Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

GESTAVET HCG 1000 / PMSG 2000

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0134/002/MR
Name, strength and pharmaceutical form	**GESTAVET 3000** powder and solvent for solution for injection for swine. (AT, BE, FR, IT, LT, MT, NL, UK) **SUIGEST 3000** powder and solvent for solution for injection for swine. (EL) **GESTAVET HCG 1000 / PMSG 2000** powder and solvent for solution for injection for swine. (ES) **GESTAVET HCG 40 IU/ml / PMSG 80 IU/ml** powder and solvent for solution for injection for pigs. (DE, UK)
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.

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

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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).

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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: 30/09/2009
Date product first authorised in the Reference Member State (MRP only)	28/03/2001
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 packaged in a carton box containing 10 vials of powder and 10 vials of solvent (25 ml/vial). The vials are properly labelled.

The freeze-dryed product is filled in 50 ml colourless Type I glass vials, closed with Type I elastomeric stopper with anodised aluminium caps.

The solvent is filled in 50 ml colourless Type II glass (containing 25 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).

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 substances 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)*

Gestavet HCG 1000- PMSG 2000 is an extension of the product Gestavet 200-400, the former was developed to treat 5 animals instead of one.
Because both products (Gestavet HCG200/PMSG400 and Gestavet HCG1000/PMSG2000) are identical regarding pharmaceutical form, indications, target species and doses, pharmacological, toxicological and clinical data are not provided.

Part III of the dossier is identical for the two products, except for user safety section where calculations were performed specifically for each product.

Gestavet HCG 1000- PMSG 2000 is administered by intramuscular route. It is indicated in sows for induction and synchronization of heat. The volume to be administrated in a single dose is 5ml, which corresponds to 200 UI of HCG and 400 UI of PMSG.

III.A Safety Testing

Pharmacological Studies

The PMSG stimulate 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.

After intramuscular administration, PMSG is slowly absorbed and reaches peak serum concentrations between 12-24 hours later. It is poorly distributed in tissues because of its high molecular weight and its elimination half-life is between 40 and 125 hours.
PMSG has a long period of activity because it does not pass through the renal filter and remains in the circulation in treated animals for hours, thereby producing prolonged ovarian stimulation in the treated animals after administration of just a single dose.

After intramuscular administration, HCG is absorbed and reaches peak serum concentrations by about 6 hours later. Its elimination occurs more slowly than other gonadotrophins, and a significant amount can be found in urine.

Toxicological Studies

Toxicological data are identical to GESTAVET HCG200/PMSG400.

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 residue data are identical to Gestavet HCG200/PMSG400.

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)

This generic application is submitted under the Article 13 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, which corresponds to 200 UI of HCG and 400 UI of PMSG.

Gestavet HCG 1000- PMSG 2000 is an extension of the product Gestavet 200-400, the former was developed to treat 5 animals instead of one. Therefore the differences between the two products only affect to the quality part. Pats III and IV of the dossier are identical for the two products, except for user safety section where calculations were performed specifically for each product.

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology (if relevant – or delete)

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 (pharmaceuticals and immunologicals)

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