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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT

GESTAVET-PROST

Dexcloprostenol, solution for injection

Procedure number: CZ/V/0102/001/MR

MAH: LABORATORIOS HIPRA, S.A.

Date: 09/09/2008

MODULE 1

PRODUCT SUMMARY

EU Procedure number	**CZ/V/0102/001/MR**
Name, strength and pharmaceutical form	**GESTAVET-PROST , 0.075 mg/ml , Solution for injection**
Applicant	Laboratorios Hipra, S.A. Avda. La Selva, 135 17170 Amer (Girona)
Active substance(s)	**Dexcloprostenol (sodium salt)**
ATC Vetcode	**QG02AD90**
Target species	**Cows, sows**
Indication for use	Cows and heifers: - Synchronisation and induction of heat - Anoestrus periods after parturition - Coadjuvant treatment in chronic endometritis and pyometra - Luteinic cysts - Persistent corpus luteum - Induction of abortion Sows: - Induction of parturition

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the veterinary Heads of Agencies website:

http://mri.medagencies.org/veterinary/.

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original <mutual recognition> <decentralised>procedure	22.12.2006
Date product first authorised in the Reference Member State (MRP only)	2001
Concerned Member States for original procedure	EL,ES,PL,PT

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 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 75 μg/ml Dexcloprostenol (as sodium salt) as active substance and Citric acid monohydrate, Sodium hydroxide, Chlorocresol, Isopropyl alcohol and Water for injections as excipients (qualitative)>

The product is filled in 10 and 20 ml, Type I colourless glass vials, which are closed with basic polymeric elastomer stoppers type I and with anodised aluminium caps. The particulars of the containers and controls performed are provided and conform to European Pharmacopoeia requirements.

The choice of 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 is adequately described and 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 Dexcloprostenol, an established active substance not described in the European Pharmacopoeia. 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.

The scientific data of the API were provided in the ASMF.

All excipients included in the product are controlled according to their monographs in the European Pharmacopoeia.

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

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 the ASMF and are in accordance with applicable European guidelines. The re-test period and storage conditions were justified.

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 claim of a 28 days stability after broaching is based on the demonstration of stability for a batch broached and stored 28 days at +5°C.

H. Genetically Modified Organisms

Not applicable

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL) (*for pharmaceuticals only)*

For generics, insert in the relevant sections as appropriate:

III.A Safety Testing

Pharmacological Studies

See Part IV

Toxicological Studies

The applicant has provided bibliographical data, which show that cloprostenol has a low toxicity. Used data supported the safety for the substance with a well-established use in veterinary medicine.

- Single Dose Toxicity for rats .

Acute s.c. toxicity has been studied in rats for two substances – LD_{50} for gliprostenol higher than 2500 μg/kg b.w. and LD_{50} for cloprostenol was higher than 5 mg/kg b.w.

- Repeated Dose Toxicity

Repeat dose toxicity was supported no standard from studies published in literature. More information about repeated dose toxicity and chronic toxicity is in the Summary Report of cloprostenol and d-cloprostenol that summarizes the 30 and 90 days toxicity studies with oral treatment of the animals.

- Reproductive Toxicity, including Teratogenicity:

No teratogenic properties of cloprostenol, and by extension of dexcloprostenol, were observed in the treated animals. In addition, because cloprostenol and d-cloprostenol can cause abortions in gestating animals, the GESTAVET-PROST product is only indicated in gestating animals when the induction of abortion or parturition is desired. This is why there would not be much reason to administer the product to gestating animals for other objectives, as the risk of teratogenic

effects is practically nonexistent. In fact, in the SCP as well as in the informative texts it is indicated that the product should not be administered to gestating cows in which is not desired to cause abortion nor in sows in which it is not desired to induce parturition.

Moreover, in the clinical studies provided in the dossier and the tolerance studies it was demonstrated that after the induction of parturition with cloprostenol and dexcloprostenol in sows toxic effects are not observed on the litter, which guarantees the safety of the product when it is administered to induce parturition.

- Mutagenicity

The mutagenic potential was determined in human lymphocytes (in vitro test) and in bone marrow or mice cells (in vivo tests), by means of monitoring the numerical and structural chromosomal aberrations as well as by determining the mitotic index. No evidence was found of potential mutagenicity of cloprostenol at the experimental concentrations and at the doses tested during the study. There is mentioned in article that cloprostenol was previously demonstrated to be potentially genotoxic in an in vitro SCE test conducted (exchange of sister chromatids). This discrepancy may be due, according to these authors, to a greater sensitivity of this test in comparison with the structural and numerical analysis of the chromosomal aberrations. These findings indicate that cloprostenol can be considered as a weak mutagen. In addition, according to these authors, it must be pointed out that cloprostenol is quickly metabolised in treated animals, which means the administration of cloprostenol in domestic animals implies that exposition by humans is nearly negligible.
No significant variations of the mitotic index were observed either in the experimental concentrations administered in vitro or for any of the doses of cloprostenol injected in mice.

