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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Sympagesic 500 mg/ml + 4 mg/ml solution for injection for horses, cattle, pigs and dogs

DATE: 2019.04.23.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0354/001/DC
Name, strength and pharmaceutical form	Sympagesic 500 mg/ml + 4 mg/ml solution for injection for horses, cattle, pigs and dogs
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531 AE Bladel The Netherlands
Active substance(s)	Metamizole sodium monohydrate 500.0 mg Hyoscine butylbromide 4.0 mg
ATC Vetcode	QA03DB04
Target species	Horses, cattle, pigs, dogs
Indication for use	Horses, cattle, pigs, dogs: treatment of smooth muscle spasms and pain associated with underlying disorders of the gastro-intestinal tract, urogenital system and bile excretory organs. Horses only: Spasmodic colics. Cattle, pigs, dogs: Supportive therapy for acute diarrhoea and gastroenteritis.

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	2019.03.13.
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, HR, HU, IE, IS, IT, LT, LU, LV, NL, NO, PL, PT, RO, SE, SI, SK, 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 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 500 mg/mL of metamizole sodium and 4 mg/mL of hyoscine butylbromide in 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.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are metamizole sodium and hyoscine butylbromide, established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substances specifications is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

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

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

Re-test periods for the active substances are set in the certificates 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

Pharmacological Studies

See IV.A

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.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline.
Warnings and precautions as listed on the product literature have been improved compared to those of the reference product.

Environmental Risk Assessment
A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will be used to treat a small number of animals in a flock or herd.

III.B Residues documentation

Residue Studies

No depletion study was provided according to the type of application. The withdrawal periods agreed for the reference product can be applied to the generic product.

MRLs

a. active substances

The active substance **metamizole** is included in table 1 of the MRL regulation 37/2010, as follows

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
4-Méthylaminoantipyrin	Bovine, porcine, *Equidae*	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg	Muscle Fat Liver Kidney	For porcine the fat MRL relates to "skin and fat in natural proportions"	Anti-inflammatory agents/ Nonsteroidal anti-inflammatory agents	37/2010 of 22.12.2009
	Bovine	50 µg/kg	Milk			

An acceptable daily intake (ADI) of 10 µg/kg bw (*i.e.* 600 µg/person) was defined for metamizole.

The active substance **hyoscine butylbromide** is included as butylscopolamium bromide in table 1 of the MRL regulation 37/2010, as follows

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Not applicable	All food producing species	No MRL required	Not applicable	No entry	No entry	37/2010 of 22.12.2009

An acceptable daily intake (ADI) of 10 µg/kg bw (*i.e.* 600 µg/person) was defined for scopolamine.

b. excipients

The MRL status of excipients of the product Sympagesic are indicated in the following table:

Excipient	MRL status
Phenol	Table1, for all species, No MRL required, without ADI
Tartaric acid (E 334)	Covered with food additives (substance with a valid E number approved as additives in foodstuffs for human consumption)
Purified water	Out of scope list

The composition of the product Sympagesic is acceptable according to the European regulation (EC) 470/2009.

Withdrawal Periods

Given the legal basis of the application, Article 13(1) of the directive 2001/82/EC as amended, and the fact that the exemption 7.1.d (see part II) is accepted, the withdrawal periods agreed for the reference product can be applied to the generic product.

Based on additional data already assessed in a CMS, the withdrawal period in bovine species following intramuscular route had to be increased to 28 days.

The following withdrawal periods are thus proposed:
Cattle
Meat and offal: 18 days following intravenous route
Meat and offal: 28 days following intramuscular route
Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant animals which are intended to produce milk for human consumption within 2 months of expected parturition.

Horses
Meat and offal: 15 days
Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant animals which are intended to produce milk for human consumption within 2 months of expected parturition.

Pigs
Meat and offal: 15 days

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

This is a generic application for a marketing authorisation in accordance with Article 13.1 of Directive 2001/82/EC, as amended. The cited reference product is ESTOCELAN INJECTABLE.

No bioequivalence study was provided. The exemptions 7.1.a & b of the European “Guideline on the conduct of bioequivalence studies for veterinary medicinal products” (EMA/CVMP/016/00-Rev.2) apply for intravenous and subcutaneous/intramuscular routes of administration, respectively. Bioequivalence of the test product with the reference product is considered established.

Tolerance in the Target Species of Animals

No tolerance study has been provided.

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of tolerance study is not required.

IV.B Clinical Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of clinical tests are not required.

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.