14 July 2011
EMA/161969/2012

EPAR Scientific Discussion post-authorisation update for ZOLVIX

International Non-proprietary Name: Monepantel

EU/2/09/101/001-010

Scope:

Extension of the indications to *H. contortus* strains resistant to salicylanilides.

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No. 1234/2008, the marketing authorisation holder, Novartis Healthcare A/S, submitted to the European Medicines Agency (the Agency) on 20 December 2010 an application for a type II variation for ZOLVIX.

1.2. Scope of the variation

Previous	Proposed
SPC	**SPC**
4.2 Indications for use, specifying the target species	**4.2 Indications for use, specifying the target species**
The veterinary medicinal product is effective against strains of these parasites resistant to (pro)benzimidazoles, levamisole, morantel and macrocyclic lactones.	The veterinary medicinal product is effective against strains of these parasites resistant to (pro)benzimidazoles, levamisole, morantel, macrocyclic lactones **and salicylanilides.**
PACKAGE LEAFLET	**PACKAGE LEAFLET**
4. INDICATION	**4. INDICATION**
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2. Scientific discussion

Haemonchus contortus isolates have been characterized showing resistance to several anthelmintics. In order to include efficacy of monepantel (ZOLVIX) against salicylanilide resistant *Haemonchus contortus* several studies were submitted.

A study on efficacy of monepantel against 4th stage larvae of resistant *H. contortus*, *T. circumcincta*, *T. axei*, *T. colubriformis* and *C. curticei* in sheep was performed to demonstrate efficacy against *H. contortus* (strain Haecon-51) resistant to benzimidazoles, levamisole, macrocyclic lactones and salicylanilides. This was a randomised, blinded and double-controlled GCP study of parallel-group design, with artificial infection using 3rd stage larvae of *Haemonchus contortus* resistant to benzimidazoles, levamisole and macrocyclic lactones and salicylanilides on Day -5. Faecal egg counts on Day 19 and worm counts on necropsy on Day 21 were performed and geometric and arithmetic means were calculated. A total of forty Swiss White Alpine and INRA401 sheep, of 6-8 or 16-19 weeks of age, were randomly allocated to five groups balanced for sex, age and also weight. No treatment-related adverse reactions were observed. This was considered a well conducted study confirming the efficacy of monepantel against *H. contortus* (strain Haecon-51), resistant to benzimidazoles, levamisole, macrocyclic lactones and salicylanilides.

A study to confirm the dose of monepantel against a strain of adult *Haemonchus contortus* (strain Haecon-51) resistant to benzimidazoles, levamisole, macrocyclic lactones and salicylanilides (closantel) infections in sheep in Australia was performed. Monepantel was administered as a 25 mg/ml oral solution once, at a dose of 2.5 mg/kg bw. The study was a randomised, blinded and placebo-controlled GCP study with artificial infection using 3rd stage larvae of multi-resistant *Haemonchus contortus* on Day -28. After allowing the parasite burdens to mature to the adult stage, faecal egg counts on Day -2 were performed and the sixteen 11 months old Merino lambs were randomly allocated to two groups of eight lambs each balanced for weight and faecal egg count. Another faecal sampling on Day 13 and worm counts on necropsy on Day 14 were performed and geometric and arithmetic means were calculated. No adverse reactions were observed. Efficacy against adult *Haemonchus contortus* resistant to benzimidazoles, levamisole, macrocyclic lactones and salicylanilides and their combinations was confirmed in this study.

A study to demonstrate efficacy against immature stages of *H. contortus* (South African strain, 2005) resistant to macrocyclic lactone, benzimidazole, levamisole, closantel and organophosphate was performed. This was a randomised, blinded and double-controlled single site GCP study with artificial infection using 3rd stage larvae of *Haemonchus contortus* on Day -5. 24 Merino lambs 5-6 months of age were randomly allocated to three groups of eight lambs each. Worm counts were performed on necropsy on Day 14-16 and geometric and arithmetic means were calculated. No adverse reactions were observed. This was considered a well conducted study confirming the efficacy of monepantel against 4th stage larvae of *Haemonchus contortus* resistant to macrocyclic lactone, benzimidazole, levamisole and organophosphate. However, resistance to salicylanilides was not shown.

A further study on efficacy of monepantel against 4th stage larvae of *H. contortus* (strain Haecon-51) resistant to benzimidazoles, levamisole, macrocyclic lactones and salicylanilides in sheep was conducted. This was a randomised, blinded and double-controlled GLP study of parallel-group design, with artificial infection using 3rd stage larvae of *Haemonchus contortus* resistant to benzimidazoles, levamisole and macrocyclic lactones and salicylanilides on Day -5. Faecal egg counts on Day 19 and worm counts on necropsy on Day 20 and 21 were performed and geometric means were calculated. A total of 32 Swiss White Alpine and INRA401 sheep, 16-19 weeks of age, were randomly allocated to four groups balanced for sex and weight. No treatment-related adverse reactions were observed. The study confirmed efficacy of monepantel against the *H. contortus* strain used.

A study was conducted to characterise the anthelmintic resistance status of the roundworm isolate *Haecon-51*, which had the initial composition of 100% *Haemonchus contortus* as determined by coproculture analysis. This isolate was characterised against representative products from the benzimidazole/imidazothiazole/macrocyclic lactone combination, benzimidazole/imidazothiazole combination, macrocyclic lactone (ivermectin and moxidectin) and salicylanilide (closantel) groups of anthelmintics. This was a blocked, randomised, double-controlled, open study with artificial infection using 3rd stage larvae of *Haemonchus contortus* resistant to benzimidazoles, levamisole and macrocyclic lactones and salicylanilides on Day -28. Faecal egg counts on Day 12 and worm counts on necropsy on Day 13 and 14 were performed and geometric and arithmetic means were calculated. Twelve Merino (10 months of age) and six Suffolk (6 months of age) wether lambs were randomly allocated to six groups balanced for breed and weight. No adverse reactions were observed. The results of this study demonstrated that this isolate shows a high degree of resistance (≤ 70% efficacy) to salicylanilide (represented by closantel) and other groups of anthelmintics. All anthelmintic groups demonstrated significantly less than 90% efficacy, as required by VICH GL 13, against the characterised isolate and thus the isolate may be regarded as resistant to tested anthelmintics.

As the efficacy of monepantel had only been tested against strains of *Haemonchus contortus* resistant to salicylanilides, the Committee considered that the claim should limited to "*Haemonchus* spp strains resistant to salicylanilides".

3. Benefit-risk assessment

3.1. Benefit assessment

Nematodes are a major cause of serious disease and impairment of productivity in sheep. *H. contortus* is responsible for a great number of severe diseases in ewes and lambs due to deficient nutrition and its haematophagous nature. Due to the number of increased reported incidences of resistance to antiparasitics the existence of therapies to treat resistant infections is beneficial.

3.2. Risk assessment

It is considered that there is no additional risk linked to extending the indications to parasitic *H. contortus* strains resistant to salicylanilides.

3.3. Evaluation of the benefit-risk balance

Overall the benefit-risk balance for this variation is considered to be favourable.

4. Conclusion

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

No change to the impact on the environment is envisaged.

5. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

- Annexes I and IIIB