COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

MOXIDECTIN

SUMMARY REPORT (1)

SAFETY FILE

1. Moxidectin, proposed for use in the treatment and control of endo- and ecto-parasites in cattle and sheep, is produced by a chemical modification of nemadectin, a natural fermentation product produced by the microorganism Streptomyces cyaneogriseus subsp. noncyanogenus. It is a semisynthetic, macrocyclic lactone, structurally similar to abamectin, ivermectin and milbemycin.

2. Administered orally, moxidectin is toxic to chickens, mice and rats (LD50 of 100-300 mg/kg). Toxicity by cutaneous administration in rabbit was low (LD50 > 2000 mg/kg).

3. Toxicity studies with repeated doses were conducted in mice (28 days), rats (28 days and 13 weeks), and dogs (28 days, 91 days and one year). Effects on the central and peripheral nervous system and decreases in bodyweight without histological lesions were reported in some cases. The NOEL was 0.3 mg/kg bw/day in the 91-day dog study.

4. Moxidectin injectable solution was well tolerated by cattle and sheep with only some transitory nervous symptoms at the three-fold therapeutic dose.

5. The multi-generation study in rats indicated a dose without effect at 5 ppm being 0.4 mg/kg (no effect on survival indices). Two teratogenicity studies were performed in rats (0, 2.5, 5, 10, 12 mg/kg bw) and in rabbits (0, 1, 5, 10 mg/kg bw). In rats, Moxidectin was maternotoxic at 10 and 12 mg/kg bw. Fetal alterations as cleft palate, micrognathia, not ossified or incomplete ossified sternebrae were reported for doses higher than 2.5 mg/kg bw. In rabbits, maternotoxicity was mentioned at 5 and 10 mg/kg bw but there was no influence on the fetal development.

   The no effect levels for maternotoxicity were 5 mg/kg bw in rats and 1 mg/kg bw in rabbits. The no effect levels for the embryotoxic effects were 2.5 mg/kg/day in the rat and more than 10 mg/kg in the rabbit.

6. In a set of mutagenicity tests (Ames, CHO/HGPRT/Test, Unscheduled DNA Synthesis in primary rat hepatocytes, In Vivo Chromosome Aberration Test in Rat Bone Marrow Celles), moxidectin did not show mutagenic activity.

7. The two carcinogenicity studies performed in rats (0, 15, 60, 100 ppm for 102 weeks) and mice (0, 15, 30, 50 ppm for 105 weeks) did not show potential carcinogenic properties of moxidectin.

8. The most appropriate end-point for setting an ADI was identified as the reduced pup survival, which was observed in the two-generation rat study at 0.8 mg/kg bw (NOEL = 0.4 mg/kg bw).

   A larger safety factor of 500 than usually used was applied in the calculation of the ADI, to compensate for the absence of data generated using the sensitive CF-1 strain of mice. This NOEL also provides an adequate margin of safety between the ADI and the effects seen in the repeat dose dog studies (NOEL = 0.3 mg/kg bw).

   Thus an ADI of 0-0.0008 mg/kg bw was established.

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RESIDUE FILE

1. The kinetic experiments using labelled moxidectin showed that the profile observed in the rat was similar, qualitatively, to that in the target species. Moxidectin did not penetrate the red blood cells. The metabolite profile of Moxidectin was identified by in vitro and in vivo studies. Moxidectin remained the main metabolite of the 7 metabolites identified, which appeared to be hydroxylation products.

   The main elimination route was via faeces.

   In cattle and sheep, moxidectin represents 40% of the total radioactivity in liver, 50% in muscle, 60-75% in kidney and 90% in fat.

2. In cattle, after subcutaneous administration, the fraction absorbed was 100 %. In sheep, after oral administration 23 % of the dose was bioavailable.

3. In the residue studies in cattle and sheep, only the residue marker Moxidectin was measured. The highest residue concentrations of moxidectin were found in fat and at the injection sites. After subcutaneous administration in cattle, it has been shown that about 98.5% of the moxidectin residues were located in the connective tissue and the sub-cutaneous fat and about 1.5% in the underlying muscles. It is considered that, as connective tissue and sub-cutaneous fat would be trimmed off, the injection site would thus create no special problem.

4. An analytical HPLC method with fluoresence detection technique is available to ensure the monitoring of moxidectin residues in the tissues of sheep and cattle : (10 ng/g as the limit of quantification).

5. Taking into account the residue depletion profile, the following provisional MRLs were elaborated :

Animal species	Marker residue	Target tissues	MRLs
Bovine	moxidectin	fat	200 µg/kg
		kidney	20 µg/kg
		liver	20 µg/kg
Ovine	moxidectin	fat	200 µg/kg
		kidney	20 µg/kg
		liver	20 µg/kg

Until data is available on the specificity of the analytical method with respect to doramectin, only provisional MRLs can be established. This data shall be provided before 1 July 1996. Provisional MRLs will be established with an expiry date of 1 July 1997