IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Curazole 100 mg/ml oral suspension for horses

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Curazole 100 mg/ml oral suspension for horses.
Active substance(s)	Fenbendazole
Applicant	Univet Limited, Tullyvin, Cootehill, Co. Cavan., Ireland
Legal basis of application	Extension application in accordance with Article 13 of Directive 2001/82/EC as amended.
Date of completion of procedure	23/10/2022
Target species	Horses
Indication for use	For the treatment of immature and mature stages of nematodes of the gastro-intestinal and respiratory tract, including encysted mucosal small strongyle larvae (cyathostomes). The veterinary medicinal product has an ovicidal effect on roundworm eggs. For the treatment of horses infected with adult large strongyles and adult and larval small strongyles. For the treatment of ascarids and Oxyuris equi.
ATC vet code	QP52AC13

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This extension to the initial marketing authorisation for 'Curazole 10% w/v oral drench' (VPA10990/015/001) was to add a food-producing target animal species (horses). The product was authorised in 1991 for use in cattle.The application was submitted in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC, as amended (a hybrid application).
The reference veterinary medicinal product cited is Panacur 10% w/v oral suspension (VPA10996/111/001, Intervet Ireland Limited) which was first granted a marketing authorisation in Ireland on 01/10/1999. The reference product has been authorised within the Community for not less than 10 years based upon a full dossier and can be accepted as being a suitable reference product.
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, horses; no adverse reactions are indicated.
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

The quality aspects of this product are identical to Curazole 10 % w/v Oral Drench (VPA 10990/015/001). The initial application for Curazole 10 % w/v Oral Drench was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is an extension to the marketing authorisation for 'Curazole 10% w/v oral drench' for the addition of a new target species, horses, in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC as amended. As bioequivalence with a reference product has not been demonstrated, additional data have been presented to support the safety of this product.
Warnings and precautions as listed on the product literature are adequate to ensure safety of the product to users, the environment, and consumers.

III. SAFETY ASSESSMENT

III.A Safety Testing

Pharmacological Studies

A well-designed *in vivo* bioequivalence study which compared the pharmacokinetics of fenbendazole in the target animal species (horses) was provided. The reference product used was 'Panacur 10% oral suspension', which is accepted as being a suitable reference product. Plasma concentrations of fenbendazole were measured following single administration of the test and reference products by the oral route, with blood samples collected at appropriate time points. Following administration of the test article at 7.5 mg fenbendazole per kg bodyweight, mean maximum plasma concentration (C_{max}) of 152.77 ng/ml was achieved at approximately 7 hours. Mean (harmonic mean) terminal half-life was 7.6 hours. Following adminsitration of the reference article at 7.5 mg fenbendazole per kg bodyweight, mean maximum plasma concentration (C_{max}) of 77.89 ng/ml was achieved at approximately 7 hours. Mean (harmonic mean) terminal half-life was 9.2 hours.
Based on the results of the analysis for bioequivalence, the 90% confidence intervals for the ratio of the geometric means for both pivotal pharmacokinetic parameters AUC_t and C_{max} were outside (above) the pre-specified limits, and it was concluded that bioequivalence was not demonstrated between the test and reference products.
Additional bibliographic data were provided that describe the pharmacokinetics of fenbendazole in horses.

Toxicological Studies

As this is an extension application for the addition of a new target species (horses) in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC, and the applicant has provided bibliographical data detailing the toxicological profile of the active substance, fenbendazole, the results of toxicological tests are not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that dermal (following accidental spillage during pre-application and application phases) and oral (following accidental ingestion via hand-to-mouth contact) exposure are considered the most likely routes of exposure. It is concluded that use of the product in horses does not present a greater risk to the user than when the product is used in cattle. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- People with known hypersensitivity to fenbendazole or any of the listed excipients should avoid contact with the veterinary medicinal product.
- Do not eat, drink or smoke while handling the product.
- Direct contact with the skin should be kept to a minimum. Wear suitable protective clothing including impermeable rubber gloves. Wash hands after use.
- If accidental contact with the skin or eyes occurs, wash off any skin contamination with soap and water immediately. Rinse the affected eyes thoroughly with clean, fresh water. Remove any contaminated clothing immediately.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the target animal species 'horse' is a minor species that is reared and treated similarly to the major species for which the product is already authorised, i.e., cattle, and the total expected exposure from use in horses is not expected to exceed exposure arising from use in the major species.

III.B Residues Documentation

Residue Studies

The applicant conducted a confirmatory residue depletion study in horses following a single oral administration of the test article at 60 mg / kg bodyweight. Residues in tissues were examined at a single timepoint, 28 days after administration of the test article. Residue concentrations of fenbendazole, fenbendazole sulfone and fenbendazole sulfoxide were assayed by a validated analytical LC-MS/MS method. At 28 days all samples were below either the limit of detection or the limit of quantification for all analytes.

MRLs

Fenbendazole is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	Equidae
Muscle	50 µg/kg
Liver	500 µg/kg
Kidney	50 µg/kg
Fat	50 µg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 31 days (addition of a 10% safety span to 28 days) for meat and offal in horses is justified.

The product is not authorised for horses producing milk for human consumption.

IV. CLINICAL ASSESSMENT

This is an extension to the marketing authorisation for 'Curazole 10% w/v oral drench' for the addition of a new target species, horses, in accordance with paragraph 3 of Article 13 of Directive 2001/82/EC as amended. As bioequivalence with a reference product has not been demonstrated, additional data have been presented to support the efficacy of this product. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

Bibliographical data have been provided which provide adequate support for an acceptable target animal safety profile of the candidate product in horses. The product literature accurately reflects the type and incidence of adverse effects which might be expected (i.e., none).

Resistance

The bibliographical information provided describes recent reports of resistance to benzimidazoles in cyathostomes. It is concluded that the resistance profile of the candidate product is not expected to differ from that of the reference product, and adequate warnings and precautions appear in the product literature.

IV.B Clinical Studies

The applicant has provided bibliographical data which show that the candidate product can be considered to be as efficacious as the reference product in the target animals species, horses.

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, horses is favourable, and the quality and safety of the product for humans and the environment is acceptable