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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

CARAZOLOL

SUMMARY REPORT (1)

1. Carazolol is a non-specific beta-adrenergic receptor blocking agent, which is used in pigs by intramuscular injection to prevent 'mors subita' during transport.

2. After oral ingestion carazolol is rapidly absorbed. Systematically available carazolol is eliminated as parent drug or as side-chain cleaved metabolites in urine and faeces with a half-life of about 20 hours. Repeated oral administration of carazolol exerts hepatotoxicity in dogs, apparent by changes in blood biochemistry and histopathology. The NOEL is 6 mg/kg bw.

   Carazolol does not exert any teratogenic effect or impairment of reproductive function. In the 'Ames' test with Salm. typhimurium and in various in vivo cytogenicity tests no evidence for genotoxicity of carazolol is found. In long term studies no carcinogenic potency is observed.

3. The beta-blocking activity of carazolol is established in specific function tests carried out in various species (mice, rats, rabbits, dogs and pigs). The NOEL based upon inhibition or an isoprenaline-induced tachycardia after a single oral administration is 20 µg/kg bw.

4. Based on the starting point that the pharmacological effect of carazolol is most relevant for the toxicological evaluation with respect to the safety of the consumer, it was not possible to extrapolate a dose without effects in human. Therefore a temporary ADI is established on the pharmacological no-effect level of 20 µg/kg bw as found in rabbits. Although this NOEL is found after a single oral administration, the sensitivity of the test model justifies the application of a safety factor of 200. Consequently a temporary ADI of 0.1 µg/kg bw has been established.

5. For the available residue data in pigs it is apparent that liver and kidneys contain the highest residues, with much lower values in fat and muscle. The Committee for Veterinary Medicinal Products recommends the following provisional MRLs for carazolol :

   liver (as target tissue), kidney 30 µg/kg and
   muscle and fat 5 µg/kg

6. High performance liquid chromatography methods to detect residues of carazolol in edible tissues are available with a limit of determination by fluorescence detection of 0.3 µg/kg.

7. The Committee noted that although residues of carazolol in most tissues deplete rapidly to values below the MRLs, residues at the injection site are at a much higher level (ppm). Therefore, unless appropriate measures can be taken in order to ensure that the injection site is not offered for human consumption, a withdrawal period for carazolol preparations must be established, which would exclude the use of these preparations during the transport of animals to the slaughterhouse.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel: (+44-171) 418 84 00 Fax: (+44-171) 418 84 16