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)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Animeloxan, 20 mg/ml

Date: 30 April 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0311/002/E/001
Name, strength and pharmaceutical form	Animeloxan, 20 mg, Solution for injection
Applicant	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell GERMANY
Active substance(s)	Meloxicam
ATC Vetcode	QM01AC06
Target species	Cattle, Pigs and Horses
Indication for use	Cattle: For use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs in cattle. For use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle. For adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. For the relief of post-operative pain following dehorning in calves. Pigs: For use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation. For adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy.

	Horses: For use in the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders. For the relief of pain associated with equine colic.

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 Decentralised procedure	26th October 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	AT, PL and UK (former RMS)
Concerned Member States for repeat use procedure	BG, CY, CZ, EE, EL, ES, HU, IE, IT, LT, LV, NL, PT, RO and SK

I. SCIENTIFIC OVERVIEW

Animeloxan 20 mg/ml, Solution for injection for cattle, pigs and horses (hereafter named Animeloxan 20 mg/ml) authorised in 2011 was a decentralised application for a generic product, submitted in accordance with article 13 (1) of Directive 2001/82/EC, as amended, with UK as RMS and Austria, Germany and Poland as CMSs. The reference product was centrally authorised in 2001 for cattle. The additional species pigs and horses were subsequently added in 2003 and 2005, respectively. Subsequently, Animeloxan 20 mg/ml was authorised in a repeat use procedure in the following member states: Bulgaria, Cyprus, Czech Republic, Estonia, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Romania, Slovakia, and Spain. Germany was RMS in this procedure.
In cattle, the indication is for use in acute respiratory infection with appropriate antibiotic therapy to reduce clinical signs, for use in diarrhoea in combination with oral re-hydration therapy to reduce clinical signs in calves of over one week of age and young, non-lactating cattle.
Additionally for adjunctive therapy in the treatment of acute mastitis, in combination with antibiotic therapy. In pigs, the indication is for use in non-infectious locomotor disorders to reduce the symptoms of lameness and inflammation, and for adjunctive therapy in the treatment of puerperal septicaemia and toxaemia (mastitis-metritis-agalactia syndrome) with appropriate antibiotic therapy. In horses, the product is indicated for the treatment of the alleviation of inflammation and relief of pain in both acute and chronic musculo-skeletal disorders and for the relief of pain associated with equine colic.

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

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 20 mg/ml meloxicam and the excipients N-methyl 2-pyrrolidone, ethanol (anhydrous), sodium hydroxide, hydrochloric acid (dilute) and water for injections.

The container/closure system consists of clear glass (Type I) bottles of 50 ml and 100 ml, closed with bromobutyl rubber stoppers and fixed with Aluminium caps or Aluminium/PP flip caps. The product is available in boxes containing 1 x 50 ml or 12 x 50 ml and 1 x 100 ml or 12 x 100 ml; not all pack sizes may be marketed. 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 meloxicam, an established active substance described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice.

[1] SPC – Summary of product Characteristics,

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. All excipients comply with appropriate Ph. Eur. monographs.

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

D. Control on intermediate products

Not applicable.

E. 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.

F. 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. Long term, intermediate and accelerated studies demonstrated the appropriateness of the product to retain a three year shelf-life.

G. Other Information

Shelf-life of the product as stored for sale: 3 years.
Shelf-life of the product after first opening: 28 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

This is a decentralised application for a generic product, submitted in accordance with article 13 of Directive 2001/82/EC. Thus, results of pharmacological and toxicological tests other than that supporting the user risk assessment are not required, as the toxicological aspects of this product can be assumed to be identical to the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, (CVMP[2] EMA/CVMP/543/03-Rev.1), citing that only professionals (veterinarians, farmers) will use the product, and that the main route of exposure is the dermal route. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- Accidental self-injection may give rise to pain. People with known hypersensitivity to NSAIDs should avoid contact with the veterinary medicinal product.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- If accidental skin contact occurs, wash the affected area thoroughly.
- Wash hands after use.
- In view of the risk of accidental self-injection and the known adverse class-effects of NSAIDs and other prostaglandin inhibitors on pregnancy and/or embryofoetal development, the veterinary medicinal product should not be administered by pregnant women or women attempting to conceive.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that environmental exposure will not be large, as only a small number of animals will be treated at one time.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[2] CVMP – The Committee for Medicinal Products for Veterinary Use.

III.B Residues documentation

Residue Studies

The formulation of the candidate generic product was slightly different from that of the reference product. The applicant conducted tissue residue depletion studies in order to accommodate the addition of the subcutaneous administration route for cattle and in order to retain the intramuscular administration route for pigs.

