The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

DOXYCYCLINE

SUMMARY REPORT (2)

1. Doxycycline is a semisynthetic tetracycline derivative. As hyclate salt, doxycycline is presented as an injectable solution (intramuscular, intravenous), water soluble or lactodispersable powders, and (for dogs and cats) tablets and capsules. Doxycycline hyclate is indicated in cattle, pigs, poultry, turkeys, dogs and cats for the treatment of infections due to bacteria sensitive to doxycycline at doses of 10-20 mg/kg bw/day, for 3-5 days. Doxycycline is not for use in lactating cattle and layers.

2. Pending the provision of fully validated routine analytical methods, doxycycline is currently entered into Annex III of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Doxycycline	Sum of parent drug and its 4-epimer	Porcine, poultry	600 µg/kg 300 µg/kg 100 µg/kg	Kidney Liver, skin/fat Muscle	Provisional MRLs expire on 1.1.1998
		Bovine	600 µg/kg 300 µg/kg 100 µg/kg	Kidney Liver Muscle	

3. Doxycycline belongs to the group of tetracycline antibiotics. All tetracyclines have a broad spectrum of activity which includes Gram-positive and Gram-negative bacteria, chlamydias, rickettsias, mycoplasmas and spirochaetes. Doxycycline tends to be more active against some of these species than other tetracyclines. It is primarily a bacteriostatic antibiotic and has its main mechanism of action on inhibition of protein synthesis. The potency of doxycycline is not less than 880 IU/mg.

4. Data have been provided on the antimicrobial activity of doxycycline on the human intestinal flora in comparison with the activity of oxytetracycline, on the residue distribution of doxycycline in pigs and poultry after oral administration, and on routine analytical methods for the determination of doxycycline residues in tissues of cattle, pigs and poultry. Data on the toxicology and pharmacology of doxycycline, and on residue depletion in other target animals than pigs and poultry have been extracted from dossiers for national marketing authorisations and from handbooks.

5. After oral administration, doxycycline is rapidly and well absorbed from the gastrointestinal tract. Doxycycline has a longer half-life (15-22 hours) and is more lipid-soluble than other tetracyclines. Following absorption through various routes of administration, doxycycline is widely distributed in the body with highest levels in kidney and liver, and in bone and dentine. Doxycycline may be metabolised for up to 40% and is largely excreted in faeces (via bile and intestinal secretion), mostly in a microbiologically inactive form.

6. Doxycycline is of low acute oral toxicity. From several repeated dose and chronic toxicity studies with rats, hamsters, mini-pigs, dogs and monkeys, it appears that sensitivity for the hepatoxic effects of doxycycline is idiosyncratic in dogs (NOEL 25 mg/kg bw in a 1-month study, although the hepatic changes did not progress upon continuation of the drug for 1 year, and the changes were reversible after drug withdrawal). There is no evidence of reproductive or developmental toxicity and there is no evidence of a genotoxic potential. It can be concluded that the toxicological profile of doxycycline is roughly comparable to that of oxytetracycline, chlortetracycline and tetracycline.

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7. The microbiological activity of doxycycline compared to that of oxytetracycline was determined in *in vitro* MIC-studies with human enteric isolates. From these data it can be concluded that the tested human enteric microorganisms have a comparable or slightly higher susceptibility for doxycycline than for oxytetracycline. These antimicrobial data provide the most appropriate endpoint for the safety evaluation of doxycycline. In view of the similarity in antimicrobial activity against human enteric microorganisms, the microbiological ADI of 3 µg/kg bw for oxytetracycline (and chlortetracycline and tetracycline) can be adopted for doxycycline.

8. From residue data with pigs, poultry and cattle after oral administration, and with cattle after intravenous administration, it can be concluded that the residue distribution of doxycycline in these food-producing animals is roughly comparable to that of oxytetracycline. Highest residues are found in kidney, followed by liver, skin and muscle. Given the polarity of doxycycline, it is not detectable in fat to any great extent.

9. In contrast to tetracycline, oxytetracycline and chlortetracycline, no epimerization of doxycycline to its 4-epimer occurs during sample treatment and assay. Therefore, the marker residue is the parent drug only.

10. For the determination of doxycycline in tissues of cattle, pig and poultry, fully validated HPLC-methods are available that are described in accordance with ISO 78/2. The limits of quantification range from 25 to 50 µg/kg.

Conclusions and recommendation:

Having considered that:

- a microbiological ADI has been set at 0.003 mg/kg bw,
- doxycycline is not epimerized to its 4-epimer,
- there are fully validated analytical methods available for the determination of doycycline in poultry, bovine and porcine tissues;

the Committee recommends the inclusion of doxycycline in Annex I of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Doxycycline	Doxycycline	Bovine	100 µg/kg 300 µg/kg 600 µg/kg	Muscle Liver Kidney	Not for use in animals from which milk is produced for human consumption
		Porcine	100 µg/kg 300 µg/kg 300 µg/kg 600 µg/kg	Muscle Skin + fat Liver Kidney	
		Poultry	100 µg/kg 300 µg/kg 300 µg/kg 600 µg/kg	Muscle Skin + fat Liver Kidney	Not for use in animals from which eggs are produced for human consumption

These MRLs will lead to a theoretical maximum daily intake of 105 µg, i.e. approximately 58% of the ADI.