# Divergent position on a CVMP opinion on an Article 34 referral for

## Milaxyn plus, Strantel Plus, Prazical Plus, Voxical Plus, Exitel Plus, Cazitel Plus, Prazitel Plus and associated names (EMEA/V/A/076)

Praziquantel: How it works

Praziquantel exerts its activity on parasites through depolarization of calcium channels. This leads to depolarised membranes on the parasite's tegument, creating vacuoles and ultimately the death of the parasite. Praziquantel is contained in Milaxyn Plus Tablets for Dogs (and the identical alternatively named products by Chanelle)[1]. Praziquantel is liberated from dissolved tablets in the gastrointestinal (GI) tract where it will be absorbed. Once absorbed, it is subject to a marked first passage effect in the liver where it is rapidly and extensively metabolized into inactive forms[2]. It follows that, though some portion of praziquantel is capable of re-circulating to the vasculature of the GI tract to be re-excreted there, praziquantel must primarily be active on intestinal parasites through direct *local* exposure before it is absorbed.

Systemic availability of praziquantel does not provide a solid "bridge" for the efficacy of Milaxyn Plus

Chanelle has studied equivalence based on praziquantel plasma concentrations of Milaxyn Plus and the reference product for the parameter $AUC_{inf}$ in support of a claim for efficacy against echinococcus infection. This bridging approach does not provide any direct information on praziquantel's behavior inside the entire GI tract resulting from the new formulation of Milaxyn Plus even though absorption of equivalent amounts of praziquantel into plasma was demonstrated. A formulation effect of Milaxyn Plus on praziquantel's activity in the GI tract can not be ruled out with sufficient confidence. Such bridging is not the appropriate tool for assessing the efficacy of a locally active substance.

The serious risk to public health of echinococcus infection

Echinococcus is a cestodal parasite, infecting dogs and other carnivores that possibly spread the parasite to humans. Human echinococcus cases are present throughout the European Union, and these cases can be fatal. With regards to the echinococcus claims, there exist:

- Specific European legislation[3] to prevent introduction of *E. multilocularis* into those countries which are still free of this parasite. This legislation underlines the particular nature of this parasite as a public health threat. Article 7 of this regulation states that the treatment to be applied to animals before the movement shall have been granted a marketing authorisation in accordance with the veterinary pharmaceutical legislation.

[1] Exitel Plus Tablets, Cazitel Plus Tablets, Prazitel Plus Tablets, Strantel Plus Tablet for Dogs, and Voxical Plus Tablets for Dogs

[2] Summary report EMEA/MRL/058rev 1/96

[3] Commission delegated regulation (EU) No 1152/2011 of 14 July 2011 supplementing Regulation (EC) No 998/2003 of the European Parliament and of the Council

- International technical guidelines[4] which were elaborated to achieve a consistent level of efficacy requirements with regards to anthelmintics, including cestodes. These guidelines quote *E. granulosus* as an example of a parasite for which higher efficacy requirements (*i.e.* up to 100%) may be imposed. These guidelines, in my opinion, apply specifically to the efficacy to be demonstrated for praziquantel.

In the specific case of the echinococcus claims (*Echinococcus granulosus* and *Echinococcus multilocularis)* a pre-specified difference of up to plus or minus 20% in pharmacokinetic (PK) parameters is not considered to be adequate. Because demonstrated equivalence in terms of plasma concentrations, in this case, is considered to provide only an indirect body of evidence, confirmatory data where experimentally infected animals are successfully treated with the final formulation of Milaxyn Plus and all alternatively named products are necessary. In the absence of such data, all reference to echinococcus treatment should be deleted from the SPC and product literature.

Availability

There are a number of products on the market that currently have the claim based on confirmatory data. Therefore, lack of this claim for this product does not pose a risk to public health regarding the need for treating this disease.

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[4] VICH guidelines 7 and 19.