ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Startect Dual Active Oral Solution for Sheep

PuAR correct as of 28/06/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0380/001/DC
Name, strength and pharmaceutical form	Startect Dual Active Oral Solution for Sheep
Applicant	Zoetis UK Limited 5th Floor 6 St. Andrew Street London EC4A 3AE
Active substance(s)	Derquantel Abamectin
ATC Vetcode	QP54AA52
Target species	Sheep
Indication for use	Startect Dual Active is a broad spectrum anthelmintic for the treatment and control of mixed gastro-intestinal nematode infections and associated diseases of sheep. The spectrum of activity is as follows: Adult and Immature Gastro-intestinal Nematodes: *Haemonchus contortus* (including inhibited larval stages) *Teladorsagia (Ostertagia) circumcincta* (including inhibited larval stages) *Teladorsagia (Ostertagia) trifurcata* *Trichostrongylus axei* *Trichostrongylus colubriformis* *Trichostrongylus vitrinus* *Cooperia curticei* *Cooperia oncophora* *Nematodirus spathiger* *Nematodirus filicollis* *Nematodirus battus* *Strongyloides papillosus* *Oesophagostomum venulosum* (adult) *Trichuris ovis*

	Chabertia ovina Lungworms: *Dictyocaulus filaria* (adult) This product is effective against strains of parasites resistant to benzimidazoles, levamisole, macrocyclic lactones, and combinations of these.

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	Full application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23rd November 2011.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Ireland.

I. SCIENTIFIC OVERVIEW

Startect is a fixed combination anthelmintic oral solution intended for administration to sheep. The product contains 10 mg/ml of a novel anthelmintic derquantel, in combination with 1.0 mg/ml abamectin. The use of a novel anthelmintic necessitated the provision of data required for a full application. The indication is for the treatment and control of a broad range of gastrointestinal nematodes and associated diseases in sheep, including those species resistant to (pro) benzimadazoles, macrocyclic lactones, closantel and levamisol, or combinations of these. The dose is 2 mg derquantel and 0.2 mg abamectin per kg bodyweight, i.e., 1 ml of product per 5 kg bodyweight. The application was submitted under Article 12.3 of Directive 2001/82/BC as amended. The product was appraised in light of a CVMP[1] evaluation of derquantel, and much of the submitted data pertained to this. The rationale behind the product was to provide efficacy against increasingly resistant strains of nematodes in sheep.

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 slight reactions observed are indicated in the SPC[2]. 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.

[1] CVMP – The Committee for Medicinal Products for Veterinary Use.
[2] SPC – Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

The product contains 10.0 mg/ml derquantel and 1.0 mg/ml abamectin and excipients butylated hydroxytoluene, glycerol formal, triacetin and propylene glycol dicaprylate.

The container/closure system consists of purple, square bottom backpack HDPE polymer bottles (1L and 5L), with draw off tubes (white LDPE, tube with EDPM valve) and child resistant lids. There is also a purple jerrycan, (15L) HDPE polymer, with a white cap. The 15L jerrycan has a polypropylene tap with an O-ring silicone seal with a tamper-proof lid. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified. The product is a novel pharmaceutical form (with regard to derquantel), 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 substances are derquantel and abamectin. Derquantel is a novel active substance and abamectin is an established substance, neither of which is described in the European Pharmacopoeia (Ph. Eur). 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 have been provided.

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

A declaration was received stating that the product complied with the CPMP/CVMP guideline on TSE's (EMEA/410/01 Rev. 2 of October 2003). A declaration was also provided by the active substance and excipients suppliers, showing that no materials of animal origin are used in manufacture. A signed Format 3 statement was also supplied.

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 substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions. In tests performed on the active substances, derquantel remained stable under the approved storage conditions. Suitable data were submitted for the stability of abamectin. Tests were performed on the finished product which supported the shelf-life claim of 2 years, and shelf-life after opening of immediate packaging of 12 months.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life:
Shelf-life of veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 12 months.

Special precautions for storage:
Do not refrigerate or freeze.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Cross-reference was made to a Maximum Residues Limit (MRL) evaluation by the CVMP for derquantel for most of the safety studies, extracts from which were included in the report. Abamectin had already been evaluated by the CVMP, and suitable extracts for this active substance were also included. Any additional data was submitted for review.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Derquantel

The mode of action of derquantel, for which the target parasites are nematodes, is the blocking of cholinergic neuromuscular transmission.

