FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

EMDOFLUXIN 50 mg/ml Solution for Injection for cattle, pigs and horses

DATE : 16/06/2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0417/001/DC
Name, strength and pharmaceutical form	EMDOFLUXIN 50 mg/ml Solution for Injection for cattle, pigs and horses
Applicant	EMDOKA bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium
Active substance(s)	Flunixin (as flunixin meglumine)
ATC Vetcode	QM01AG90
Target species	Cattle, pigs and horses
Indication for use	Horses: Alleviation of inflammation and pain associated with musculoskeletal disorders. Alleviation of visceral pain associated with colic. Cattle: Reduction of clinical signs during respiratory infections in association with an appropriate anti-infective treatment. Pigs: Adjunctive therapy in the treatment of MMA (Mastitis-Metritis-Agalactia) syndrome in sows. Reduction of fever associated with respiratory disorders in association with an appropriate anti-infective treatment.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	13/05/2020
Concerned Member States for original procedure	AT, BE, BG, DE, DK, EE, ES, HU, HR, IE, IT, LT, LU, LV, NL, SI, UK

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 adverse 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 (as meglumine) and excipients phenol, sodium formaldehyde sulfoxylate, disodium edetate, sodium hydroxide, hydrochloric acid, dilute, propylene glycol and water for injections.
The packaging of the finished product is as described on the SPC. The particulars of the containers and controls performed are provided and conform to the regulation.
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.
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is flunixin meglumine, an established 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

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.
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 site have been provided demonstrating compliance with the specification.

G. Stability

A re-test period for the active substance is set in the certificate of suitability issued by EDQM.

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.
An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Toxicological Studies

As this is a generic application according to Article 13, 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.

User Safety

Although this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, a user safety assessment has been provided.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant has provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

III.B Residues documentation

Residue Studies

Two depletion studies of flunixin in bovine edible tissues and one study for porcine edible tissues are performed following intramuscular injection to assess the withdrawal period of the candidate product.

In cattle, a study was performed with a previous formulation containing diethanolamine and another one with the final formulation of the candidate product, *i.e*. without diethanolamine. This study is a confirmation depletion study (only injection sites were sampled).

In pigs, it is a confirmation depletion study (only injection sites were sampled).

MRLs

The active substance, flunixin meglumine, is included in table 1 of the annex of Commission regulation (EU) N° 37/2010, as follows :

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Flunixin	Bovine	20 µg/kg 30 µg/kg 300 µg/kg 100 µg/kg	Muscle Fat Liver Kidney	No entry	Anti-inflammatory agents/ Nonsteroidal anti-inflammatory agents	37/2010 of 22.12.2009
	Porcine	50 µg/kg 10 µg/kg 200 µg/kg 30 µg/kg	Muscle Skin + 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 MRL status of excipients of the product EMDOFLUXIN 50 MG/MLSOLUTION FOR INJECTION FOR CATTLE, PIGS AND HORSES is indicated in the following table.

Excipient	MRL status
Phenol	Table 1, all species, no MRL required, No ADI
Disodium edetate	Table 1, all species, no MRL required, No ADI
Sodium formaldehyde sulfoxylate	Table 1, all species, no MRL required, No ADI
Propylene glycol	Table 1, all species, no MRL required, ADI = 25 000 µg/kg
Hydrochloric acid	Table 1, all species, no MRL required, No ADI for use as excipient
Sodium hydroxide	*

Purified water	Out of scope list

*Covered with food additives (substance with a valid E number approved as additives in foodstuffs for human consumption)

The composition of the product EMDOFLUXIN 50 MG/MLSOLUTION FOR INJECTION FOR CATTLE, PIGS AND HORSES is acceptable according to European Regulation (EC) N° 470/2009.

Withdrawal Periods

The acceptable withdrawal periods are summarized in the following table.

Species	Tissues	**Withdrawal periods**
Horse	Meat & offal	10 days
	Milk	Not authorized for use in mares producing milk for human consumption
Cattle following iv administration	Meat & offal	10 days
	Milk	24 hours
Cattle following im administration	Meat & offal	31 days
	Milk	36 hours
Pig	Meat & offal	20 days

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

It is a generic application for a marketing authorisation in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC. The cited reference product is FINADYNE, marketed by Intervet, which has been authorized in France since 04/08/1981.

Pharmaceutical form
The test and the reference products have the same pharmaceutical form: solution for injection.

Active substance qualitative and quantitative composition
The test and reference products have the same qualitative and quantitative composition in active substance: 50 mg of flunixin (as flunexin meglumine) per mL.

Bioequivalence studies

A bioequivalence study was realised in cattle and in pig following intramuscular injection.

The exemption 7.1.a is justified following intravenous injection for horses and cattle.

7.1 a) The product is to be administered solely as an aqueous intravenous solution containing the same active substance as the currently approved product. However, if any excipients interact with the active substance (e.g. complex formation), or otherwise affect the disposition of the active substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance.

The two products FINADYNE and EMDOFLUXIN 50 MG/MLSOLUTION FOR INJECTION FOR CATTLE, PIGS AND HORSES are bioequivalent.

Tolerance in the Target Species of Animals

The applicant has not provided tolerance study, which is acceptable because the tested product and the reference product are bioequivalent, have similar formulations and are recommended for use at the same posology and route of administration.

The tolerance aspects of this product are identical to the reference product. Based on the conclusion made for the reference product, the product literature accurately reflects the type and incidence of adverse effects, which might be expected.

IV.B Clinical Studies

As this is a generic application according to Article 13, and bioequivalence with the reference product FINADYNE has been demonstrated, efficacy studies are not required. The efficacy claim for this product is based on the indications for use of the reference product.

The indications of the reference product have been slightly amended to better reflect the expected efficacy of the product, as follows:

“Horses:	**Alleviation of inflammation and pain** associated with musculoskeletal disorders. **Alleviation of visceral pain associated with colic.**
Cattle:	Reduction of clinical signs during respiratory infections in association with an appropriate anti-infective treatment.

Pigs: **Adjunctive therapy in the** treatment of MMA (Mastitis-Metritis-Agalactia) **syndrome** in sows.
Reduction of fever associated with respiratory disorders in association with an appropriate anti-infective treatment."

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).

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.

None