ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Deccox, 6% Premix for Medicated Feeding Stuff, for Sheep and Cattle

PuAR correct as of 23/04/2018 when RMS was transferred to ES. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0289/001/MR
Name, strength and pharmaceutical form	Deccox 6% Premix for Medicated Feeding Stuff for Sheep and Cattle
Applicant	Zoetis UK Limited 5th Floor 6 St. Andrew Street London EC4A 3AE
Active substance	Decoquinate
ATC Vetcode	QP51AX14
Target species	Sheep and Cattle
Indication for use	For the treatment and prevention of coccidiosis in lambs and calves. As an aid in the control of coccidiosis in lambs, by medication of ewe feed. As an aid in the prevention of abortions and perinatal losses due to toxoplasmosis by medication of ewe feed.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	30 April 2008
Date product first authorised in the Reference Member State (MRP only)	28 July 2004
Concerned Member States for original procedure	Spain

I. SCIENTIFIC OVERVIEW

Deccox 6 % Premix for medicated feeding stuff for sheep and cattle is a premix and contains 6 % decoquinate. The product has the following indications:

- For the treatment and prevention of coccidiosis in lambs and calves.
- As an aid in the control of coccidiosis in lambs, by medication of ewe feed.
- As an aid in the prevention of abortions and perinatal losses due to toxoplasmosis by medication of ewe feed.

In order to treat and prevent disease in lambs and calves the medicated feed should be fed for 28 days. To prevent losses due to toxoplasmosis, ewes should be fed medicated feed for the last two-thirds of pregnancy.

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 efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substance decoquinate and excipients wheat middlings, anhydrous colloidal silica and soya bean oil.

The container/closure system comprises a three ply paper sack, with spray coated polyethylene interior face, closed with stitching, containing 10 kg of product. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is 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 from a licensed manufacturing site.

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

C. Control of Starting Materials

The active substance is decoquinate an established active substance described in the British Veterinary 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.
The excipient anhydrous colloidal silica complies with described in the European Pharmacopoeia Monograph. The remaining excipients comply with the manufacturer's specifications.

A specification was also provided for the polyethylene lined paper sacks. The sacks are commonly used for animal feedstuffs hence presumed suitable for food contact products.

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

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

E. Control on intermediate products

Not applicable.

F. 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.

G. 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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale - 3 years.
Shelf life after incorporation into final feed - 3 months.

Special precautions for storage
Store in a dry place.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies
The applicant has provided bibliographical data which justify what is included in the SPC: Decoquinate is a 4-hydroxyquinoline antiprotozoal compound active against *Eimeria* spp. and *Toxoplasma* spp. Decoquinate inhibits the development of coccidia in the small intestine in the early part of the infective cycle, resulting in lower morbidity and mortality. The exact mode of action is unknown.

The applicant has also provided bibliographical data which support what is written in the SPC. The main site of action of the drug is within the gastro-intestinal tract. It is poorly absorbed by the target species and is largely eliminated in faeces unchanged. Consequently, tissue residues are low and deplete rapidly with time. Recovery of the administered material via excretion is essentially complete.

Toxicological Studies
Single Dose Toxicity
The applicant provided reference to a study where groups of rats were given a single oral dose of 2000 mg/kg bw of regular or micronised decoquinate. No rats died and no signs of toxicity were observed during the 7 day observation period. Autopsies were subsequently carried out on a sample of rats and there were no abnormal findings. The acute oral LD50 was >2000 mg/kg bw.

Repeated Dose Toxicity
References to several repeated dose studies in rats were provided. In these studies groups of rats were administered repeat doses and several observations were made, typically clinical signs, food consumption, body weights, haematology, blood chemistry, urinalysis, organ weights and histopathology. In one study the NOEL was 2,000 mg/kg feed, equivalent to approximately 100 mg/kg bw/day). In another study the NOEL was 1,000 mg/kg feed, equivalent to approximately 25 mg/kg bw/day.

Reproductive Toxicity, including Teratogenicity:
The applicant provided a reference to a three generation reproductive study. There were no significant treatment related effects on conception rate, litter size, numbers of live or dead pups, pup body weight or survival. Only one malformed pup was born in one of the control litters. The top dose level of 1,000 mg/kg feed (equivalent to 61-87 mg/kg bw/day in males and 71-98 mg/kg bw/day in females) was a NOEL.

