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Efficacy of a combined oral formulation of derquantel–abamectin against the adult and larval stages of nematodes in sheep, including anthelmintic-resistant strains

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ABSTRACT

Derquantel (DQL), a semi-synthetic member of a novel anthelmintic class, the spiroindoles, in combination with abamectin (ABA) [as the combination product STARTECT®] is a new entry for the treatment and control of parasites in sheep. The 19 studies reported herein were conducted in Australia, New Zealand, South Africa and the United Kingdom to demonstrate the efficacy of derquantel–abamectin (DQL–ABA) against a broad spectrum of gastrointestinal and respiratory nematodes of sheep, and to support registration of the combination product. Eleven studies were conducted using natural or experimental parasite infections with unknown or unconfirmed resistance, while eight studies utilised isolates/strains with confirmed or well characterised resistance to one or more currently available anthelmintics, including macrocyclic lactones. All studies included DQL–ABA and negative control groups, and in selected studies one or more reference anthelmintic groups were included. In all studies the commercial formulation of DQL–ABA was administered orally at 2 mg/kg DQL and 0.2 mg/kg ABA; placebo was administered in the same volume as DQL–ABA; and reference anthelmintics were administered as per label recommendations, except in one instance where levamisole was administered at twice the label dose. Infection, necropsy, worm collection and worm counting procedures were performed using standard techniques. Efficacy was calculated based on the percentage reduction in geometric mean worm count relative to negative control for each nematode species and lifecycle stage targeted. Twenty-two isolates/strains used in the eight studies targeting resistant worms had proven resistance: three to one anthelmintic class, eleven to two classes and eight to three or more classes; of these resistant strains, 16 demonstrated resistance to a macrocyclic lactone anthelmintic. Regardless of resistance status in the 19 studies, DQL–ABA controlled a broad range of economically important gastrointestinal and respiratory nematode parasites of sheep, as follows: ≥98.9% efficacy against *Haemonchus contortus* (adult and L4); *Teladorsagia circumcincta* (adult, L4 and hypobiotic L4); *Teladorsagia trifurcata* (L4);

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Trichostrongylus axei (adult and L4); *Trichostrongylus colubriformis* (adult and L4); *Trichostrongylus falculatus* (adult); *Trichostrongylus rugatus* (adult); *Trichostrongylus vitrinus* (adult and L4); *Cooperia curticei* (adult and L4); *Cooperia oncophora* (adult and L4); *Nematodirus spathiger* (adult); *Nematodirus battus* (adult); *Nematodirus* spp. (hypobiotic L4); *Strongyloides papillosus* (adult); *Strongyloides* spp. (L4); *Chabertia ovina* (adult); *Oesophagostomum venulosum* (adult); *Dictyocaulus filaria* (adult); and *Protostrongylus rufescens* (adult); ≥97.0% efficacy against *Trichuris ovis* (adult); and ≥95.9% efficacy against *T. trifurcata* (adult). Derquantel–abamectin is a highly effective combination anthelmintic, which will provide an important new tool for controlling helminths of sheep when used in conjunction with sustainable drenching practices.

1. Introduction

Treatment with broad-spectrum anthelmintics has been the cornerstone of internal parasite control in small ruminants for the last 50 years. However, the reliance on anthelmintics has driven rapid development of anthelmintic resistance following the introduction of new anthelmintic classes to the market. For each new class, resistance has developed in at least one important nematode species of sheep (and goats) within a few years of introduction (Kaplan, 2004; McKellar and Jackson, 2004). The continuous stream of new classes (modes-of-action) of anthelmintics had for several decades compensated for parallel development of resistance (von Samson-Himmelstjerna and Blackhall, 2005); however, from the introduction of ivermectin in the early 1980s until the recent discovery of the amino-acetonitrile derivatives and identification of monepantel as an anthelmintic (Ducray et al., 2008; Kaminsky et al., 2008a,b), over a quarter of a century had elapsed before a chemical class with a new mode-of-action was developed for use in livestock. Additional chemistries with novel modes-of-action are urgently needed to control nematodes in small ruminants as available products, including combinations, are failing (Besier, 2007).