Abamectin

Abamectin possesses broad spectrum activity against arthropod and nematode parasites of plants and animals.

It was noted that no pharamcodynamic interactions occur between the two active substances.

Pharmacokinetics

Derquantel

Peak plasma levels of derquantel given orally to rats in appropriate studies was demonstrated at 0.5-4 hours post administration, with C_{max}[3] and AUC[4] being higher in females than males. Oral administration produced C_{max} in dogs at 0.5 hours, with no differences in C_{max} and AUC seen between males and females. The $t_{1/2}$[5] in dogs was 3 to 4 hours.

Abamectin

Radioactivity from tritium-labelled avermectin B1 given to rats at 1.4 mg/kg bodyweight were found in kidney and fat, liver and muscle. Depletion rates were independent of dose and tissue, with excretion being predominantly performed via elimination of the faeces, and the remainder via the urine. A study in cattle following subcutaneous administration of 0.3mg/kg bodyweight tritium-labelled abamectin showed mean peak plasma levels of radioactivity which corresponded to approximately 0.09 mg/l. Depletion rates for various tissues

[3] C_{max} – Maximal plasma concentration.
[4] AUC – Area under the curve.
[5] $t_{1/2}$ – Half life of the active substance.

occurred over between 4.6 and 8.1 days, which the majority of elimination occurring in the faeces.

Toxicological Studies

- Single Dose Toxicity

Derquantel

No mortality was observed in rats when given up to 1000 mg/kg bodyweight. Effects on the nervous system were observed at over 350 mg/kg bodyweight. In dogs, acute effects were noted at the lowest dose, 1 mg/kg bodyweight. Horses are very sensitive to derquantel, doses of 2 and 20 mg/kg twice a day prove lethal.

Abamectin

In male and female mice respectively, LD_{50}[6] values of 9.2 mg/kg bodyweight and 19.7 mg/kg bodyweight were found, with LD_{50} in rats seen at 8.7 mg/kg bodyweight in males and 12.8 mg/kg bodyweight in females. A study in rhesus monkeys demonstrated that the species tolerated higher abamectin doses than that seen in other species. Acute dermal studies in rabbits (up to 200 mg/kg bodyweight) and rats (330 mg/kg bodyweight), showed reversible clinical signs. In guinea pigs, no sensitising potential was seen. Mildly positive results were observed in ocular irritation studies in rabbits.

- Repeated Dose Toxicity

Derquantel

Repeated oral dose toxicity studies were performed in rats and dogs. At a NOEL[7] of 0.5 mg/kg bodyweight/day, effects were seen on the liver and thyroid gland in rats. In two further unrelated studies in rats, (one 90 day, one 1 year), the LOAEL[8] was established as 1 mg/kg/bodyweight/day.

In dogs, a 28 day oral toxicity study with doses in the range 0.01 to 0.1 mg/kg bodyweight/day showed no neurological or behavioural effects. In two further unrelated studies, the NOAEL was shown to be 0.1 mg/kg bodyweight/day.

Abamectin

Repeated dose studies on oral toxicity were performed in rats (0.75 – 2.0 mg/kg bodyweight), mice (2.0 – 8.0 mg/kg bodyweight), and dogs (0.25 – 8.0 mg/kg bodyweight).The highest dose NOEL in rats and dogs was 0.25 mg/kg bodyweight and 1.5 kg/mg bodyweight respectively. Tremor was noted in mice as an irregular treatment-related effect in females.

[6] LD_{50} – The median lethal dose.
[7] NOEL – No Observable Effect Limit.
[8] LOAEL – Lowest Observed Adverse Effect Limit.

Startect

Results of tests using the product, which has the combination of the two active substances, did not reveal an increase in toxicity.

- Reproductive Toxicity

Derquantel

Derquantel was given to rats at 0, 1, 5 and 25 mg/kg bodyweight/day in a two-generation study. No reproductive effects were seen at these doses. A further study used doses of 0, 20, 70 and 120 mg/kg bodyweight/day. Maternal toxicity was seen at 70 mg/kg bodyweight/day, and foetal development retarded at 120 mg/kg bodyweight/day. In rabbits the NOAEL when given 0, 0.1, 1 and 10 mg/kg bodyweight/day was 1 mg/kg bodyweight/day.