A reference to a study concerning foetotoxicity in rats was also provided. Only limited details were provided. No effects attributable to decoquinate were found. Another foetotoxicity study in rats gave rise to a NOEL of 60 mg/kg bw/day.

Mutagenicity
The applicant provided a battery of mutagenicity studies both with and without metabolic activation in a number of bacterial and mammalian cells. The results indicated that decoquinate was not genotoxic.

Carcinogenicity
Given the lack of genotoxic potential the applicant was not required to submit carcinogenicity studies.

Other Studies
SPECIAL STUDIES (E.G. SPECIFIC TARGET ORGAN TOXICITY, IMMUNOTOXICITY)
Toxicological manifestations in repeat dose studies and skin sensitisation studies in the rat did not suggest that decoquinate was immunotoxic.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline that considered all of the potential routes of exposure and included an appraisal of the exposure to the user. Decoquinate is of low toxicity and does not cause any serious concern with regard to safety. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required. The assessment concluded that the use of Deccox 6 % Premix in cattle and sheep indicates that the risk to the environment is acceptable.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies
Residue depletion studies using acceptable formulation have been conducted in young cattle and sheep. Samples of liver, kidney, muscle and fat were taken from animals at several time points. Residue levels were low from one day up to the last treatment. The total residue burden was a fraction of the acceptable daily intake (ADI).

MRLs
Decoquinate is listed in Annex II of Council Regulation 2377/90 and no MRL has been assigned.

Withdrawal Periods

Based on residues findings above, a withdrawal period of zero days for meat in cattle and sheep have been justified. As no information was available concerning residue depletion in milk, decoquinate cannot be used in animals from which milk is produced for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided references relating to pharmacoynamic properties of decoquinate. Little is known about the mechanism of action of deccoquinate and this is reflected in the SPC.

A number of references to pharmacokinetics studies have been provided. The studies indicate that the main site of action of decoquinate is in the gastrointestinal tract and that relatively little is absorbed. The pharmacokinetics are described appropriately in the SPC.

Tolerance in the Target Species of Animals

Cattle

The applicant has provided a target animal tolerance study using multiples of the recommended dose young cattle. A placebo was used as a control.
All animals were observed twice daily for abnormal clinical signs during the dosing periods and all were subjected to detailed necropsy examination and gross pathological investigation at the end of dosing. The data were analysed statistically. .
No adverse effects were seen following doses up to 5 times the recommended dose. It was concluded that administration of the product at 5 times the recommended dose for 28 days to calves had no effect upon general health, monitored blood parameters, or histological abnormality that could be attributed to the overdose of the active substance.

Sheep

The applicant provided two similar studies to that described above. The results indicated that when decoquinate was administered to sheep at 5 times the recommended dose rate for the recommended duration of therapy (28 days), or at the recommended dose rate for 7 days longer than the recommended dosing period, it was well tolerated.

Resistance

The published reference provided reviews the use of anticoccidials and states that there have been no reports of drug resistance in bovine coccidia after the use of decoquinate. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

The applicant submitted a number of studies in the target species. Efficacy was considered as reduction or elimination of clinical signs with a reduction in the faecal oocyst count. In the early studies, these parameters were not scored, however a reduction in the severity and occurrence of clinical signs with a concurrent reduction in faecal oocyst output was evident from all the results presented.

Cattle

The studies submitted confirm the effective dose as 1 mg/kg per day for treatment of coccidiosis in calves. Studies were presented which demonstrated efficacy of the product for prevention of coccidiosis confirm that 0.5 mg/kg is the optimum dose.

Sheep

The clinical data for sheep were not up to modern standards. Dose titration studies were supportive of the selection of a dose effective against recent European strains of coccidia. Results from a series of studies in housed young sheep and young sheep at pasture were also provided. However, the data obtained from the artificial and field studies in young sheep support the efficacy of the dose rate of 1 mg/kg for treatment and prevention of coccidiosis. The data presented in support of the claim related to the indirect control of coccidiosis in young sheep by the medication of ewe feed showed that decoquinate did not prevent the development of clinical coccidiosis in the young sheep, however oocyst shedding was reduced. The toxoplasmosis claim was well supported and the studies demonstrated that a dose rate of 2 mg/kg for the last 14 weeks of pregnancy prevented toxoplasmosis related abortion and improved the viability of lambs. It was shown that decoquinate did not affect the immune response therefore treated sheep will develop immunity to further challenge. The study's findings are reflected in the SPC.

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 Product Information Database of the Veterinary Medicines Directorate website.

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

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.

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