Divergent position on a CVMP opinion on an Article 33.4 referral for

Prontax 10 mg/ml solution for injection for sheep, cattle and pigs (EMEA/V/A/073)

The residue data package for cattle provided by the applicant includes information from seven studies. Of these, five studies investigated depletion of residues following administration of the product at the recommended treatment dose by the proposed route of administration (subcutaneous). From these studies, it is clear that the critical tissue for the determination of the withdrawal period in cattle is injection site.

Of the five studies where the product was administered by the subcutaneous route, four investigated the depletion of residues from the injection site. The findings of these studies in respect of injection site residues can be summarised as follows:

- **Studies 1535N-60-89-009 / 1535N-60-89-010:** This study was conducted in accordance with GLP. Injection site residues were variable at the first two time points (21 and 28 days), but all were below the MRL of 40 μg/kg at 35 days post-dose. A 500 g sample of injection site tissue was taken at sacrifice. Concentrations in the non-injection site tissues are all below the respective MRLs at 21 days.
- **Study 1531N-60-90-049 :** This study was conducted in accordance with GLP. The target tissue, which had the slowest rate of residue depletion (for non-injection site tissues) was fat. The non-injection site tissue concentrations deplete to < MRL in respective tissues by 28 days. At the final slaughter time point of 35 days, residues at the injection site are above the muscle MRL. The results confirm that the withdrawal period is determined by depletion of injection site residues.
- **Study 2539A-14-92-190:** This is a non GLP study. However, the final formulation was used and the product was administered by the authorised route of administration. Residues at the injection site exceeded the muscle MRL in two of six samples at both 42 and 49 days post-treatment. Given its non-GLP status and the fact that there are concerns about the data quality in the study (reported in summary form, no information on sample size and injection sites were not assayed at both the first (35 day) and last (56 day) time points), it is not possible to set a meat withdrawal period for cattle based on the findings of this study.
- **Study no. 5531N-50-02-240: Pivotal residue depletion study:** This study was conducted in accordance with GLP. In this study, only injection site samples were harvested/analysed. This is considered justified given that the findings of previous studies confirm that the rate-limiting tissue for the determination of the withdrawal period following subcutaneous administration to cattle is injection site. This was a comprehensive study conducted with 5 groups of cattle, representing 10 withdrawal time points with data from 6 animals at each time point. The study was designed to encompass a withdrawal period of up to 70 days. The study design is above the minimum recommended number of animals or time points per current guidelines. It is acknowledged that the study did not include an analysis of the surrounding injection site tissue; however, this requirement was not in force at the time the study was conducted.

From the data set available, Study 5531N-50-02-240 is the pivotal study for the determination of the cattle withdrawal period. None of the studies with the exception of the pivotal residue study 5531N-50-02-240 collected data after 49 days post-treatment. The data from Study 5531N-50-02-240 were

analyzed according to the CVMP guideline “Note for Guidance: Approach towards harmonization of withdrawal periods,” (EMEA/CVMP/036/95-FINAL) and a withdrawal time was calculated based on the depletion of doramectin residues to below the muscle MRL (40 μg/kg) with 95:95 certainty. A withdrawal time of 54 days was calculated.

While it is acknowledged that Study 5531N-50-02-240 was not in full compliance with current guidance (absence of a ‘ring’ sample), it was otherwise well conducted. In this study, the absence of doramectin residues at concentrations above the current muscle MRL was confirmed at three time points (Day 56, Day 63 and Day 70) after the proposed withdrawal period of 54 days. In view of these data, the application of a 30% safety span is considered overly conservative and unnecessary. A withdrawal period less than the 70 days proposed by CVMP can be justified based on available data.

London, 8 February 2012

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