Abamectin

A slight increase in foetal malformation was seen in rats, (1.0 mg/kg bodyweight) developmental retardation in rabbits, (0.2 mg/kg bodyweight). In mice, foetal malformations were observed only at maternotoxic doses. This was the most sensitive determinator for mice, and was used to establish the ADI[9] (NOEL 0.05 mg/kg bodyweight).

- Carcinogenicity

For derquantel, no carcinogenicity studies were required. For abamectin, studies in rats and mice gave no evidence of carconigenicity.

Other Studies

Studies were performed for derquantel, which was found not to be a skin sensitiser or irritant. The active substance was a slight ocular irritant. The LC_{50}[10] was found to be >2.4 mg/l in albino rats after a 4 hour nose only exposure.

Observations in Humans

No human toxicological data with derquantel and abamectin are available.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

[9] ADI – Acceptable Daily Intake.
[10] LC_{50} - Median Lethal Concentration.

Ecotoxicity

The applicant provided a comprehensive second phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required; reports and appropriate justifications were provided. PEC[11] and PNEC[12] values for a large variety of species, groundwater, soil and plants, were ultimately shown to be 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

Studies were provided for the CVMP evaluation, and such as were pertinent to the application were reported.

Pharmacokinetics

Derquantel

The oral bioavailability of derquantel was cited as approximately 56%, with maximal plasma concentration attained at about 4 hours post-administration. Intravenous dosing studies showed that bodily distribution was wide with moderate clearance. A C_{max}[13] in oral studies of between 92.8 and 108 ng/ml with a T_{max}[14] of between 2.60 and 4.17 hours was observed. Bioaccumulation was not anticipated. Excretion occurred mainly via the faeces. Further studies reported that derquantel is extensively metabolised in all tested species, undergoing metabolism over a short time period.

Abamectin

Investigated in conjunction with the final product.

Startect

In GLP[15]-compliant studies and the ensuing CVMP assessment, it was shown that the pharmacokinetic parameters of derquantel were not significantly compromised by co-administration with abamectin.

[11] PEC – Predicted Environmental Concentration.
[12] PNEC – Predicted No Effect Concentration.
[13] C_{max} – Maximum Concentration.
[14] T_{max} – Time at which maximal concentration observed.
[15] GLP – Good Laboratory Practice.

Residue Studies

Residue Depletion Studies

It was demonstrated in sheep that abamectin in fat depletes more slowly than in other tissues.

MRLs

	µg/kg Derquantel	µg/kg Abamectin
Muscle	2	20
Liver	20	25
Kidney	5	20
Fat	40	50

Withdrawal Periods

Based on the data provided above, a withdrawal period of 14 days for meat and offal was granted. The product is not to be used in lactating ewes producing milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Data were provided describing the unique mode of action of derquantel. The active substance acts as a nicotinic cholinergic antagonist which induces flaccid paralysis in the target parasites. Abamectin is a member of the macrocyclic lactone class of active substances, which acts against glutamate or GABA-gated channels within the target parasite, leading to muscular paralysis and death.

Pharmacokinetics

A large amount of data were submitted for this section - for absorption, metabolism, and excretion. Studies were performed on each active substance individually, and in combination for this section. A brief overview of data related to plasma concentration for the individual active substances, which contributed to the dosage parameters is cited in the SPC.

Derquantel

Data were provided showing that pharmacokinetic parameters were calculated from intravenous, subcutaneous and oral doses given to sheep at 5 mg/kg. Derquantel was cleared at approximately 55% liver blood flow after intravenous

administration, demonstrating that oral bioavailability was limited to approximately 50% maximum, due to first pass metabolism. Half-life was similar following intravenous and oral administration (5 hours), with oral bioavailability at approximately 60%.

Abamectin

A summary of pharmacokinetic data from published data for ivermectin (little data in the literature for abamectin), in addition to suitable studies were submitted. Abamectin has a similar mode of action to ivermectin, with a more potent effect against gastrointestinal nematodes. This along with study data provided by the applicant, helped to establish the dose of abamectin of 0.2 mg/kg as being justified.