Cattle:
The applicant has conducted a tissue residue depletion study for Animeloxan 20 mg/ml in bovines after subcutaneous administration using a dosing regimen in accordance with the SPC. No residues of meloxicam above the respective MRL for muscle tissue were found in edible tissues (i.e. muscle tissue of the injection site) at 10 days after subcutaneous injection. The withdrawal period of the reference product is therefore also justified for the generic product.

Pigs:
The applicant has conducted two residue depletion studies for Animeloxan 20 mg/ml in pigs after repeated intramuscular administration using a dosing regimen in accordance with the SPC. No residues of meloxicam above the respective MRL for muscle tissue were found in edible tissues (i.e. in the injection site) at 8 days after the last intramuscular injection. The withdrawal period of the reference product is therefore also justified for the generic product.

Horse:
This was a generic application submitted under Article 13(1) of Directive 2001/82/EC as amended. For horses only i.v. administration was applied for. Therefore, no studies to assess the residue depletion at the injection site were required.

Maximum Residue Limits (MRLs)

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues
Meloxicam	Meloxicam	Equidae, Bovine, Porcine,Caprine, Rabbit	20 µg/kg 65 µg/kg 65 µg/kg	Muscle Liver Kidney
		Bovine, Caprine	15 µg/kg	Milk

All of the excipients are in Table 1 of the Annex to Regulation (EU) No 37/2010 with a “No MRL required” status for all food producing species.

Withdrawal Periods

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

Cattle:	
Meat and offal:	15 days
Milk:	5 days
Pigs:	
Meat and offal:	8 days
Horses:	
Meat and offal:	5 days

Do not use in horses producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

Although this was a generic product, bioequivalence and tolerance studies were required in order to permit the use of the product via the subcutaneous route (cattle) and the intramuscular route (pigs).

IV.A Pre-Clinical Studies

Pharmacology

In-vivo bioequivalence could be demonstrated between the two products in an experimental bioequivalence study after subcutaneously administration of the intended dose in cattle (0.5 mg meloxicam/kg body weight) using the test and reference product. C_{max}[3] and AUC[4] confidence intervals of the test product were within the parameters of the reference product, and Animeloxan 20 mg/ml Solution for Injection for Cattle Pigs and Horses was therefore considered to be bioequivalent to the reference product for this species and route of administration. A similar assay in pigs (intramuscular route, 0.4 mg meloxicam/kg bodyweight), confirmed that the product could also be used as appropriate in this species.

Tolerance in the Target Species of Animals

Suitable studies showed that the product was generally well-tolerated in the target species (cattle, pigs). Any possible adverse effects are cited in the SPC and product literature. The product literature was revised regarding the frequency of

[3] C_{max} – maximum plasma concentration of the active substance.
[4] AUC – Area under the curve.

anaphylactoid reactions in the target population after administration of Animeloxan 20 mg/ml. Therefore, the benefit/risk profile remains positive.

IV.B Clinical Studies

Laboratory Trials

As this was a generic application submitted under Article 13 (10 of Directive 2001/82/EC as amended, and a reference product was already established, no data were required for this section.

Field Trials

As this was a generic application submitted under Article 13 (10 of Directive 2001/82/EC as amended, and a reference product was already established, no data were required for this section.

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 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.

•	30 April 2019	Change in the SPC, labelling or package leaflet after the repeat use procedure
•	17 April 2019	Closure of Repeat Use procedure
•	21 August 2018	RMS change from UK to DE
•	24 April 2018	Deletion of a manufacturing site for an active substance. Submission of an updated Ph. Eur. certificate of suitability for an active substance from an already approved manufacturer.
•	06 December 2017	Increase in the shelf-life of the finished product as packaged for sale, from 2 years to 3 years.
•	24 May 2017	Change in the SPC, labelling or package leaflet following assessment of the same change for the reference product.
•	20 April 2017	Renewal – UK as RMS
•	23 March 2017	Change in address of manufacturer of the finished product. Deletion of a manufacturing site. Replacement of a manufacturer for secondary packaging.
•	19 April 2016	Deletion of a manufacturing site for the finished product, and primary and secondary packaging.
•	30 March 2016	Submission of an updated Certificate of Suitability
•	24 June 2015	Addition of a site for batch control/testing for the finished product. Addition of a site for batch release for the finished product. Deletion of an active substance manufacturer. Addition of two sites for secondary packaging for the finished product. Addition of a manufacturing site for part of the manufacturing process of the finished product. Addition of a manufacturing site for the finished product.
•	07 November 2014	Change to the wording in section 4.6. of the SPC and

		section 6. of the package leaflet.
•	10 July 2014	Submission of a new Ph. Eur. Certificate of Suitability for a new manufacturer of the active substance.
•	07 December 2012	To change the QPPV.