European Medicines Agency
Veterinary Medicines and Inspections

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NOTE REGARDING THE ESTABLISHMENT OF MAXIMUM RESIDUE LIMITS FOR PROGESTERONE

Applications for the establishment of maximum residue limits for progesterone were submitted to the European Commission in 1993 under Article 7 of Council Regulation (EEC) No 2377/90, as a so-called "old substance". The Committee for Veterinary Medicinal Products (CVMP) with the support of its Safety of Residues Working Party assessed the data in October 1994 and agreed a list of questions to be addressed by the applicant.

The response to the list of questions was submitted in September 1995 to the EMEA. The CVMP concluded the assessment of the data in October 1996 and considered that there was no need to establish maximum residue limits for progesterone, mainly taking into account the fact that progesterone is of endogenous origin, is a natural constituent of food of animal origin, has low oral bioavailability (less than 10%) and that milk and plasma levels after treatment were shown to be at or within physiological limits. Therefore, the CVMP recommended the inclusion of progesterone in Annex II of Council Regulation 2377/90, for bovine and *Equidae* species, restricted to therapeutic and zootechnical use.

In May 1999 the European Commission requested the CVMP to re-consider the assessment of sexual hormones in view of the opinion of the Commission's Scientific Committee on Veterinary Measures Relating to Public Health (SCVPH). The CVMP concluded the re-evaluation of the concerned hormones in December 1999 and for progesterone confirmed its previous recommendation of inclusion in Annex II of Council Regulation (EEC) No 2377/90.

In April 2002 the Commission requested the CVMP to inform on which physiological levels, in the relevant tissues, it had based its conclusions that the administration of progesterone as veterinary medicinal product would not result in a durable change of these levels and if those levels were deduced using a validated analytical method or not. The Committee provided to the Commission information on physiological plasma concentrations in several animal species and in humans, average physiological concentrations in cattle tissues, milk and milk products, as well as average concentrations after treatment.

Subsequently the Commission taking into account the fact that progestogen hormones are subject to restrictions of use and control measures provided for hormones established in Council Directive 92/22/EC as amended by Directive 2003/74/EC of the European Parliament and of the Council, adopted Commission Regulation (EC) No 1873/2003[1] including progesterone in Annex II of Council Regulation (EEC) No 2377/90, and restricting the terms of use of progesterone, for intravaginal use only, to female animals of bovine, ovine, caprine and *Equidae* species as a safeguard to the possibility of misuse of veterinary medicinal products containing progesterone, as follows:

Pharmacologically active substance	Animal species	Other provisions
Progesterone	Bovine, ovine, caprine, *Equidae* (female)	For intravaginal therapeutic and zootechnical use and in accordance with the provisions of Directive 96/22/EC

[1] OJ L 275, 25.10.2003, p.9 - http://pharmacos.eudra.org/F2/register/regpdf/2003_10_24-1873.pdf

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Article 12 of Council Regulation (EEC) No 2377/90 requires that, after amendments to the annexes of the Regulation, the summary of the assessment of the substances concerned that have been examined by the CVMP be published. The summary report on progesterone, now published on the EMEA web site, is the summary of the assessment carried out by the CVMP, which recommended inclusion of progesterone in Annex II of Council Regulation (EEC) No 2377/90 for bovine and equine species. For the reasons given above, the entry for progesterone in Annex II of Council Regulation (EC) No 2377/90 is not entirely consistent with the recommendation of the CVMP.

Progesterone summary report

CVMP Safety Report of Steroid Sex Hormones