Tolerance in the Target Species of Animals

The applicant conducted a series of controlled target animal tolerance studies using multiples of the recommended dose in the target species. An authorised reference product containing the same active substance, or a placebo was used as controls as appropriate. All doses were administered by oral gavage, and animals received x1, x3 or x5 the recommended dose. Minimal adverse effects were seen following doses up to 5 times the recommended dose. The SPC carries suitable warnings with regard to dosage, bodyweight and the avoidance of using the product is certain species other than sheep, which may prove fatal.

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

Resistance

Appropriate data were received with regard to resistance, with little or no data being available for derquantel as a novel active substance. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant conducted/reported on a large series of dose determination and confirmation studies, which when reviewed, provided sufficient evidence to support the indication claims as described in the approved SPC.

Dose Confirmation Studies

All studies in sheep were negatively-controlled, single site, randomised block design studies which used the individual animal as the experimental unit. Efficacy was established by total worm count following treatment. Animals used as negative controls received either a placebo treatment (the majority of studies), or no treatment was given. For studies in which resistant strains of parasite were used, appropriate reference groups received a commercially-

available single-active anthelmintic, in order to confirm the resistance profile. In studies where an artificial infection was used in parasite–free animals, faecal egg counts were performed before and after infection, and in studies where naturally-infected animals were used, number of parasites was confirmed by faecal egg count and larval differentiation of pooled faeces. In all studies, animals were acclimatised prior to treatment. Where the product was used, animals were orally dosed to individual body weight with 0.2 ml Startect (2.0 mg/kg derquantel, 0.2 mg/kg abamectin). Placebo or reference product was administered at the same volume, or at the recommended dose rate respectively. At necropsy, parasite burden was performed according to standard techniques.

Seven studies were performed against adult and/or hypobiotic L4 parasites. Eight studies were used to confirm the efficacy of Startect against resistant strains of gastrointestinal nematodes in sheep. Where studies targeted adult and hyperbiotic L4 stages, pre-treatment faecal egg counts were summarised for each group with geometric mean and minimum and maximum egg counts. If other species were present these were also summarised. At Day 0 dosing data were summarised for treatment and control groups.

Primary outcome was the percentage reduction in geometric mean worm count compared to untreated controls for each species and life cycle stage. A separate analysis was performed on each stage and species. Log transformed data were analysed with a general linear model including the random effect of blocking and the fixed treatment effect. Geometric means and 95% confidence levels were calculated via back transformation. Untransformed data was used to define the arithmetic mean. The level of significance for treatment differences was set at $P \leq 0.05$, or 5%. Statistical evaluation was only performed where there were a suitable number of negative animals.

Any changes in bodyweight (performed at the beginning and end of the in-life phase) were analysed using a general linear mixed model, compensating for relevant variables: fixed effect of treatment group, random of block effect and pen and pre-treatment bodyweight as a covariate.

In all studies the efficacy of the product was demonstrated to be greater than 95% based on geometric means. Where abamectin was included as a reference anthelmintic, efficacy was ≥98.48% against all target parasites. Startect was 100% efficacious against two species recognised as dose-limiting parasites for abamectin in sheep. These data among other confirmed that there was no negative interaction between derquantel and abamectin. Startect was shown to be effective against two abamectin-resistant strains; *Teladorsagia circumcincta* and *Haemonchus contortus*. *T. Circumcincta* is known to have a varying response to treatment with derquantel alone.

Field Trials

A large number of field studies were performed. The studies were performed against natural infections of gastrointestinal and respiratory nematodes in sheep, measuring the reductions in faecal egg count, with the product used at the dose

defined in the SPC. In all instances, the efficacy of Startect was greater than 98%. All studies were single-site, negatively controlled, block design studies, with the individual animal as the experimental unit. Negative controls received placebo at the dose rate of the product, or were untreated.

Faecal samples were collected shortly before treatment, and all relevant or associated target species were counted. Post-treatment, faecal samples were collected and analysed, and samples from animals in the same treatment group were pooled. Egg counts were analysed statistically, in the same manner as that described for the dose determination studies. High efficacy values were obtained for all species cited 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 benefit/risk 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)