MINISTERIO DE SANIDAD Y CONSUMO
agencia española de medicamentos y productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0127/001/MR
Name, strength and pharmaceutical form	NIGLUMINE 50 mg/ml solution for injection for cattle, horses and pigs
Applicant	LABORATORIOS CALIER, S.A. C/ Barcelonès, 26 (Pla del Ramassà) 08520 Les Franqueses del Vallès (Barcelona) SPAIN
Active substance(s)	Flunixin meglumine
ATC Vet code	QM01AG90
Target species	Bovine, equine and porcine
Indication for use	Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs. Horses: For the alleviation of inflammation and pain associated with musculoskeletal disorders, especially in acute to sub-acute stages and to relieve visceral pain associated with colic. Pigs: For alleviation of Mastitis-Metritis-Agalactia Syndrome (MMA) with appropriate antibiotic treatment to reduce clinical signs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

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 mutual recognition procedure	Day 90: 28/05/2008
Date product first authorised in the Reference Member State (MRP only)	27/02/2007
Concerned Member States for original procedure	AT, BE, BG, DE, FR, HU, IT, NL, PT and RO

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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

II. QUALITY ASPECTS

A. Composition

The product contains 50 mg/ml of flunixin meglumine and excipients propylene glycol, diethanolamine, phenol, disodium edetate, HCl and water for injection.

The container/closure system are clear glass vials, type II (Eur. Ph.), of 50 and 100 ml, or 250 ml provided with grey or pink rubber stoppers of bromobutyl, formulation PH 4001/45 and metallic aluminium capsules with blue or gold flip-off ring.
The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the presence/absence 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.

The applicant justifies the quality of the raw material by means of an Active Substance Master File (ASMF Number TH/1462/05 in Spain).

Disodium edetate, propylene glycol, phenol, water for injections in bulk and hydrochloric acid concentrated comply with the monographs number 01/2005:0232; 01/2005:0430; 01/2005:0631; 01/2005:0169 and 01/2005:0002 of the European Pharmacopoeia, respectively. Diethanolamine complies with the monographs number USP 23-NF 18, p. 2241.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control on intermediate products (pharmaceuticals)

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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.

III. SAFETY AND RESIDUES ASSESSMENT

As this is a generic application according to Article 13 results of safety tests are not required.
The product NIGLUMINE has the same qualitative and quantitative composition as the reference product FINADYN® solution for injection (SCHERING PLOUGH S.A.).

III.A Safety Testing

Pharmacological Studies

Flunixin meglumine acts as a reversible non-selective inhibitor of cyclo-oxygenase (COX), an enzyme that converts arachidonic acid to unstable cyclic endoperoxides, which are transformed into prostaglandins, prostacyclines and thromboxanes.

Flunixin meglumine administered by intravenous route to cattle and horses, as a single dose of 2.2 mg/kg and 1.1 mg/kg respectively leads to an elimination half-life of 4 hours and 2 hours respectively.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that Niglumine is safe for the user.
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 is 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

Residue Studies

The applicant has conducted a residue depletion study to determine flunixin meglumine residues in injection site tissues samples obtained from sows.

In case of bovine and equine, because the route of administration is intravenous, the applicant is not required to provide the results of residues studies because all these data are in the documentation that supports the marketing authorization of the reference product, FINADYN® solution for injection **(**SCHERING PLOUGH S.A.).

The analytical method was HPLC with UV detection. The method was fully validated.

MRLs

Flunixin meglumine is listed in Annex I of Council Regulation 2377/90 by the Regulation 2728/1999. The marker substance is 5-hydroxy flunixin for milk and flunixin for muscle, liver, kidney and fat.

MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissue
Flunixin	Flunixin	Bovine	20 µg/kg 30 µg/kg 300 µg/kg 100 µg/kg	Muscle Fat Liver Kidney
	5-hydroxy flunixin	Bovine	40 µg/kg	Milk
	Flunixin	Porcine	**50 µg/kg** 10 µg/kg 200 µg/kg 30 µg/kg	Muscle Skin+Fat Liver Kidney
	Flunixin	Equidae	10 µg/kg 20 µg/kg 100 µg/kg 200 µg/kg	Muscle Fat Liver Kidney

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:

Cattle: Meat: 14 days
Milk: 2 days
Horses: Meat: 28 days
Pigs: Meat: 28 days

Not permitted for use in lactating horses producing milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

For generics, insert in the relevant sections as appropriate:

As this is a generic application according to Article 13.1 of Directive 2001/82/EC as amended, based on the bioequivalence of Niglumine 50 mg/ml solution for injection for cattle, horses and pigs and the reference product Finadyne 5% solution for injection, efficacy studies are not required. The efficacy claims for this product are equivalent to those of 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 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 veterinary Heads of Agencies website (www.hma.eu).