College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Enzaprost Bovis 12.5 mg/ml solution for injection for cattle

NL/V/0256/001/DC

Created: March 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0256/001/DC
Name, strength and pharmaceutical form	Enzaprost Bovis 12.5 mg/ml solution for injection
Applicant	Ceva Santé Animale 10 avenue de la Ballastiere 33500 Libourne France
Active substance(s)	Dinoprost (as dinoprost trometamol)
ATC Vetcode	QG02AD01
Target species	Cattle (heifers and cows)

Indication for use	The veterinary medicinal product is used in the following indications:
	- Induction of oestrus,
	- Controlled breeding in normally-cycling dairy cows:
	  - oestrus synchronisation,
	  - ovulation synchronisation in combination with GnRH or GnRH analogues as part of timed artificial insemination protocols.
	- Treatment of sub-oestrus or silent heat in cows which have a functional corpus luteum,
	- As supportive treatment of endometritis with the presence of functional corpus luteum and pyometra,
	- Induction of abortion,
	- Induction of parturition, including cases with complications such as hydrops amnii, etc,
	- Expulsion of mummified foetuses.

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MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	31 July 2019
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK(NI)

I. SCIENTIFIC OVERVIEW

Enzaprost Bovis is a generic application; the reference product is 'DINOLYTIC HOGE CONCENTRATIE 12,5 mg/ml oplossing voor injectie voor runderen,' from Zoetis B.V., with a marketing authorisation granted in the Netherlands (REG NL 116575) since 21 December 2015.

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. Qualitative and quantitative particulars

The products contain 12.5 mg/ml dinoprost (as dinoprost tromethamol) and the following excipients: benzyl alcohol, sodium hydroxide, hydrochloric acid and water for injections.

The product is packed in clear type I glass bottles of 2, 10 and 20 ml or in multi-layer PP-EVOH vials (branded CLAS vials) of 50 and 100 mL fitted with bromobutyl rubber stoppers and aluminium caps. The glass vials and stoppers are in conformity with the Ph.Eur. requirements and the multi-layer PP-EVOH vials are in conformity with regulation 10/2011.

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

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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 product is manufactured using conventional manufacturing techniques. Process validation results for three commercial batches filled into different pack sizes spanning the production size range have been provided. The tests performed during production are described.

C. Control of Starting Materials

The active substance is Dinoprost Trometamol, an established active substance 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.

In general the excipients are in conformity with Ph.Eur. requirements. Concentrated sodium hydroxide has an in-house monograph and specifications, which are based on the Ph.Eur monograph.

The glass vials and stoppers are in conformity with the Ph.Eur. requirements.

No excipients are within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on intermediate products

Not applicable.

E. Control Tests on the Finished Product

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

The shelf life specification limit for 15-epiPGF2α is considered qualified.

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.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, confirming the retest period of 36 months with storage condition store in refrigerator (5°C).

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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 of 24 months when stored below 30 °C.

The claim of 12 weeks stability after broaching has been justified.

The claimed shelf-life and in-use shelf-life and storage conditions are accepted.

G. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

The warnings and safety measures as approved for the reference product have been adopted and updated in line with the current guidance.

III.A Safety Testing

Pharmacological Studies

No data on pharmacological studies are required. From the MRL summary report it can be derived that dinoprost tromethamine is a synthetic analogue of prostaglandin F2α. F2α is an autocrine hormone present in many mammalian tissues. It is used to cause luteolysis in the cow, sow and mare; rapidly absorbed from the injection site and has an extremely short half-life of only a few minutes.

