IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Quanifen (50 mg Praziquantel / 500 mg Fenbendazol) Tablets for Cats and Dogs.

PRODUCT SUMMARY

EU Procedure number	IE/V/0175/001
Name, strength and pharmaceutical form	Quanifen (50 mg Praziquantel / 500 mg Fenbendazole) Tablets for Cats and Dogs
Active substances	Praziquantel, Fenbendazole
Applicant	Chanelle Pharmaceuticals Manufacturing Ltd. Loughrea Co. Galway Ireland
Legal basis of application	Well established veterinary use application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of Authorisation	22/04/2005
Target species	Dogs and cats
Indication for use	For the treatment of mixed infections of roundworms and tapeworms in dogs and cats.
ATCvet code	QP52AA51
Concerned Member States	AT, DE, PL, HU

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the 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

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, 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

A. Qualitative and Quantitative Particulars

The product contains the active substances praziquantel (50 mg/tablet) and fenbendazole (500 mg/tablet) and the excipients sodium laurilsulfate, povidone 30, sodium starch glycolate and magnesium stearate.

The product is packaged in white high density polyethylene containers with white polypropylene caps, or in aluminium/aluminium foil blisters or in strips consisting of aluminium foil coated with extruded polythene.

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.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are praziquantel and fenbendazole, established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification has been provided.

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

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

D. Control on Intermediate Products

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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

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

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that praziquantel causes spastic paralysis of the musculature of the parasites due to a membrane depolarisation of the muscle cells. It damages the normal function of the tegument, the glucose intake from the medium is inhibited and the production of lactate stimulated. The membrane is more permeable for glucose and more sensitive to the action of proteolytic enzymes.
At the molecular level the mechanism of action that produces the tetanic paralysis is still not fully understood. Several groups have suggested that praziquantel opens calcium channels in the tegument to bring about this effect. Praziquantel is rapidly absorbed and metabolised by the liver. It is rapidly excreted entirely as metabolites in the urine and bile. Disintegrated and partially digested fragments of tapeworm segments may occasionally be seen in the faeces.

Bibliographical data on fenbendazole was also provided. Fenbendazole acts against parasites by disrupting the formation of microtubules by binding to tubulin in parasitic intestinal cells hence preventing the absorption of glucose, parasites are gradually starved to death. Fenbendazole displays preference for parasitic as opposed to mammalian tubulin. This appears to be due to the fact that the formation of the parasitic tubulin-fenbendazole complex is more favourable kinetically under physiological conditions than the mammalian complex. Fenbendazole may also inhibit energy production in helminths by inhibition of glucose uptake and glycogen breakdown.

The applicant has also provided bibliographical data which show that praziquantel is extensively absorbed after oral administration (75-100%) with about 80% of PRZ bound to protein in plasma. Serum concentration of non-metabolised praziquantel is low. There is an extensive first pass effect. Most praziquantel and metabolites are eliminated via the kidneys. It is rapidly eliminated from blood and is undetectable after 24 hrs.

Fenbendazole is poorly absorbed. The parent drug is metabolised in the liver and eliminated within 48 hours. The main metabolite, oxfendazole, also possesses anthelmintic activity. Excretion is mostly in the faeces with only 10% via urine.

Following administration of this product with food in dogs, Cmax for fenbendazole was 393 ng/ml, Tmax was 14 hours, AUC was 5057 ng/mUhr and mean half-life was 5 hours. Maximum concentrations of the active metabolite, oxfendazole were 332 ng/ml, Tmax was 16 hours, AUC was 4480 ng/mUhr and mean half-life of elimination was 5 hours. Praziquantel was rapidly absorbed, Cmax was 935 ng/ml, Tmax approximately one hour, AUC was 2765 ng/ml/hr and mean half-life was 3.5 hours

Toxicological Studies

The applicant has provided bibliographical data which show that both praziquantel and fenbendazole demonstrate low toxicity in a variety of species. As reproductive studies were not presented for fenbendazole use in cats, the product is not recommended for use in pregnant cats. There is no indication of mutagenic or carcinogenic effects.

User Safety

The applicant has provided a user safety assessment showing that both active substances are of a low order of toxicity to mammals and display negligible dermal and ocular irritancy or local toxicity.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I
The environmental risk assessment can stop in Phase I because the product is for administration to cats and dogs on an individual basis. In addition, both active constituents are extensively metabolised.

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.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted three target animal tolerance studies using multiples of the recommended dose in the target species. Untreated animals were used as a control. All doses were administered by the oral route on three occasions.

Both fenbendazole and praziquantel were very well tolerated. With multiple overdose administration transient diarrhoea was observed. From 3 times the recommended dose, loose faeces in dogs and crying and restlessness in puppies were reported. At 5 times the recommended dose, excessive salivation was observed in dogs and puppies. Vomiting also occurred. At 5 times the recommended dose, inappetance was observed in cats.

Bibliographical data have also been provided which show similar results to those observed in the target animal tolerance studies.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography provided suggests that there is no evidence of resistance in target parasites in dogs and cats.

IV.B Clinical Studies

The applicant has provided bibliographical data which includes, for both active constituents, dose titration and dose confirmation studies as well as field studies against the various target parasites of cats and dogs. Confirmatory efficacy studies have been carried out which were considered supportive of the claimed indications.

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

VI 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 HPRA website.

Changes:
None.