European Medicines Agency
Veterinary Medicines and Inspections

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COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

OPINION FOLLOWING AN ARTICLE 33 (4) REFERRAL

FOR DOXYPREX 100mg PREMIX

BACKGROUND INFORMATION

Doxyprex 100 mg premix presented in 5 kg, 20 kg and 25 kg bags containing 100 mg/g doxycycline base as hyclate. The product is authorised with the indication the treatment of swine respiratory disease caused by *Pasteurella multocida, Bordetella bronchiseptica* and *Mycoplasma hyopneumoniae.*

In December 2005, a Mutual Recognition Procedure (MRP) started with Spain acting as Reference Member State and ten Concerned Member States.

Germany could not agree to the granting a marketing authorisation and the matter was referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures, CMD(v), and subsequently to the Committee for Medicinal Products for Veterinary Use (CVMP).

Germany considered that the product could represent a potential serious risk to animal health on the grounds that the efficacy had not been sufficiently substantiated.

The CVMP during its meeting of 21-22 June 2006 started a referral procedure under Article 33(4) of Directive 2001/82/EC, as amended, for Doxyprex 100 mg premix. The Marketing Authorisation Holder (MAH) was requested to substantiate the efficacy of the product.

The applicant provided a justification for submission of this application on a "well-established use" basis. Within the EU doxycycline-based premix products for pigs at recommended dose rates of 10mg/kg once daily for 5 days are stated as having been authorised since 1985. Similar products with 8 or 10 days treatment durations are also available within the EU. Annex I of Directive 2001/82/EC as amended by directive 2004/28/EC notes that post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue. Therefore, the CVMP considered that the reports mentioned above give favourable evidence for the safety and efficacy of doxycycline in general, but also for the specific final formulation as marketed in Spain.

The applicant submitted a scientific report on Porcine Respiratory Disease Complex (PRDC). In the pivotal clinical trial, the presence of *P. multocida* and *B. bronchiseptica* was clearly demonstrated in sick pigs, however, no post treatment sampling was done to show bacteriological cure. The applicant justifies that the presence of *M. hyopneumoniae* was not determined by bacteriological methods because it was difficult to isolate at that time. The presence was assumed. The applicant provided evidence of efficacy of the active substance, doxycycline, against *M. hyopneumoniae* in pigs from published literature and from MIC studies. These are all references provided with the original submission. However, the CVMP considered that the fact that no post treatment bacteriological samples were taken mean that bacteriological cure cannot be assumed or claimed.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 47
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

The CVMP recommended the granting of the marketing authorisation to Doxyprex 100 mg/g Premix for medicated feeding stuff for pigs for the following indication because a positive benefit/risk analysis has been demonstrated and no potential serious risk has been identified.

"For the treatment and prevention of porcine respiratory disease, caused by *Pasteurella multocida* and *Bordetella bronchiseptica*, susceptible to doxycycline, when the disease has been diagnosed in the herd."

A benefit-risk analysis could not be conducted due to the lack of pivotal evidence on clinical efficacy for the indication *M. hyopneumoniae*. Therefore, the recommendation is to remove this pathogen from the indications.

The CVMP Opinion was adopted on 14 February 2007 and the subsequent Commission Decision on 22 May 2007.
