

NATIONAL PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A
VETERINARY MEDICINAL PRODUCT**

**Dinolytic
(dinoprost tromethamine)**

Asp no: 2015-0031

MODULE 1

PRODUCT SUMMARY

Asp no	2015-0031
Name, strength and pharmaceutical form	Dinolytic, 12,5 mg/ml, Solution for injection
Applicant	Zoetis Finland Oy Tietokuja 4 00330 Helsinki Finland
Active substance(s)	dinoprost tromethamine
ATC Vetcode	QG02AD01
Target species	Cattle
Indication for use	Brunstkontroll och synkronisering av brunst hos mjölkkor med normal brunstcykel, synkronisering av ovulation hos mjölkkor med normal brunstcykel i kombination med GnRH eller GnRH analoger som del av ett protokoll för artificiell inseminering på fastställd tid. Behandling av utebliven brunst (vid närvaro av aktiv gulkropp). Induktion av abort. Avbrytande av patologiska dräktigheter (dött foster, stenfoster, hydroallantois). Behandling av kronisk metrit och pyometra.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Medical Products Agency's website (<http://www.lakemedelsverket.se/english/>).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Article 12(3), Known active substance, in accordance with Directive 2001/82/EC as amended.
Date of completion of the original national procedure	2016-01-14

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 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. Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

B. Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and

6.4.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Due to the type of application (line extension to a new strength of dinoprost [as dinoprost tromethamine], i.e. from 5 to 12.5 mg /ml), no new pharmacological studies, except for a bioequivalence study, have been conducted. The active substance is a synthetic analogue of prostaglandin F_{2α} (PGF_{2α}) which have luteolytic properties and induces contractions of smooth musculature in the gut and uterus. As with Dinolytic vet. 5 mg/ml, Dinolytic vet 12.5 mg/ml is indicated for its luteolytic and/or oxytocic effects in cattle.

The new formulation with the higher strength of 12.5 mg/ml was shown to be bioequivalent to Dinolytic vet. 5 mg/ml following intramuscular injection of 25 mg dinoprost (as dinoprost tromethamine) to cattle. For details, see Part IV.

Toxicological Studies

Due to the type of application no new toxicological studies except for an injection site tolerability study in cattle have been conducted. Dinolytic vet. 12.5 mg/ml was shown to be well tolerated when injected intramuscularly to dairy cows at the recommended dose of 25 mg/animal. For details, see Part IV.

Observations in Humans

According to the CVMP summary report the lowest dose of dinoprost with pharmacological effect was 5 mg which failed to induce parturition but did increase amplitude and frequency of uterine contractions when given in late pregnancy. A dose of 5 mg (or 0.083 mg/kg for a 60 kg person)/kg can thus be considered a LOEL for dinoprost.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the use of Dinolytic vet. 12.5 mg/ml may be related to a pharmacological risk to the user in terms of bronchospasm or miscarriage as previously concluded for Dinolytic vet. 5 mg/ml. For the two primary routes of exposure, i.e. accidental injection and spillage on the skin, the margins of exposure to the human pharmacological LOEL of 0.083 mg/kg were estimated to 4 or less.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Due to that the margins of exposure were lower than those estimated for Dinolytic vet. 5 mg/ml, the warning phrases for Dinolytic vet. 12.5 mg/ml are somewhat more stringent.

Environmental Risk Assessment

An environmental risk assessment in line with applicable guidelines was provided. The assessment was stopped in Phase I as Questions 2 and 6 could be answered with "Yes". It was concluded that dinoprost is a naturally occurring substance that is extensively metabolised in the target species cattle and that the potential environmental exposure to dinoprost following the recommended use of Dinolytic vet. 12.5 mg/ml in cattle can be considered as negligible. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues documentation

Residue Studies

As this is an application for an extension to a higher strength of a solution of dinoprost for injection to cattle with the same indications, treatment duration, administration route and dosage as for the currently approved product no residue depletion studies have been conducted. The bioequivalence study shows that Dinolytic vet. 12.5 mg/ml is bioequivalent to

Dinolytic vet. 5 mg/ml following intramuscular injection of 25 mg dinoprost (as dinoprost tromethamine) to cattle. This indicates that the plasma pharmacokinetics of dinoprost (PGF_{2α}), including a rapid absorption from the injection site, are not markedly changed by the increased concentration of the solution for injection. For details, see Part IV.

