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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

AZAPERONE

SUMMARY REPORT (1)

1. Azaperone is a sedative agent mainly used in pigs after intramuscular administration.

2. Azaperone is rapidly absorbed and completely excreted in urine and faeces with only a small portion present as parent compound. The major metabolite present in edible tissue is azaperol.

   The acute oral toxicity (LD_{50}) is relatively low. In subacute oral toxicity studies in rats and dogs and in a 3-generation study with rats the lowest effect dose was 1.25 mg/kg bw. No NOEL can be established. No data on subchronic or chronic toxicity are available.

   In teratogenicity studies in mice and hamsters malformations are observed at dose levels associated with maternal toxicity. In rats and rabbits no malformations are observed.

   With respect to mutagenicity no data are available with the exception of a dominant lethal test in mice showing no effect of azaperone.

3. Based on the norepinephrine antagonistic activity of azaperone, a pharmacological NOEL of 0.08 mg/kg has been established following single subcutaneous administration of azaperone to rats.

4. Based on the starting point that the pharmacological effect is most relevant for the toxicological evaluation with respect to the safety for the consumer, an ADI is established on the pharmacological NOEL. From a comparison between oral and subcutaneous administration it is shown that both routes are equally effective. Therefore the NOEL of 0.08 mg/kg bw after a single subcutaneous administration has been used to establish an ADI for the oral route. Although this NOEL is found after a single subcutaneous administration, the sensitivity of the test model justifies the application of a safety factor of 100. Consequently an ADI of 0.8 µg/kg bw for azaperone has been established.

5. Residue studies in pigs show that highest residues are found in the kidney and lower residues in other tissues. With the exception of fat the major portion of the residue in edible tissue consists of the metabolite azaperol. Therefore, azaperol can be used as the marker residue to control the use of azaperone. Although some evidence exists that azaperol is pharmacologically less effective than azaperone, for an adequate safety evaluation for the consumer, residues of azaperol are considered to be as harmful as those of azaperone. The Committee for Veterinary Medicinal Products recommends the following MRLs for the marker residue azaperol :

   kidney (as target tissue) 100 µg/kg, and
   muscle (and other tissues) 50 µg/kg.

6. High performance liquid chromatography methods to detect residues of azaperone or azaperol in edible tissues are available with a limit of determination of 1 µg/kg for azaperone by UV detection and 2 µg/kg for azaperol by fluorescence detection.

   The Committee noted that although residues of azaperone in most tissues deplete rapidly to values below the MRLs, residues at the injection site are at a much high (ppm) level. 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 azaperone preparations must be established, which would exclude the use of these preparations during the transport of animals to the slaughterhouse.

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