Toxicological Studies

No data on toxicological studies are required.
From the MRL summary report it can be derived that

- Dinoprost tromethamine a low acute oral and parental toxicity has, with oral LD_{50}'s of 1300 -1550 mg/kg in respectively male and female mice and 1170- 1210 mg/kg in respectively male and female rats.
- Repeated dose studies were performed in rats, dogs and monkeys.
  Rats: an intravenous dose of 3.2 mg/kg bw/day during 28 days produced no evidence of toxicity; by the subcutaneous route, first signs of intolerance (diarrhoea and depression) were observed at 32 mg/kg bw/day in a 6 day study. Dermal application over 37 days produced no observable toxic effects.
  Dogs: an intravenous dose of 0.6 mg/kg bw/day for 30 days produced no signs of toxicity; oral doses of up to 30 mg/kg bw/day for 5 days were judged non-toxic.
  Monkeys: At 15 mg/kg bw/day by continuous intravenous infusion for 2 weeks dinoprost was considered non-toxic, although slight changes in blood parameters were observed. From a 90 day oral study the toxicological NOEL was determined to be 8 mg/kg bw/day. The pharmacological NOEL was set to 1.25 mg/kg bw/day.
- Some teratogenic changes were noted in rats and rabbits exposed to high doses of dinoprost tromethamine by the subcutaneous route (estimated to be 30x recommended dosage rate) for 3 days. It is likely that those effects are produced by the physiological activity of dinoprost which results in foetal hypoxia.

- The substance was non-mutagenic in the Ames test and DNA damage/alkaline elution test in Chinese hamster lung fibroblast cells.

Observations in Humans

In humans, oral doses up to 30 mg did not produce any obvious effects on the gastrointestinal tract, on pulse rate or on blood pressure. Oral doses of 25 mg caused uterine contractions in early pregnancy. An oral dose of 5 mg give in late pregnancy increased amplitude and frequency of uterine contractions, but failed to induce parturition. The minimal cumulative dose to induce labour in a study using various repeat doses was 30 mg while the maximal oral dose was in excess of 115 mg dinoprost.
Dinoprost is a bronchoconstrictor in humans. However, hundreds of patients have been infused to induce abortion or labour without bronchial complications. Patients give dinoprost orally in a number of studies were not observed to have any bronchial distress.

The most sensitive organ appears to be the uterus of the near term pregnant woman, a dose of 5 mg produces a minimal response in this organ. Taking 10% of this dose and a safety factor of 10 an ADI of 0.83 µg/kg bw/day was derived (corresponding to 50 µg for a 60 kg person).

User Safety

The applicant did not provide an URA in accordance with the guideline on user safety (EMEA/CVMP/543/03-Rev.1), thought completely refers to the product being identical to its reference product.

It can be concluded that this product is to be administered by professional users. The most likely route of exposure is dermal exposure. However, also accidental self-injection may occur. The product will not be stored in the household, therefore, there is no risk anticipated for young children ingesting the product.

The proposed warnings for pregnant women, women of child-bearing age and people with bronchial or other respiratory problems are considered appropriate based on the information on the active substance. An ADI was derived of 50 µg for a 60 kg person, based on an acute effect (increased amplitude and frequency of uterine contractions) observed in a pregnant woman. It is expected that the exposure levels after accidental self-injection and dermal exposure are much higher. Pregnant women, women of child-bearing age and people with bronchial or other respiratory problems should therefore avoid contact with the product, or wear disposable gloves when administering the product.

Hypersensitivity reactions and skin- and or eye-irritation cannot be excluded when in contact with the product. Warnings and precautions are in place in the product information.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:
The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment, the active substance is extensively metabolised in the treated animal, and the initial predicted environmental concentration in soil is less than 100 µg/kg for both intensively reared and pasture animals.

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III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because this product contains the same active ingredient (dinoprost as tromethamine salt) and the same excipients in the same Concentration as reference product 'DINOLYTIC Hoge Concentratie'.

When bioequivalence with the reference product has been demonstrated as the qualitative and quantitative composition is identical to the reference product, no residue depletion studies need to be provided, including no information on injection site residues.

The withdrawal periods from the reference product can be adopted. Residue data however justify a withdrawal period of 2 days for meat.

MRLs

Dinoprost is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

No MRL required	All mammalian food producing species

Withdrawal Periods

Based on the data provided, a withdrawal period of 2 days for meat in cattle and zero days for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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 Heads of Veterinary Medicines 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.

Summary of change	**Section updated**	**Approval date**
C.I.1.a – Changes in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure; the medicinal product is covered by the defined scope of the procedure. (NL/V/0256/001/IA/001)	III.B (SPC updated)	11 November 2020