MRLs

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

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Dinoprost	NOT APPLICABLE	All mammalian food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
Dinoprost tromethamine	NOT APPLICABLE	All mammalian food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY

Withdrawal Periods

Based on that pharmacokinetic bioequivalence between the two formulations has been shown and that the local tolerance of the new formulation is acceptable, the currently approved withdrawal periods for meat and offal (1 day) and milk (zero hours) in cattle species for Dinolytic vet. 5 mg/mL are adopted for the new formulation Dinolytic vet. 12.5 mg/mL.

Due to the rapid absorption of dinoprost (i.e. PGF_{2α}, as indicated by the short t_{max} values for PGFm, the primary metabolite of PGF_{2α}, in plasma) and slightly shorter t_{max} value for PGFm after Dinolytic vet. 12.5 mg/ml, the residue levels at the injection site are not expected to be higher for Dinolytic vet. 12.5 mg/ml than for Dinolytic vet. 5 mg/ml.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Dinolytic contains the active substance dinoprost (Prostaglandin F_{2α}) which have luteolytic properties and induces contractions of smooth musculature in the gut and uterus. In account of the fact that this application concerned an extension from Dinolytic 5mg/mL to Dinolytic 12,5 mg/mL with no change in active substance no new pharmacodynamics data was submitted in connection to this application which was regarded acceptable.

Pharmacokinetics

A study to test the bioequivalence of the higher strength of Dinolytic 12.5 mg/ml solution for injection as compared to the previously authorised product (Dinolytic 5 mg/ml) was conducted in cattle. The normally recommended dose of 25 mg was given to female cattle (24 young estrous-cycling non-lactating dairy heifers) in a randomized two-period, two-treatment single-dose crossover study with a 48 hour washout period between doses. Blood-samples were collected pre-dose and up to 12 hours after dosing. The study design is

adequate. Plasma samples were analysed using an adequately validated LC/MC/MS method. It was prospectively pre-specified in the protocol that bioequivalence should be based on data for the primary metabolite PGF_m due to the short half-life of the parent drug $\text{PGF}_{2\alpha}$ in plasma and due to the artifactual formation of $\text{PGF}_{2\alpha}$ that can occur during sampling. Also, endogenous $\text{PGF}_{2\alpha}$ can interfere with the measurement of exogenous $\text{PGF}_{2\alpha}$. According to the Guideline of the conduct of bioequivalence studies for veterinary medicinal products the use of metabolite data as a surrogate for an active parent compound is not encouraged, but in this case the use of metabolite data is considered justified. PGF_m is an endogenous compound but with the synchronisation of estrous cycles prior to the study, baseline levels were very low compared to the post-treatment data and thus baseline adjustment was unnecessary. For AUC_{0-t} and C_{\max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for the metabolite PGF_m . Thus, bioequivalence has been adequately demonstrated between the approved strength 5 mg/ml and the applied strength 12.5 mg/ml following intramuscular injection of a 25 mg dose.

Tolerance in the Target Species of Animals

In account of the higher strength of Dinolytic 12,5 mg/mL solution for injection as compared to the previously authorized product (Dinolytic 5mg/mL) a GLP local tolerance study was performed in eight non-lactating, non-pregnant dairy cows. The animals were administered the recommended dose (25mg/animal) intramuscularly twice with 10 days in between. Signs of systemic and local adverse events were continuously monitored and post mortem examination was performed the day after last dose. No sign of systemic adverse reaction was noted. Local reactions were detected in many animals but the changes were minimal and short lasting. Histopathology confirmed the occurrence of only slight reactions. The study demonstrated that dinoprost 12,5 mg/mL is well tolerated during intramuscular administration.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

The current application concerned an extension of the previously authorised veterinary medicinal product Dinolytic 5 mg/mL to a higher strength (12,5 mg/mL). Given that no new claim were made for the new product no new clinical data was been submitted and this was regarded acceptable.

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 Medical Products Agency's website (<http://www.lakemedelsverket.se/english/>).

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.

Quality changes

Summary of change (Application number)	Section updated in Module 3	Approval date
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	Section updated in Module 3	Approval date
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	