Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Amprol 12% w/v Solution for Use in Drinking Water

Date Created: July 2016

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Amprol 12% w/v Solution for Use in Drinking Water
Applicant	Pharmsure International Ltd Unit 28, Moorlands Trading Estate Moor Lane Metheringham Lincolnshire LN4 3HX
Active substance	Amprolium hydrochloride
ATC Vetcode	QP51AX09
Target species	Chickens (broilers, pullets, layers, breeder hens) and turkeys.
Indication for use	For the treatment of intestinal coccidiosis caused by Eimeria *spp.* susceptible to amprolium.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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.

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended. Bioequivalence with a reference product was successfully claimed under EMEA/CVMP/016/00-cor-FINAL sections 4 b) and 4 c), as superseded by EMA/CVMP/016/00-Rev.2. The reference product is Nemaprol 120 mg/ml Oral Solution, authorised in France since March 1992. The reference product is not authorised in the UK. The indication is for the treatment of intestinal coccidiosis caused by Eimeria *spp.* susceptible to amprolium.

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, any 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 [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains amprolium hydrochloride 120 mg (equivalent to 106 mg amprolium and the excipients sorbic acid (E200) and purified water.

The container/closure system consists of high density polyethylene bottles of 1 litre and 5 litre, closed with a polyethylene screw cap with integral heat seal liner. 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a basic dissolution, homogenisation, filtration and filling process.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is amprolium hydrochloride, an established active substance described in the French Pharmacopoeia, British Pharmacopoeia and the United States 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. A suitable Active Substance Master File was submitted describing the specification used by the manufacturer.

The excipients comply with monographs in the European Pharmacopoeia.

II.C.4. Substances of Biological Origin

A declaration is provided stating that Amprol 12% Solution complies with the latest version of the CPMP/CVMP guideline on transmissible spongiform encephalopathies (EMEA/410/01 Rev. 2 of October 2003).

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include those for appearance, solution colour, fill volume, identification of the active substance and sorbic acid. Tests are also included for pH and microbiological quality.

II.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. A retest period of 48 months was supported. Stability studies were presented for 3 batches filled into appropriate pack sizes. Batches of product stored in 1 litre 5 litre or 10 litre bottles were analysed after storage at 36 months at 25°C/60% RH, 30°C/60% RH, or 6 months at 40°C/75% RH.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 12 weeks.

Shelf life after dilution according to directions: 24 hours.

Medicated drinking water should be replaced every 24 hours.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this is an application for a generic product according to Article 13 (1), and bioequivalence with a reference product has been established, pharmacological and toxicological data are not required.

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

III.A Safety Documentation

User Safety

The user safety is the same as that defined by the reference product. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The user safety warnings were amended to bring them in line with the current user safety guidelines, as follows:

- This is an irritant and corrosive product. It could cause airway, eye and skin irritation. Wear impervious gloves and protective glasses when handling the product.
- The selected protective gloves have to satisfy the specifications of EU Directive 89/686/EEC and the standard EN 374 derived from it.
- Avoid inhalation of vapours.
- Avoid contact with the skin and eyes. In the case of contact with skin or eyes, wash the affected area with clean running water immediately and remove any contaminated clothes. If irritation persists, seek medical advice and show the leaflet or the label to the doctor.
- This product is harmful when ingested. In case of accidental ingestion, rinse the mouth with fresh water, seek medical advice immediately and show the package leaflet or label to the doctor.

Environmental Safety

An Environmental Risk Assessment (ERA) was conducted in accordance with VICH and CVMP guidelines.

Phase I:
As the calculation of initial predicted environmental concentration (PEC) in soil resulted in a value greater than 100 µg/kg, a Phase II ERA was required.

Phase II Tier A:
A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physicochemical properties, environmental fate and effects. Studies were carried out using the active substance amprolium.

Physicochemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	Equivalent to 1000 mg/l	Freely soluble Published source
Dissociation constants in water pKa	OECD 112	5.01	Published source
Melting Point/Melting Range	OECD 102	Decomposes at 248 - 249°C	Published source
Vapour Pressure	OECD 104	0.0000001 kPa	Published source
n-Octanol/Water Partition Coefficient $logP_{OW}$	OECD 107	log P_{OW} -1.12	$logP_{OW}$ <4, indicates low bioaccumulation potential

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/Desorption	OECD 106	K_{oc} >1533	Non-mobile in soil, strongly binds to soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} >56.6 days in soil	Amprolium is classified as a persistent in soil

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition *Anabaena flos-aquae*	OECD201	EC_{50}	100 mg/l
Daphnia sp. immobilisation	OECD202	EC_{50}	>100 mg/l
Fish, acute toxicity *Oncorhynchus mykiss*	OECD203	LC_{50}	>100 mg/l
Soil Microorganisms: Nitrogen Transformation Test (28 days)	OECD216	<25% of control	No long term effects at 10x PEC_{soil}
Terrestrial Plants, Growth Test *Brassica rapa, Phaseolus vulgaris, Beta vulgaris, Lactuca sativa, Zea mays* and *Allium cepa*	OECD208	EC_{50}	>980 mg/kg $soil_{dwt}$
Earthworm *Eisenia foetida*	OECD207	NOEC	250 mg/kg

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Broilers	1242	11.3*	3.8
Laying hen	145	1.3*	0.4
Replacement Layer	275	2.5*	0.8
Broiler breeder	78	0.7*	0.2
Turkey	619	5.6*	1.9

* As the initial $PEC_{Groundwater}$ is >0.1 µg/l, refinement using the more advanced environmental model, FOCUS PEARL was conducted (see below).

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for the worst-case target animal (broiler chickens), as follows.

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC_{50} 72 hour 100 mg/l	100	1000 µg/l	3.8 µg/l	0.0038
Daphnia sp. immobilisation	EC_{50} 48 hour >100 mg/l	1000	100 µg/l	3.8 µg/l	0.038
Fish, acute toxicity	LC_{50} 96 hour >100 mg/l	1000	100 µg/l	3.8 µg/l	0.038
Terrestrial Plants	EC_{50} >980 mg/kg $soil_{dwt}$	100	9800 µg/l	1454 µg/kg*	0.15
Earthworm reproduction	250 mg/kg	10	25 000 µg/l	1454 µg/kg*	0.058

* Using highest established $PEC_{Plateau}$

As the initial $PEC_{Groundwater}$ is >0.1 µg/l, refinement using the more advanced environmental model, FOCUS PEARL was conducted which demonstrated that the 80th percentile $PEC_{Groundwater}$ value at a depth of 1 m was calculated to be 0.000036 µg/l. Therefore, it can be concluded that the use of amprolium according to the provisions stated in the SPC will not present a risk to drinking water.

As all RQ values were <1 the ERA. The product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation
Residue Studies

The product complies with exemption 4b of the CVMP's Bioequivalence Guideline as it represents a product which is orally administered as a solution and contains the same active substance (amprolium) and excipients in the same concentrations as the European reference veterinary medicinal product (Nemaprol), currently approved for use in the same target species (chicken and turkeys). As a result, no bioequivalence study is submitted and the justification not to provide any residue data is accepted.

MRLs

Amprolium is included in Table 1 of Commission Regulation (EU) No 37/2010 as not requiring an MRL for meat and offal, and eggs.

Withdrawal Periods

Based on the data provided, the same withdrawal periods as authorised for the reference product are justified, as follows:

Chickens (broilers, pullets, layers, breeder hens)
Meat and Offal: Zero days
Eggs: Zero days

Turkeys
Meat and Offal: Zero days

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1), and bioequivalence with a reference product was successfully claimed under EMEA/CVMP/016/00-cor-FINAL sections 4 b) and 4 c), as superseded by EMA/CVMP/016/00-Rev.2, bioequivalence and further efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacological data were not required due to the nature of this application. A statement noting that the active substance is excreted mainly via the faeces is included in the SPC.

Tolerance in the Target Species

No data were submitted for this section of the dossier, due to the nature of the application. The product literature accurately reflects the type and incidence of adverse effects which might be expected. The SPC was updated to carry suitable warnings with regard to tolerance.

Resistance

Adequate warnings and precautions appear on the product literature:

- As with all anticoccidials, prolonged use may result in the development of resistant strains. Use of anticoccidial drugs having the same mode of action should be avoided due to the development of cross-resistance.

IV.II. Clinical Documentation

No clinical documentation was provided or required, due to the nature of the application.

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 of the product(s) is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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