- Carcinogenicity (if necessary):

Cloprostenol is an old substance, which is not known to be mutagenic or carcinogenic.

Observations in Humans

See section “User safety”.

User Safety

User safety has been addressed adequately. SPC contains adequate warnings: The product must not be handled by pregnant women, asthmatics or people with bronchial or other respiratory diseases. Avoid contact with eyes. In case of accidental contact, wash with abundant water. Avoid contact with skin. In case of

accidental contact, immediately wash the affected area with abundant water. In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

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. The assessment concluded that there is no need to carry out studies on environmental effects as the product is intended for use in individual animals. dexcloprostenol is quickly metabolised and excreted. No warnings regarding dexcloprostenol are therefore required.
The SPC contains a standard phrase in section 6.6 as required.

III.B Residues documentation

Residue Studies

The applicant has provided bibliographical data which contain satisfactory information regarding the residues of cloprostenol in cows and sows tissues and in cows milk and provide adequate information regarding the excipients used in the final product formulation.

Results presented in the bibliographical sources show that the active ingredient cloprostenol is eliminated rapidly in both species. At 24 hours after treatment the maximum amount of total residues from pig meat and milk amounts is less that the 7% (including 300 g of the injection site) and is less than 1% (without the injection site) of the ADI for cloprostenol. Less than 0.75% of the dose is eliminated via milk after an intramuscular treatment with 500 μg cloprostenol. The applied withdrawal periods are in compliance with the residue depletion profile in plasma, tissues and milk.

MRLs

In the Regulation (EC) No 1838/97 of the Commission of 24th of September 1997, cloprostenol and R-cloprostenol were included in the Annex II of the Regulation (EEC) No 2377/90, for bovine, porcine and equine, because it was considered that no MRLs were needed for these substance.

The ADI of cloprostenol is 0.075μg/kg bw/day (i.e. 4.5 μg cloprostenol/person/day).

Pharmacologically active substance	Animal species	Other provisions
Cloprostenol	Bovine, porcine, equidae	
R-cloprostenol	Bovine, porcine, equidae	

Excipients:

Chlorocresol and isopropyl alcohol, which are excipients of this injectable product - according to the Regulation (EC) No 1742/96 of the Commission of 6th of September 1996 and the Regulation (EC) No 2796/95 of 4th of December 1995, respectively - are also included in Annex II of the Council Regulation (EEC) No 2377/90 for all feed producing species.

Citric acid (E-330) and hydroxide sodium (E-524) are included in the Part V of Annex II of this Regulation (Substances with an E number for all food producing species). According to the same directive, all preservatives listed in the Part C of Annex III of this Directive are excluded, which not occur with citric acid and hydroxide sodium.

Withdrawal Periods

Based on the data provided above, a precautionary withdrawal period of 24 hours for meat of bovine and porcine and zero hours for cow's milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The study on pharmacodynamics is based in the bibliographic documentation on the mechanism of action of this luteolytic agent and also in the pharmacological effect after its administration. Also, Laboratorios Hipra, S.A. conducted an experimental study in order to compare the luteolytic activity of the product Gestavet-Prost (d-cloprostenol) and the product Estrumete (cloprostenol racemic mixture) in cows, by comparison of the serum progesterone concentrations after treatments and also by comparison of the oestrus signs. Serum progesterone levels as well as oestrus signs that are not significant differences in the luteolytic activity of Gestavet-Prost and Estrumate, that means that the activity of 150 µg of d-cloprostenol (Gestavet-Prost) and 500 µg of cloprostenol (racemic mixture) is also the same. Oestrus signs showed by the animals indicated also a very similar activity. These result, and the statistical analysis, showed that there not statistical differences between the two treatments.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance studies using multiples of the recommended dose, three time the recommended dose, in the target species.

Parameters evaluated were: the local and general tolerance, biochemical screening, organic system affected.

No adverse effects were seen following doses up to 3 times times the recommended dose.

Bibliographical data and Post marketing information have also been provided which show/s the same affirmation.

IV.B Clinical Studies

The applicant based the clinical efficacy of the product in one study where the luteolytic effect of the product ESTRUMATE (racemic mixture of cloprostenol) and the product GESTAVET-PROST (d-cloprostenol) was studied. The results obtained in that study confirmed the results of some bibliographic studies that indicate that a dose of 500 μg de cloprostenol is equivalent to a dose of 150 μg d-cloprostenol in cows, and that a dose of 150 μg of cloprostenol is equivalent to a dose of 75 μg in sows.

So, based on this equivalent effect, the applicant documents the clinical efficacy of d-cloprostenol by using the bibliographic documentation on cloprostenol, as indicated in the Note for Guidance "*Investigation of chiral active substances*". According to this Guideline, the data related to the racemic can be used for the enantiomer.

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

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.