MINISTERIO DE SANIDAD Y CONSUMO
agencia española de medicamentos y productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CUNISER 500, 1000, 5000

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0124/001/MR ES/V/0124/002/MR ES/V/0124/003/MR
Name, strength and pharmaceutical form	Cuniser 500 Cuniser 1000 Cuniesr 5000
Applicant	Laboratorios HIPRA, S.A. Avda. La Selva, 135 17170 Amer – Girona España
Active substance(s)	Pregnant mare serum gonadotrophin
ATC Vet code	QG03GA03
Target species	Rabbits (doe)
Indication for use	Doe rabbits: induction and synchronisation 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).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 16/01/2008
Date product first authorised in the Reference Member State (MRP only)	18/04/2007
Concerned Member States for original procedure	EL, PT

I. SCIENTIFIC OVERVIEW

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 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.

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II. QUALITY ASPECTS

A. Composition

The products are presented as powder and dissolvent for injectable solution. The lyophilisates contain Pregnant mare serum Gonadotrophin (500, 1000 and 5000 IU) and as excipients Potassium dihydrogen phosphate, Disodium hydrogen phosphate dodecahydrate, Mannitol, Povidone, Simethicone and Water for injectable preparations.

Solvent is a phosphate buffer solution (PBS). Each vial of lyophilisated powder is dissolved in the proper volume of solvent for reconstitution. The final concentration of PMSG is 25 IU/ml.

The lyophilisated powder is contained in glass vials, sealed with elastomer closures and flip-off caps, in a cardboard box. The solvent is contained in glass vials in a cardboard box.

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

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 manufacturing process of the lyophilisated powder is independent from the manufacturing of the solvent. Both methods are well described in the dossier and are 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 substance Pregnant mare serum Gonadotrophin (PMSG) is a glycoprotein hormone naturally synthesised by the cells of the chorionic girdle of the equine trophoblast. It can be found in blood circulation from the second to around the fourth month of gestation. PMSG is extracted by Syntex from a pool of pregnant mare plasma. The PMSG used in this product complies with the current edition of the European Pharmacopoeia. Its quality is documented by means of a European Drug Master File.

The active substance specifications are considered adequate to control the quality of the material. The methods used to control these specifications are those described in the current edition of the Eur. Pharmacopoeia.

Batch analytical data demonstrating compliance with this specification have been provided.

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

A statement of compliance with the current guideline in relation to the requirements for TSE is included in the dossier.

E. Control on intermediate products (pharmaceuticals)

Not applicable.

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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The product has to be used immediately after reconstitution.

III. SAFETY AND RESIDUES ASSESSMENT

III.A Safety Testing

Pharmacological Studies

The applicant submits pharmacological data about PMSG that he has obtained of bibliographic documentation. These data show relevant pharmacodinamic and pharmacokinetic properties.

Toxicological Studies

The toxicological data submitted are data from bibliographic documentation and they show the same information than Summary Report (EMEA): PMSG has an acceptable level of safety.
The possible single dose toxicity is derived mainly from the administration of large amount of the hormone.
Repeated PMSG administrations may bring about anaphylactic shock.

Also, the applicant submits data about reproduction toxicity of PMSG in the target specie: the rabbit, and in various laboratory species.

If recommended PMSG doses are administered to the target animals, not side effects, neither pregnancy or prenatal problems may occur. Therefore, the SPC and package insert present the next warning in section about the use during pregnancy and lactation: “Do not administer to gestating females”.

The applicant has not conducted additional studies about genotoxicity and carcinogenicity, but it is not considered to be necessary taking into account the information included in the dossier.

Other Studies

The applicant considers that possible effects of PMSG and their studies have been described in part III.A.3. of the dossier.
In conclusion, PMSG can produce allergic reactions in treated animals, especially in repeated PMSG administrations. Also, immunotoxic reactions have been described in the bibliographic documentation.

User Safety

The applicant has provided a user safety assessment with the following information*:* The type of user, the routes of exposure and the risk communication in the SPC and package insert (the concerned risk and what to do in the event of exposure).

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

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The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product is intended to be used only to perform individual treatments, so the phase II is not necessary

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 depletion studies

No residue depletion studies were conducted because:

- PMSG is included in the Annex II of Regulation (EEC) No. 2377/90 and its excipients too or are substances used as additives for food, so not falling within the scope of council regulation 2377/90.
- No ADI has been published for this hormone.
- Residues at injection sites are not a consumer safety issue for products without any potencial for acute effects, such as PMSG. It is a naturally occurring hormone present in plasma and serum of pregnant mares and even in non equine species there is no fixed any limit.
- In the Summary Report (EMEA), the expert consider the residues as orally inactive.
- It is only used in single treatment in very concrete animals which are unlikely to be sent to slaughter immediately after drug use, because they will be involved in breeding programmes.
- There are other products in the market containing the same active ingredient with zero days withdrawal period.
- In conclusion, the product does not present any risk to consumer.

MRLs

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

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat in rabbits is justified.

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IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology (if relevant – or delete)

Tolerance in the Target Species of Animals

The applicant carries out two tolerance studies conducted on the target species. Also different bibliographic references in order to show the safety profile of the product are provided.
A target animal safety study was performed in accordance with the guideline. The study included 20 animals, female rabbits, 9 weeks old. The animals were divided into 4 groups: Group A- 1ml Cuniser (25 UI) /doe by IM route (n=6) ,Group B- 1ml PBS /doe by IM route (n=4) ,Group C- 1ml Cuniser (25 UI) /doe by SC route (n=6) and Group D- 1ml PBS/doe by SC route (n=4)

No adverse effects were reported in the tolerance study; no local reaction was observed by neither IM nor SC route

In the second study a Systemic tolerance of the product at the recommended dose and 5X administered by IV route was assessed. The study included 20 animals 9 weeks old does. The animals were randomized divided into 4 groups: Group A- 25 UI of Cuniser /doe by IV route (n=6), Group B- 1ml PBS /doe by IV route (n=4) , Group C- 125 UI Cuniser /doe by IV route (n=6) and Group D- 5 ml PBS/doe by IV route (n=4)
No adverse effects were reported in the tolerance study
The two target animal safety studies were performed in accordance with the guideline. The existing toxicity data showed a low toxicity. Furthermore, no adverse effects were reported at both studies carried out by the applicant at the recommended dose or at 5X dose

Resistance (if relevant – or delete)

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Field Trials

The applicant has carried out a comprehensive literature review to support the efficacy of the product

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Five studies/references were provided to assess the efficacy of the product administered at 25 UI/animal, 48 hours before the natural mating or artificial insemination for the induction and synchronisation of heat in female rabbits. Different efficacy parameters are included in these studies (receptivity, prolificacy and fertility) with different dose regiments. The conclusion is that the best results are obtained whit the administration of the 25 UI/animal 48 before the mating or AI. All efficacy parameters are increased and the best improvement in non-receptive animals was obtained too.

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.

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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).

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