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

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

OESTRADIOL

SUMMARY REPORT

1. Oestradiol benzoate, oestradiol valerate and oestradiol hexahydrobenzoate are synthetic esters of the naturally occurring oestrogen oestradiol. After administration the esters are absorbed and subsequently hydrolysed to the active compound oestradiol. Oestradiol is the most active natural oestrogen, which can act at many different sites in both female and male animals. In cattle, the synthetic oestradiol esters are indicated for induction and synchronisation of oestrus and for hormonal therapy (placenta retention, anoestrus, metritis, pyometritis and foetus mummification).

2. In animals, oestradiol and its esters are readily absorbed following parenteral administration. In humans, oestradiol and its esters are quickly absorbed after oral administration. However, due to metabolic processes in the G.I.-tract, the intestinal wall and the liver (first pass effect), not only the ester is hydrolysed quite quickly, but also free oestradiol is subject to further metabolism for the greater part of the dose. Only about 3% of an oral dose becomes bioavailable as metabolically unchanged oestradiol-17ß. However, if oestrone is included, the bioavailability might be higher.

   After conversion to oestradiol, the esters are metabolised and excreted in the same way as the naturally occurring oestradiol. In ruminants, the main metabolites are oestradiol-17α and its conjugates and glycosidic derivatives, and excretion is mainly via bile and faeces (>75%). In humans, the main metabolites after oral administration are oestrone and oestradiol-17ß and their conjugates, while urinary excretion (78% dose) is more important than faecal excretion (3-15% dose).

3. Toxicological effects found after oestradiol administration comprise hyperplasia of the endometrium, behavioural changes and effects on metabolic processes. Oestradiol does not induce gene mutations *in vitro*, but conflicting results are found in chromosomal aberration assays. Following long term exposure the incidence of tumours in tissues with a high level of hormone receptors is increased (e.g. mammary tumours). It is concluded that the toxic effects including carcinogenicity occur as an extension of the physiological effects of oestradiol.

4. After administration of oestradiol-17β, oestradiol benzoate, oestradiol hexahydrobenzoate and oestradiol valerate to cattle levels in plasma (0.06-0.12 ng/ml) and milk (0.007-0.07 ng/ml) are within physiological limits. After administration of oestradiol hexahydrobenzoate to cattle levels in muscle, liver and kidney were above the physiological limits at day 1 after injection, but values returned to control values within 7 days. Tissue residue data for the other compounds were not provided.

5. After administration of oestradiol hexahydrobenzoate maximum concentrations of free oestradiol in the injection site were 26 and 20 ng/g at respectively 1 and 7 days after treatment. After a withdrawal time of 14 days the levels of free oestradiol in the injection sites were within the physiological limits for muscle tissue. Data about oestradiol levels in injection sites after treatment with oestradiol benzoate and oestradiol valerate were limited.

6. None of the provided RIA's for the determination of oestradiol in serum, tissues and milk have been validated.

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7. The conclusion of the FAO/WHO Expert Committee on Food Additives (JECFA) that no ADI and MRLs for oestradiol need to be established is adopted. Milk and plasma residue levels after treatment with oestradiol benzoate and oestradiol valerate have shown to be at or within physiological limits. Although it is likely that tissue residue levels will also be within physiological limits, this cannot be guaranteed, given the results with oestradiol hexahydrobenzoate. Still, compared to the lowest human daily production rate of oestradiol in prepubertal boys (6 µg/d) and compared to the amount of oestradiol in other food stuffs that are part of the human diet, the amount of exogenous oestradiol that humans will be exposed to through ingestion of tissue from treated animals is biologically insignificant, and will be incapable of exerting a hormonal effect in human beings.

8. Considering the above, it is proposed to place oestradiol in Annex II for therapeutical purposes in cattle and horses.