 100 µg/kg 200 µg/kg	Muscle Fat Liver Kidney
	5-Hydroxyflunixin	Bovine	40 µg/kg	Milk

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 Regulation (EC) No. 470/20091, with regard to residues of veterinary medicinal products in foodstuffs of animal origin” (EMA/CVMP/519714/2009 Rev. 48) 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

Not authorised for use in mares producing milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

This is an application for a grouped type II variation (B.II.a.3.b.2) including the exchange of the excipient diethanolamine with sodium hydroxyide from the formulation of the product Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs (Norbrook Laboratories Limited).

The reason for the required exchange is that, since carcinogenic potential of diethanolamine has been shown in mice, this excipient, used in veterinary medicinal products as a solubiliser/pH adjuster, was classified as possible carcinogenic (EMA/CVMP/473059/2018). Therefore, diethanolamine was removed from the MRL (Maximum residue limit) listing and should no longer be included in any veterinary medicinal products intended for use in food producing species.

IV.A Pre-Clinical Studies

Pharmacology

Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs is intended for use in cattle and horses by intravenous administration and in pigs by intramuscular route.

Since the product is intended for intravenous administration in horses and cattle, demonstration of *in vivo* bioequivalence for the new formulation of this product for these target species can be waived in accordance with the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/2000 Rev.2), section 7.1.a.

Regarding the intramuscular injection in pigs, no waiver according to the above mentioned guideline applies. Thus, the applicant conducted a bioequivalence study with the two formulations of the product to evaluate plasma levels of flunixin following intramuscular administration in pigs, see section "Pharmacokinetics".

Bioequivalence of the two formulations has been demonstrated satisfactorily.

Pharmacodynamics

Bioequivalence of the two formulations has been accepted for the intravenous injection in horses and cattle and has been demonstrated for the intramuscular injection in pigs. Therefore, no new pharmacodynamic data need to be presented.

Pharmacokinetics

In order to conclude on a comparable efficacy and safety profile of the new formulation with the former composition of the veterinary medicinal product, the applicant conducted a bioequivalence study to determine plasma levels of flunixin in pigs in accordance with VICH Guideline VICH GL 52 “Bioequivalence: blood level bioequivalence study” (EMA/CVMP/VICH/ 751935/2013-Corr.1.1).

A cross-over study with two treatment periods was carried out in pigs with the two formulations of the product.

Comparison of the plasma concentrations of groups treated with either the new or the old formulation revealed bioequivalence of the two formulations of Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs after intramuscular administration in pigs.

Changes concerning section 5.2 “Pharmacokinetic particulars” arising from the exchange of the excipient diethanolamine with sodium hydroxide has been included in the product literature.

Tolerance in the Target Species of Animals

Bioequivalence of the two formulations with respect to the intravenous administration in horses and cattle can be assumed. Therefore, no data on tolerance for the target animal species horse and cattle is required.

Bioequivalence of the two formulations of the product Flunixin 50 mg/ml Solution for Injection for Cattle, Horses and Pigs (Norbrook Laboratories Limited after intramuscular administration in pigs has been demonstrated successfully by an *in vivo* bioequivalence study. No adverse events were observed during the bioequivalence study in pigs.

No local reactions were noted for any of the injection sites monitored during the study. Both formulations were well tolerated by the pigs on study.

Given that the two formulations of Flunixin are intended to be administered to the same target species, using the same routes of administration at the same dose rates, a similar safety profile can be assumed. In addition, it is considered that the risk to the target species will be similar for both formulations of the product.

IV.B Clinical Studies

Since bioequivalence has been accepted for intravenous application for horses and cattle and moreover, has been demonstrated for the intramuscular injection in pigs, clinical efficacy is considered to be the same for the two formulations of the product. Further information regarding clinical data is not considered necessary.

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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section 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.

•	16 April 2021	Changes in the composition (excipients) of the finished product
•	28 March 2019	Change in manufacturer responsible for batch release in the EU from UK to Ireland.
•	23 January 2019	Change in RMS from UK to DE.
•	23 July 2018	Changes to a test procedure for the finished product.
•	23 January 2018	Update of the test procedure to comply with the updated general Ph. Eur monograph. Change in the specification parameters and/or limits of the finished product. Change in the specification limits of the finished product.
•	15 January 2018	Increase in batch size (2000 litre and 4000 litre) of the finished product.
•	28 November 2014	Update to the DDPS.
•	23 December 2013	Renewal.
•	26 October 2012	Variation to change the name of the Veterinary Medicinal Product.
•	27 September 2012	Submission of an updated European Pharmacopoeia Certificate of Suitability from an active substance manufacturer.
•	25 January 2012	Variation to change the distributor address.
•	09 August 2010	Repeat Use – To add Iceland as a CMS.
•	16 July 2009	To change the medicinal product name in the UK from “Norixin 50mg/ml Solution for Injection for Cattle, Horses and Pigs” to “Flunixin 50mg/ml Solution for

		Injection for Cattle, Horses and Pigs”
•	26 March 2009	To change the product name in Sweden from Norixin vet for Cattle, Horses and Pigs to Fluxin N-Vet for Cattle, Horses and Pigs.
•	20 February 2009	MRP (UK as RMS).
•	07 March 2008	Submission of a new European Pharmacopoeia Certificate of Suitability.
•	20 July 2007	Line extension.
•	19 March 2007	Change of legal category from POM to POM-V.
•	06 March 2006	Addition of safety warnings.
•	23 November 2005	Addition of a site of secondary assembly.
•	18 March 2004	Renewal.
•	16 February 2004	Addition of a safety warning.
•	21 August 2003	Addition of a pack size.
•	17 May 2001	Addition of an active substance manufacturer.
•	26 November 1998	Copycat.