24 January 2011
EMA/822733/2010

EPAR Scientific Discussion post-authorisation update for ZOLVIX

International Non-proprietary Name: Monepantel

EU/2/09/101/001 - 010

Scope of the variation:

Change to therapeutic indication to include the inhibited larvae of the following parasites: *Haemonchus contortus, Teladorsagia circumcincta, Teladorsagia trifurcata, Teladorsagia davtiani, Trichostrongylus axei* and change to section 4.8 of the SPC and section 12 of the package leaflet regarding interaction with other medicinal products and special warnings.

Details of the amendments made by means of this variation are shown below:

Previous product information details	Amended product information details
Spectrum of activity includes fourth larvae and adults of: *Haemonchus contortus* *Teladorsagia circumcincta* *Teladorsagia trifurcata* *Teladorsagia davtiani* *Trichostrongylus axei* *Trichostrongylus colubriformis* *Trichostrongylus vitrinus* *Cooperia curticei* *Cooperia oncophora* *Nematodirus battus* *Nematodirus filicollis* *Nematodirus spathiger* *Chabertia ovina* *Oesophagostomum venulosum* **4.8 Interaction with other medicinal products and other forms of interaction** No data available. **12. SPECIAL WARNINGS** No data are available regarding interaction with other medicinal products and other forms of interaction	Spectrum of activity includes fourth larvae and adults of: *Haemonchus contortus** *Teladorsagia circumcincta** *Teladorsagia trifurcata** *Teladorsagia davtiani** *Trichostrongylus axei** *Trichostrongylus colubriformis* *Trichostrongylus vitrinus* *Cooperia curticei* *Cooperia oncophora* *Nematodirus battus* *Nematodirus filicollis* *Nematodirus spathiger* *Chabertia ovina* *Oesophagostomum venulosum* * including inhibited larvae **4.8 Interaction with other medicinal products and other forms of interaction** None known. **12. SPECIAL WARNINGS** No interaction with other medicinal products and other forms of interaction are known.

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1. Scientific discussion

Extension of the indication to the inhibited larvae of various parasites

Nematodes are a major cause of serious disease and impairment of productivity in sheep. Some nematodes may interrupt development at the stage of early fourth larvae and resume further development and egg laying when the conditions outside the animals are more favourable to the non-parasitic stages. Ideally, anthelmintics should control these inhibited larvae. A number of studies were conducted to examine the effectiveness of ZOLVIX, 25mg/ml oral solution for sheep against inhibited larvae of the following parasites: *Haemonchus contortus, Teladorsagia circumcincta, Teladorsagia trifurcata, Teladorsagia davtiani, Trichostrongylus axei*.

The studies performed followed VICH and World Association for the Advancement of Veterinary Parasitology (WAAVP) guidelines. The expert report provided documented that the commonly used key to identify inhibited nematode larvae in sheep does not differentiate between different *Teladorsagia* species. The studies provided confirmed the presence of *Teladorsagia circumcincta* and *Teladorsagia trifurcata* and it may be extrapolated that monepantel is efficacious against inhibited larvae of all *Teladorsagia* spp. (i.e. *Teladorsagia circumcincta*, *Teladorsagia trifurcata* and *Teladorsagia davtiani*).

Based on the data provided the CVMP concluded that the marketing authorisation holder had demonstrated the efficacy of monepantel against inhibited larvae of *Haemonchus contortus*, *Teladorsagia spp*. and *Trichostrongylus axei*.

Interaction with other medicinal products and other forms of interaction

On this point the marketing authorisation holder applied to change the wording in section 4.8 of the SPC from "No data available" to "None known". To support this numerous reports were examined where ZOLVIX 25 mg/ml oral solution for sheep had been administered together with another medicinal product or vaccine.

Concomitant administration of ZOLVIX and other medicinal products has been examined in the time frame between one week before the first ZOLVIX dose and two weeks after the last dose. This time period has been chosen based on the half life of monepantel sulfone (five days). Thus three half-lives will cover almost two weeks.

In a small number of cases adverse events were observed after concomitant treatment of monepantel and tolfenamic acid, monepantel and penicillin and monepantel and penicillin, ceftiofur, vitamins ADE+B, bicarbonate and calcium borogluconate. In none of these cases could the adverse events be related to the medicinal products administered.

Based on the other reports no interaction has been observed between ZOLVIX treatment and the concomitant administration of dicyclanil, vaccines, oxytetracycline, flugestone acetate, Pregnant Mare Serum Gonadotropin, zinc sulfate, spinosad, penicillin, trace element and vitamin supplements, electrolytes, potentiated sulfonamide, ceftiofur, tolfenamic acid, mastalone, dexamethasone, danofloxacin and flunixin meglumine.

Whilst it was not clear why the time period for observing interactions included one week before administration of ZOLVIX, the number of cases during this week included a very small number of administered spinosad, penicillin and vaccines and do not detract from the general results that monepantel is tolerated together with other commonly used products in sheep. It is agreed that interactions of monepantel with other drugs are not known at present. Overall, with respect to the safety aspect of ZOLVIX on interactions, the proposed change to the SPC is supported and interactions with routinely used veterinary medicinal products are unlikely to occur.

2. Benefit-risk assessment

2.1. Benefit assessment

Nematodes are a major cause of serious disease and impairment of productivity in sheep. Some nematodes may interrupt development at the stage of early fourth larvae and resume further development and egg laying when the conditions outside the animals are more favourable to the non-parasitic stages. Ideally an anthelmintic should control these inhibited larvae. Such efficacy is substantiated for ZOLVIX (2.5 mg/kg) for the species *Haemonchus contortus*, *Teladorsagia* spp. and *Trichostrongylus axei* based on the data provided in this application and represents an important therapeutic benefit for the treatment of nematode infections in sheep.

2.2. Risk assessment

It is considered that there is no additional risk linked to the extended indication or by changing the wording in SPC section 4.8 "Interaction with other medicinal products and other forms of interaction" from "No data available" to "None known", with the consequential change in wording in section 12 of the package leaflet "SPECIAL WARNINGS… No interaction with other medicinal products and other forms of interaction are known."

2.3. Evaluation of the benefit risk balance

Efficacy against all stages of parasites is substantiated. Frequency of use of the product is not expected to be higher and consequently there is no reason to expect a higher impact on the environment. Overall the benefit/risk balance for this variation is considered to be favourable.

3. Conclusion

The CVMP considered 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.