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

Spasmium comp. 500 mg/ml + 4 mg/ml solution for injection

Date: 28 September 2015

Revision: 08.03.2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0159/001/DC
Name, strength and pharmaceutical form	Spasmium comp., 500 mg/ml + 4 mg/ml, solution for injection
Applicant	Richter Pharma AG Feldgasse 19, 4600 Wels Austria
Active substance(s)	Metamizole sodium monohydrate, Hyoscine butylbromide
ATC Vetcode	QA03DB04
Target species	Cattle, Pig, Horse, Dog
Indication for use	Horses, cattle, pigs, dogs: Treatment of spasms or sustained increased tonus of smooth muscles of the gastro-intestinal tract or of the urine and bile excretory organs associated with pain Horses only: Spasmodic colics Cattle, pigs, dogs only: As supportive therapy for acute diarrhoea

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	17 June 2015
Date product first authorised in the Reference Member State (MRP only)	N.A.
Concerned Member States for original procedure	AT, BG, CZ, DK, EE, EL, ES, FI, HR, HU, IE, IS, IT, LT, LV, 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 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 overall risk/benefit analysis is in favour of granting a marketing authorisation.
The safety and efficacy aspects of this product are identical to Buscopan compositum. The initial application for Buscopan compositum was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains the active substances 500 mg Metamizole sodium monohydrate and 4 mg Hyoscine butylbromide, and the excipients phenol (preservative), Tartaric acid (E 334), and Water for injections.

The container/closure system consists of a 100-ml amber glass vial, which is closed by a bromobutyl rubber stopper and an aluminum cap, and packed in a cardboard box.

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 at a licensed manufacturing site.

The product is manufactured using conventional manufacturing techniques. Process validation data on the product have been presented, and process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance metamizole sodium monohydrate is 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 for metamizole sodium monohydrate is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The second active substance hyoscine butylbromide is also 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 for hyoscine butylbromide is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Certificates of suitability issued by the EDQM have been provided for both active substances.

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been declared.

D. Control on intermediate products (pharmaceuticals)

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 substances 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 days stability after broaching is based on the demonstration of stability for two batches broached and stored 29 days at + 25°C.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

The safety aspects of this product are identical to the reference product.

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

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.

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.

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 and from accidental self-injection. No data on NOELs in man or experimental animals were available and in the absence of a toxicological endpoint a reliable safety margin could not be calculated. A volume of 2 ml (equivalent to 1000 mg Metamizole and 8 mg Hyoscine butylbromide) of the veterinary medicinal product represents the upper limit of recommended daily dose for metamizole.
However, taking into account that

- the risk of exposure to the veterinary medicinal product is limited as it is a prescription only medication and therefore restricted to professional users
- the product is filled in a glass vial sealed by rubber stopper preventing accidental exposure during storage or handling the vials
- the medicinal product is intended for use in single animals only
- there has been virtually no reporting of adverse advents in humans over the last years for the reference product (one case between 2003 and 2013)

the following safety warnings are considered sufficient to reasonably ensure user safety:

- In a very small number of people, metamizole can cause reversible, but potentially serious agranulocytosis and other reactions such as skin allergy. Take care to avoid self-injection.
- In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
- People with known hypersensitivity to metamizole or hyoscine butylbromide should avoid contact with the veterinary medicinal product. Avoid use of the product if you are known to be sensitive to pyrazolones, or are sensitive to acetylsalicylic acid.
- Wash splashes from skin and eyes immediately.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because the product is only used to treat a small number of animals in a flock or herd.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted as this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the identical reference product can be assumed because of the nature of the product, results of residue depletion studies are not required.

MRLs

The following maximum residue limits for metamizole have been implemented in Table 1 (allowed substances) of Commission Regulation (EU) No. 37/2010:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissue
Metamizole	4-Methyl-aminoantipyrin	Bovine	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney Milk
		Porcine	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg	Muscle Fat Liver Kidney
		Equine	100 µg/kg 100 µg/kg 100 µg/kg 100 µg/kg	Muscle Fat Liver Kidney

According to Commission Regulation (EU) No. 37/2010 for butylscopolaminium bromide no MRLs are required for all food producing species.
All excipients are authorised food additives in the EU and included in Table 1 (allowed substances) of Commission Regulation (EU) 37/2010. No MRL is required.

Withdrawal Periods

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

Cattle: Meat and offal: 12 days

Milk: 4 days

Pig: Meat and offal: 15 days

Horse: Meat and offal. 12 days

The product is not authorised for use in mares whose milk is intended for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, 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 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.

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
Change in the shelf-life of the finished product (DE/V/0159/001/IB/002)	N/A	03/03/2017