Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

GESTAVET HCG 200 / PMSG 400

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0134/001/MR
Name, strength and pharmaceutical form	**GESTAVET 600** powder and solvent for solution for injection for swine. (AT, BE, FR, IT, LT, MT, NL, PT & UK) **SUIGEST 600** powder and solvent for solution for injection for swine. (EL) **GESTAVET HCG 200 / PMSG 400** powder and solvent for solution for injection for swine. (ES) **GESTAVET HCG 200 IU/ PMSG 400 IU** powder and solvent for solution for injection for swine. (DE)
Applicant	**LABORATORIOS HIPRA, S.A.** Avda. la Selva, 135 17170-AMER (Girona) Spain
Active substance(s)	Equine Serum Gonadotrophin (PMSG) Chorionic Gonadotrophin (HCG)
ATC Vet code	**QG03GA99** Gonadotropins, combinations **QG03GA01** Chorionic gonadotrophin-HCG **QG03GA03** Serum gonadotrophin-PMSG
Target species	Swine (sows)
Indication for use	**Sows:** Induction and synchronization of heat.

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 13.1 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 27/05/2009
Date product first authorised in the Reference Member State (MRP only)	16/01/2001
Concerned Member States for original procedure	AT, BE, DE, EL, FR, IT, LT, MT, NL, PT and UK

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 80 UI/ml of Equine Serum Gonadotrophin (PMSG) and 40 UI/ of Chorionic Gonadotrophin (HCG) and excipients potassium dihydrogen phosphate, disodium phosphate dodecahydrate, lactose and water for injection.

The product is presented in a Carton box containing 5 vials of powder + 5 vials of solvent (5 ml/vial).

The freeze-dryed product is filled in 10 ml colourless Type I glass vials, closed with Type I elastomeric stopper with anodised aluminium caps.

The solvent is filled in 10 ml colourless Type I glass (containing 5 ml of solvent), closed with Type I elastomeric stopper with anodised aluminium caps.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the presence/absence of preservative is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are equine serum gonadotrophin and chorionic gonadotrophin and they are described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The actives substances specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

The applicant justifies the quality of the raw materials by means of an Active Substance Master Files (GE/037/99 for PMSG and GC/556/00 for HCG in Spain).

Potassium dihydrogen phosphate, disodium phosphate dodecahydrate, lactose and water for injection comply with the monographs number 01/2008:0920, 01/2008: 0118, 01/2008: 0187 and 01/2008: 0169 of the European Pharmacopoeia, respectively.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control on intermediate products (pharmaceuticals)

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

For generics, insert in the relevant sections as appropriate:

As this is a generic application according to Article 13, results of toxicological, pharmacological and clinical tests are not required. The safety and residue aspects of this product are identical to the reference product.

GESTAVET HCG200/PMSG400 and the reference product PG 600 (Intervet, S.A.) contain

the same active substance (HCG and PMSG) in the same dosage form (powder and solvent for solution for injection) and concentration (PMSG400 IU/vial and HCG20 IU/vial). Both products are considered to be bioequivalent when they are equally bioavailable.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13, results of pharmacological tests are not required.

The PMSG stimulates the follicular development and the HCG unleashes the ovulation and the corpus luteum formation. Both hormones allow the restoration of a fertile sexual cycle in the sow.

Toxicological Studies

As this is a generic application according to Article 13, results of toxicological tests are not required.

Taking into account that different excipients may have significant effects on local tolerance, studies have been carried out on the target specie. No adverse side effects and no local reaction at the injection site, which could be attributed to treatment with the product, were observed during the study.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is safe when is used under the labelled conditions. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this is a generic application according to Article 13 and the identicalness of GESTAVET HCG200/PMSG400 and the reference product has been demonstrated in part IV of the dossier (Efficacy).

MRLs

HCG and PMSG are listed in Annex II of Council Regulation 2377/90 for all food producing species.

Withdrawal Periods

A withdrawal period of zero days for meat in swine is justified basing on the following data:

- HCG and PMSG are active substances included in the Annex II.
- Both substances are peptides inactive orally.
- HCG and PMSG are hormones that are used only in a single-dose treatments in animals where the possibility of being slaughtered immediately after drug administration in nearly zero, since these animals are involved in breeding programs.

Withdrawal period: Meat & offal: zero days.

IV. CLINICAL ASSESSMENT (EFFICACY)

For generics, insert in the relevant sections as appropriate:

This generic application is submitted under the Article 13.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC. It is a generic PMSG-HCG, in an extemporaneous form. Its reference product PG 600 from Intervet, have the same composition, dosage schedule and the same claims. The bioequivalence was carried out by means therapeutic equivalence studies, as pharmacokinetics parameters comparison is not possible. The applicant has not to submit toxicological nor pharmacological documentation.

The recommended dose is 5 ml of the test product in a single dose by IM route.

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology

A comprehensive literature review of the pharmacodynamics of serum gonadotrophin and chorionic gonadotrophin has been done. It is considered as support data as it is considered generic submission.

Tolerance in the Target Species of Animals

Local tolerance studies should be submitted as the final product is a parenteral solution and contains different excipients than the reference product. Local tolerance studies are nor carried out by SC route, authorized for the reference product, but the applicant do not claim this administration route for his product, they have been carried out by IM route.

The applicant has conducted a local controlled target animal tolerance study using the recommended dose in the target species. An authorised reference product containing the same active substance and an untreated control group were included. Recommended dose were administered by IM route in a single dose.

Parameters evaluated were: General aspect of injection site and CPK serum values assessed on D-1, D1 an D6 post-treatment .

No adverse effects nor local reaction were seen following recommended doses by IM route.

Resistance (if relevant – or delete)

Not applicable for this type of application.

IV.B Clinical Studies

Field Trials

The applicant has conducted one pilot study and a field study to demonstrate therapeutic equivalence among test product and reference product. Both studies were carried out administrating the products by IM route, due that only the IM route is claimed.

The pilot clinical study was performed in two subsequent weanings, including 51 sows allocated in three treatment groups: test, reference and no treatment, the treated groups received 5 ml in a single dose by IM route. Clinical parameters were appearance of heat and percentage of pregnancies. 85 % of the sows presented heat within 3-5 days after treatment. Any sow in untreated group had gone into heat.
The validity of the study has been demonstrated using a negative control group, as FDA guideline states, the study should be adequately sensitive to detect differences when actually there are differences

A GCP study was carried out to demonstrate the bioequivalence between the test product GESTAVET HCG 200/PMSG 400 and reference product, PG 600, in sows by comparison of the clinical effects produced by the two treatments.

Both studies were designed as three groups of treatment: Test group, reference group and placebo group that received the recommended dose (5 ml equivalent to 200 UI HCG and 400 UI PMSG) after few days after several weanings. The success criteria was the external signs of heat within the 7 days after the treatments or the administration of placebo. Results regarding proportions of success were statistical ly different comparing test product and reference product with placebo, validating the sensitivity of the study according to the Guideline for the conduct of bioequivalence studies for veterinary medicinal products EMEA/CVMP/016/00, results regarding proportions of success between test and reference product were not statistically different indicating a clinical equivalence between the two products. A 90 % confidence interval of the difference of proportions between test and reference product ranged within -9.22 % to 3.89 % and indicates that difference is lower than a 20 % indicating clinical equivalence.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

None