Divergent position on a CVMP opinion on an Article 35 of Directive 2001/82/EC

For veterinary medicinal products containing tylosin base (as a single active substance) presented as solutions for injection for intramuscular use in pigs

Procedure no: EMEA/V/A/131

This referral procedure includes 132 veterinary medicinal products containing tylosin base (as a single active substance) presented as solutions for injection for intramuscular use in pigs. The procedure was started with the aim to reassess the varying withdrawal periods and the necessity for a limit of injection volumes.

Based on the available data, the CVMP concluded that a withdrawal period of 16 days would be sufficient for all products containing up to 200 mg/ml with a limitation of the injection volume to 5 ml. For one product containing 250 mg/ml the withdrawal period was set at 18 days and the maximum volume of injection was limited to 4 ml.

We, the undersigned, have a divergent position to the outcome of the Article 35 referral for veterinary medicinal products containing tylosin base (as a single active substance) presented as solutions for injection for intramuscular use in pigs.

We, the undersigned, have a divergent position to the outcome of this referral procedure for the following reasons:

Tylosin is a macrolide which belongs to a group of antibiotics categorised as critically important. A very large group of 134 products is concerned by this referral procedure. Both aspects indicate that considerable responsibility and care concerning consumer safety is associated with this procedure.

The data basis available for the assessment is sparse. In total seven residue depletion studies were available, from which five were considered as insufficient with regard to analytical methods and/or to animal weights, resulting in low volumes of injection. In contrast to CVMP, two studies were taken into account for the assessment by this CVMP member (Study 2 and Study 7).

Study 2 was mostly conducted in accordance with current standards and leads to a withdrawal period of 16 days with a limitation of the injection volume to 5 ml/per site (for a posology of 20 mg/kg/every 24h for 5 days). CVMP considered that the slightly more acidic pH of the test product compared to the specification of the authorised product does not have an impact on residue depletion from injection sites. However, no data substantiating this assumption were available. According to VICH GL 48 the test article used for the study should be representative of the commercial formulation, which was not the case in this study. Furthermore, some of the core injection sites samples from treated pigs were below the weights recommended by the CVMP guideline of 500 ± 20% (EMEA/CVMP/542/03), and ranged between 366-400 g (core sample), and 215-288 g (surrounding injection site sample) and might, therefore, not represent the relevant residue.

Study 7 (JECFA 1991a)[1] is available as summary only. 28 days after treatment is the first time where all residues were below the MRL at the injection site. This study has some methodological limitations, from which the following are considered relevant: Tissue samples were analysed using a microbiological method, which is not specific to the marker residue tylosin A. No validation data for the analytical method were available and the LOD (100 µg/kg) is equal to the MRL of tylosin. The number of animals per time point was three, which is not in accordance with VICH GL 48 (n=4). The dosage used (8.8 mg/kg bw) was slightly below the recommended dosage (10 mg/kg bw). Furthermore, weights of injection site samples were 100-110 g only.

This CVMP member takes the position that, despite the shortcomings mentioned above, the results of Study 7 should not be entirely disregarded for the following reasons: Although residue concentrations may be somewhat overestimated by the microbiological method, concentrations show clear residue depletion over time. At Day 14 residue concentrations far above the MRL in injection site tissue were measured (up to 16x MRL), indicating that a withdrawal period of 16 days may not be suitable to ensure consumer safety. Even when a certain overestimation of the marker tylosin A is taken into account, residue concentrations may not deplete to below the MRL at day 16 with the necessary certainty. As the LOD of the method is identical to the MRL and the dosage used was somewhat lower than the recommended dose, residue concentrations in injection sites >MRL might occur at much later time points. Hence, the withdrawal period for the products concerned should not be shorter than 28 days, which is, as stated above, the first time point where all residues are below the MRL according to the result from study 7.Moreover, the data for the microbiological measurement also clearly show that the ADI (360 µg/person) which refers to the sum of microbiologically active tylosin components is clearly exceeded at Day 14 (from injection site residues alone!), indicating that there is a reasonable probability for a relevant consumer risk at day 16 (the proposed withdrawal period). In contrast, at 28 days, it is very unlikely that the total residue intake would be above this ADI, and therefore, this withdrawal period can be considered to be safe for consumers. Furthermore, sufficient evidence should be available for a significant reduction of established withdrawal periods. This was clearly not the case here and would also indicate that a withdrawal period of 28 days is much more suitable than the currently proposed shorter withdrawal period of 16 days.

Taking together the evidence provided in the available studies, this CVMP member considers a longer withdrawal period of 28 days necessary to ensure consumer safety.

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Gesine Hahn

Miguel Escribano

Leona Nepejchalová

Niels Kyvsgaard

[1] JECFA (1991). Tylosin. In: Residues of Some Veterinary Drugs in Animals and Foods. FAO Food and Nutrition Paper 41/4, Monographs prepared by the thirty-eight meeting of the Joint FAO/WHO Expert Committee on Food Additives, Rome 22-31 January 1991, FAO, Rome 1991, 109-127.