

COMMERCIAL IN CONFIDENCE

MEDICINES ACT - VETERINARY PRODUCTS COMMITTEE

REVIEW OF VETERINARY MEDICINES CONTAINING HORMONES

1. The review of veterinary medicines containing hormones is shortly to be announced. At the September meetings of the Veterinary Products Committee and Scientific Secretariat, members made some amendments to VPC(88)139, which contained the proposed guidance notes to be sent to applicants for this review.
2. Officials have now amended the guidance notes in accordance with members comments and a final draft is attached to this paper for agreement and information.
3. It is the intention of the Licensing Authority to issue review call up letters and these guidance notes to licence holders in October/November 1988.

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MEDICINES UNIT
WEYBRIDGE
(AKG/GCE/JOB)
VLA 8575Distribution

To the Veterinary Products Committee - for agreement and information
To the Scientific Secretariat Committee - for information

GUIDANCE NOTES FOR THE REVIEW OF VETERINARY PRODUCTS CONTAINING HORMONES

- 1.1 Data should be presented in accordance with EC Directives 81/851 and 81/852 on Veterinary Medicinal Products: paragraph 11 and Parts II to VIII of the MAFF guidance document "Notes on Applications for Product Licences for Veterinary Medicinal Products" (MAL 10) which is available on request from the licensing authority at Tolworth Tower. The general guidance notes on the data requirements for residues which have been provided for every review so far are also attached. The following notes should also be taken into account.
- 1.2 Acceptable maximum residue limits for hormones have not yet been established, and applicants must propose withdrawal periods which should be determined from appropriate toxicology data:-
- a) Data will be required to show that there is a lack of carcinogenic hazard both to consumers of produce from treated animals and to users of the product. An adequate and comprehensive range of appropriate mutagenicity tests should be carried out and life span carcinogenicity studies may be required. In the absence of data, justification must be provided on why such data are not presented. Some natural steroid hormones are not genotoxic but may have tumourigenic effects and potential hazards must be addressed. Relevant literature may be utilised.
 - b) Metabolism data will be required and data on residues of metabolites in test and target species as appropriate. It should not be assumed that bound residues are metabolically inactive unless this has been proven.
 - c) Information will be required on bioavailability and pharmacokinetics in the target species.
 - d) A range of appropriate toxicology studies should be carried out to determine no effect levels including no hormonal effect levels in suitably sensitive species. Histology will need to be carried out on hormone sensitive target organs.
 - e) Validated assay methods of sufficient specificity and sensitivity must be used and the animal's endogenous hormone levels taken into account in terms of cross reactivity.
 - f) Residue depletion data will be required from use of the product as recommended in each target species and residue assays performed on a full range of edible tissues including milk where appropriate and skin where appropriate. A sufficiently large number of animals should be used in residue studies so that the withholding period can be reliably calculated.
 - g) Although residues in meat and milk may be very low following use of the product, the significance of these residues must be assessed. An

adequate safety margin must be applied between the residues without hormonal effect in suitably sensitive species and the levels of exposure of human beings to residues with hormonal effect from treated animals. The potential for absorption of the active ingredient or metabolites from the human digestive tract should be addressed.

- h) The calculation of withholding periods should be based on the achievement of a residue tolerance taking into account the ADI (Acceptable Daily Intake) calculated from appropriate studies and using appropriate safety factors. The safety factor to be used would depend on the information available on metabolism and toxicology. x100 might be appropriate for compounds with no significant toxic potential. x1000 or greater might be appropriate for compounds with greater toxic potential or where full information on metabolism is not available. When calculating a tissue residue tolerance applicants should in their calculations take account of average human bodyweight, as well as daily dietary intake of meat, offal and fat, and when calculating a milk residue tolerance, take account of daily dietary intake of milk.
- 1.3 It is known that the duration of action of hormones and the onset of action can vary considerably depending on formulation, structure and route of administration. Data on metabolism and biological half life must be provided.
- 1.4 Information should be provided on the effects of the product on the animal's endogenous hormone production.
- 1.5 Justification of the formulation, the proposed dose and route of administration must be provided.
- 1.6 Efficacy data from published sources on the active ingredient will generally be acceptable but an adequate review of it must be provided and it must be capable of providing clear evidence for supporting the proposed dose of the product in the target species. The relevance of literature or studies provided must be justified where these refer to a salt other than that included in the product. The salt form could affect the physical properties of the active ingredient (e.g. particle size, solubility etc) and thus the activity.
- For applications for products used in non-food producing animals extensive controlled efficacy trials as described in paragraph 1.7 may not be necessary if other data are adequate.
- 1.7 The range of indications proposed must be fully supported by the evidence provided. Efficacy data should be provided from use of the proposed product as recommended in each target species and statistical analyses carried out. Such efficacy data should be provided from a range of UK animal husbandry conditions and the nutritional status of animals recorded as this may also affect the results.

1.8 In relation to implant products:-

- a) In-vivo release data will be required in an adequate number of animals.
- b) Residue data will be required covering the full length of the claimed efficacy and to support the proposed withdrawal periods.
- c) Where appropriate, withdrawal periods must be stated from the removal of the implant.
- d) Data will be required from trial work on the efficiency of recovery of implants from treated animals.

1.9 Target species tolerance data from the use of the product at the maximum recommended dose in each indicated species must be provided and must address the full duration of treatment proposed.

1.10 Applicants should address operator safety and include safety warnings in product literature where appropriate e.g. use of impervious gloves, coveralls and thorough washing of skin.

1.11 Applicants should provide with each application a brief section containing the following information in the format of a suspect adverse reaction Type A report which is:-

- a) Product name
- b) Product licence number
- c) Period of report (preferably the last 5 years of marketing)
From: To:
- d) Number of doses sold in period specified at (c)
- e) Number of suspected adverse reactions recorded at (c) for each animal species
- f) Number of deaths at (e) for each animal species
- g) Brief general description of reactions recorded.

Where efficacy trials using the proposed product are provided applicants must comment on the occurrence of any adverse reactions, including injection site reactions.

1.12 For those constituents which are derived from natural sources full information will be required on the manufacture, purification, isolation and control of the substance. In particular, the country of origin of the material from which the substance is derived must be stated and a full account given of the measures followed to ensure that the substance is free from pathogenic contamination. It should also be noted that

substances derived from glandular extracts or serum intended for treatment of ruminants or pigs require authorisation under the Serum and Glandular Products Order, and account should be taken of any risk of contamination with B.S.E.

- 1.13 Product licences issued after the implementation of EC Directives 81/851/EEC and 81/852/EEC will not need to be reviewed fully. It will be necessary to ensure that the data supplied in support of the product meets current requirements. In particular it will be necessary to ensure that the data are sufficient to give assurances that the withdrawal periods are acceptable and the product literature is acceptable.

As there are no established maximum residue limits for hormones, companies holding such product licences will be requested under section 44(2) of the Medicines Act to provide the following information to the Medicine Unit:-

- 1) A summary of the data on which current withdrawal periods are based, with adequate reference to the full data at which the full results can be seen. In addition comment or argument is required to assure the Licensing Authority that the proposed withdrawal periods would be satisfactory, even though this information may have been previously provided at the time the original product licence application was considered.
- 2) Current product literature for the product.
- 3) A type A report as described at paragraph 1.11 above.

Following receipt of the above information, consideration will be given as to whether further data will be required.