MINISTERIO
DE SANIDAD
Y POLÍTICA SOCIAL

agencia española de
medicamentos y
productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

LUTEOSYL 0.075 mg/ml solution for injection for cows and sows

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0143/001/MR
Name, strength and pharmaceutical form	Luteosyl 0.075 mg/ml solution for injection for cows and sows (in Poland: Luteosyl 0.075 mg/ml solution for injection for cattle and pigs)
Applicant	Laboratorios SYVA, S.A. Avda. Párroco Pablo Díez, 49-57 24010 León España
Active substance(s)	D-cloprostenol (as D-cloprostenol sodium)
ATC Vet code	QG02AD90
Target species	Cows and sows.
Indication for use	**Cows** **Indications for reproduction:** synchronization or induction of oestrus. Induction of parturition. **Therapeutic indication:** ovarian dysfunction (persistent corpus luteum, luteal cyst), interruption of pregnancy including foetal mummification, endometritis/pyometra, delayed uterine involution. **Sows** **Indications for reproduction**: Induction of parturition.

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: 25/02/2009
Date product first authorised in the Reference Member State (MRP only)	20/06/2007
Concerned Member States for original procedure	DE, FR, HU, IT, NL, PL, 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 D-cloprostenol (0.075 mg) as D-cloprostenol sodium (0.079 mg/ml as the active substance and excipients (ethanol, citric acid monohydrate, chlorocresol, sodium hydroxide and water for injections).

The container/closure system consists of type II colourless glass vials containing 2 ml, 10 ml and 20 ml with type I bromobutyl stoppers and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are 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.

The manufacturing process consists of the sequential addition of the excipients and the active substance to a portion of water for injections. The flow chart of the manufacturing process has been included.

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

C. Control of Starting Materials

The active substance is d-cloprostenol sodium, an established substance whose specification is based on the monograph for the racemic form, (d,l)-cloprostenol sodium, described in the British Veterinary Pharmacopoeia, with some exceptions. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

A copy of the ASMF of the active substance manufacturer has been included.

All excipients comply with their respective Ph. Eur. monographs.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

The bulk product 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 (Store at 5ºC). A retest period of 2 years has been established.

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 (2 years) when stored under no special storage conditions.

The claim of 28 days stability after first broaching is based on the demonstration of stability for two experimental batches broached and stored 28 days at 25º±2ºC/60%±5%RH.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

A study on the composition of the formulation of the reference medicinal product and Luteosyl including related substances is provided, concluding that both formulations are identical.

III. SAFETY AND RESIDUES ASSESSMENT

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.

LUTEOSYL and the reference product (DALMAZIN) have the same qualitative-quantitative composition in active substance and excipients, the same pharmaceutical form and the same administration route.
The applicant submits, in part II-Quality of the dossier, a study carried out to demonstrate the identicalness of both products.

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 active substance, cloprostenol, acts as a luteolytic agent causing functional and morphological regression of the corpus luteum followed by return to oestrus and normal ovulation. It may also be used for the induction of parturition in pregnant cows and sows.
The absorption, distribution and elimination of cloprostenol are quick.

Toxicological Studies

As this is a generic application according to Article 13, results of toxicological tests are not required.
The acute toxicity of cloprostenol is low.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is safe when it 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

No residue depletion studies were conducted because this is a generic application according to Article 13 and the identicalness of LUTEOSYL and the reference product has been demonstrated.

MRLs

Cloprostenol is listed in Annex II of Council Regulation 2377/90.

Withdrawal Periods

As the two formulations (LUTEOSYL and DALMAZIN) are identical it can be stated that they have the same residue profile and therefore the withdrawal periods for the authorised product can be applied to LUTEOSYL.

Cows: Meat and offal: 1 day
Milk: 0 hours

Sows: Meat and offal: 1 day

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and equivalence with a reference product DALMAZIN 0.075 mg/ml solution for injection (Fatro Uriach Veterinaria, S.L.) has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

In accordance with Council Directive 2001/82 (amended by 2004/28/EC) and "Guideline for the conduct of bioequivalence studies for veterinary medicinal products" (EMEA/CVMP/016-00 corr-final) pre-clinical and clinical data and bioequivalence studies are not required. Omission of bioequivalence studies is justified because LUTEOSYL is to be administered by intramuscular route, as solution, and contains the same active substances and excipients with the same pH as the reference product DALMAZIN.

The formulations identity of the LUTEOSYL and DALMAZIN is demonstrated in Part II Q of the file.

IV.A Pre-Clinical Studies (pharmaceuticals only)

Pharmacology (if relevant – or delete)

As this is a generic application according to Article 13, and equivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and equivalence with a reference product has been demonstrated, results of tolerance tests are not required.

Moreover, the tolerance profile of the active substance component of the test product is similar to that of the reference product because LUTEOSYL is a solution that contains the same active substances and excipients with the same pH as the reference product DALMAZIN

IV.B Clinical Studies

As this is a generic application according to Article 13, and the identicalness of LUTEOSYL and the reference product has been demonstrated, clinical studies are not required.

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).