AGENCE NATIONALE DU

MEDICAMENT VETERINAIRE

FRENCH AGENCY FOR FOOD, ENVIRONNEMENTAL AND OCCUPATIONAL HEALTH SAFETY

FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

NEMAPROL 440 MG/ML
Solution for use in drinking water

PRODUCT SUMMARY

EU procedure number	FR/V/0522/001/DC
Name, strength and pharmaceutical form	NEMAPROL 440 MG/ML Solution for use in drinking water for chickens and turkeys
Applicant	Dopharma Research B.V Zalmweg 24, Noord-Brabant 4941 VX Raamsdonksveer Netherlands
Active substance(s)	Amprolium (as amprolium hydrochloride)
ATC vetcode	QP51BX02
Target species	Chickens and turkeys
Indication for use	Treatment of coccidiosis caused by *Eimeria spp*.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	Hybrid application in accordance with Article 19 of Regulation (EU) 2019/6
Reference product	Nemaprol
Marketing authorisation holder	Dopharma France
Marketing authorisation number	FR/V/5336886 7/1992
Date of authorisation	17/02/1992

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

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

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains the active substance amprolium (as amprolium hydrochloride) at a concentration of 440 mg/mL and the following excipients are present: benzyl alcohol, hydrochloric acid dilute, sodium hydroxide and purified water.

The container and closure system consist of plastic bottles/containers and plastic caps.

The choice of the formulation and the presence of preservative are justified.

The VMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

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

C. Production and control of starting materials

The active substance is amprolium hydrochloride, an established active substance. 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.

Scientific data have been provided through an ASMF.

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

D. Control tests carried out on isolated intermediates during the manufacturing process

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 VMP.

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.

The tests performed on the final VMP conform to the relevant requirements.

F. Stability tests

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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

The in-use shelf life of the broached VMP is supported by the data provided. The recommendations in the product leaflet should be followed.

3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a hybrid application according to Article 19 of Regulation (EU) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of pharmacological and toxicological tests are not required.

A. Safety tests

Pharmacological studies

See part 4.

Toxicological studies

As this is a hybrid application according to Article 19 of Regulation (EU) 2019/6 and bioequivalence with a reference VMP has been demonstrated, toxicological studies are not required.

User safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that that the most likely routes of accidental contact with the product are dermal and ocular exposure.

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

Environmental Risk Assessment

The application for marketing authorisation of NEMAPROL 440 mg/ml solution for use in drinking water for chickens and turkeys is exempt from submitting an Environmental Risk

Assessment (ERA) according to Article 18 (7) of Regulation (EU) 2019/6, as an ERA has already been performed for the same active substance and exposure level in the EU in accordance with relevant guidelines. Therefore, as comparable products have already been authorized in the EU after October 2005 (EMA/CVMP/ERA/622045/2020), a complete data package for the environmental risk assessment is not required. Suitable risk mitigation measures and/or advice have been included in the SPC for this product in line with the SPCs of these comparable products.

B. Residues documentation

Maximum Residue Limits

The active substance, amprolium, is an allowed substance as described in Table 1 of the Annex to Commission Regulation (EU) No 37/2010, as follows:

Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions	Regulation
Not applicable	Poultry	No MRL required	Not applicable	For oral use only	37/2010 of 22.12.2009

An acceptable daily intake (ADI) of 100 µg/kg bw (*i.e*. 6000 µg/person) was defined for amprolium.
The composition of the candidate product NEMAPROL 440 mg/ml solution for use in drinking water for chickens and turkeys is acceptable according to the Regulation (EU) 470/2009.

Residue tests

No residue depletion studies were conducted because this application is made in accordance with Article 19 of Regulation (EU) 2019/6.

Withdrawal Periods

As bioequivalence with the reference product has been demonstrated (see part 4) and since both products are administered by oral route at the same dose in the same target species, no residue depletion studies were conducted. Consequently, the following withdrawal periods agreed for the reference product have been applied to the candidate product as proposed by the Applicant:

Meat and offal: zero days
Eggs: zero days

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a hybrid application according to Article 19 of Regulation (EU) 2019/6 and bioequivalence with the reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

A. Pre-Clinical Studies

Pharmacology

Pharmaceutical form

The test and the reference products have the same pharmaceutical form: solution for use in drinking water.

Active substance qualitative and quantitative composition

The test and reference products have the same qualitative but not the same quantitative composition in active substance: amprolium hydrochloride 498 mg/mL for the candidate product; amprolium hyrdrochloride 120 mg/mL for the reference product.

Bioequivalence studies

The bioequivalence between the reference and the candidate product has been demonstrated based on section 7.1.c of the bioequivalence guideline (EMA/CVMP/016/2000) which states:

If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved reference veterinary medicinal product presented as an aqueous oral solution at time of administration, bioequivalence studies may be waived if the excipients contained in it do not affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), solubility (e.g. co-solvents) or in-vivo stability of the active substance. Any differences in the amount of excipients should be justified by reference to other data, otherwise an in-vivo bioequivalence study will be required. The same requirements for similarities in excipients apply for oral solutions as for biowaivers according to the relevant criteria (see Appendix I, section IV.2).

Development of resistance and related risk in animals

The provided bibliography provided suggests that resistance exists in non-European countries. Adequate warnings and precautions appear on the product literature.

Dose determination and confirmation

As this is a hybrid application according to Article 19 of Regulation (EU) 2019/6 and bioequivalence with a reference VMP has been demonstrated, dose determination and confirmation studies are not required.

Tolerance in the target species of animals

As this is a hybrid application according to Article 19 of Regulation (EU) 2019/6 and bioequivalence with a reference VMP has been demonstrated, results of tolerance studies are not required. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

B. Clinical trials

The application for Nemaprol 440 mg/ml solution for use in drinking water for chickens and turkeys is made in accordance Article 19 of Regulation (EU) 2019/6, a so called hybrid application.

As bioequivalence with the reference product has been demonstrated, clinical trials are not required.

In studies conducted in accordance with the current Guideline on the demonstration of palatability of veterinary medicinal products, similar palatability results between the test-product and reference product have been obtained in chickens and turkeys.

The efficacy claim for this product is equivalent to that of the reference product.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.