Derquantel (DQL), also known as 2-desoxoparaherquamide, 2-deoxyparaherquamide and PNU-141962 (Lee et al., 2002), is a semi-synthetic member of a new anthelmintic class, the spiroindoles. This class includes natural products with known anthelmintic activity, e.g., paraherquamide (Yamazaki et al., 1981; Ostlind et al., 1990; Shoop et al., 1990; Blanchflower et al., 1991) and the marcfortines (Lee et al., 2001, 2002; Mauragis et al., 2002; Johnson et al., 2004). The spiroindoles are characterised by an indole or oxindole moiety fused with a carbocycle, more specifically a cyclopentyl ring, at the spiro quaternary carbon atom at position C-3 of the indole. Derquantel was identified through a spiroindole medicinal chemistry program, and this work has been reported elsewhere (Lee et al., 2001, 2002; Mauragis et al., 2002; Johnson et al., 2004). The chemical structure of DQL is shown in Fig. 1. Derquantel and the other spiroindole anthelmintics are nicotinic cholinergic antagonists, which block cation channels in nematode muscle cell membranes. This novel mode-of-action blocks cholinergic neuromuscular transmission, rapidly inducing flaccid paralysis in parasitic nematodes in vitro (Robertson et al., 2002; Zinser et al., 2002).

The efficacy of DQL against gastrointestinal nematodes of sheep was assessed early in its development, and in subsequent dose-determination studies; in the dose range tested (0.5–8.0 mg/kg), DQL was found to be a mid-spectrum anthelmintic. At the dose rate selected for the combination product, derquantel alone was consistently found to have excellent anthelmintic activity (>95% reduction in mean worm count) against the adult and fourth larval (L4) stages of *Trichostrongylus* and *Nematodirus* spp., and the adult stage of *Haemonchus contortus*; it demonstrated variable efficacy (≤95%) against *Teladorsagia* (=*Ostertagia*) *circumcincta*, the L4 of *H. contortus*, and some large intestinal nematodes (PR Little and SJ Maeder, unpublished data).

Derquantel has been developed as an oral anthelmintic for sheep in combination with abamectin (ABA), to provide broad-spectrum utility, efficacy against nematodes resistant to existing anthelmintics, and a means of protecting the new class from the rapid emergence of anthelmintic resistance. The derquantel–abamectin combination (STARTECT®, Pfizer Animal Health) is a solution containing 10 mg/mL DQL and 1 mg/mL ABA, and is intended for oral use in sheep at a dose of 2 mg/kg derquantel and 0.2 mg/kg abamectin.

The data reported herein were generated in a series of studies utilising nematodes with unknown or unconfirmed resistance (11 studies) or with isolates/strains having proven single, dual, or multiple anthelmintic resistance (eight studies). These studies were conducted across four countries (Australia, New Zealand, South Africa and the United Kingdom) to support registration of DQL–ABA as an oral anthelmintic for sheep.

2. Materials and methods

A total of 19 studies utilising the controlled anthelmintic test (Wood et al., 1995) were conducted during 2006–8 to confirm the efficacy of DQL–ABA, in the commercial formulation, when administered orally to sheep at a dose of 2 mg/kg DQL and 0.2 mg/kg ABA. The study design and technical procedures used were consistent with the following regulatory guidelines: *Efficacy of Anthelmintics: General Requirements* (VICH GL7, 2000a); *Efficacy of Anthelmintics: Specific Recommendations for Ovines* (VICH GL13, 2000b); and WAAVP recommendations for evaluating the efficacy of anthelmintics in ruminants (Wood et al., 1995). In addition, all studies were conducted in accordance with Good Clinical Practice (VICH GL9, 2001), were subject to local eth-