IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Genestran 75 microgram solution for injection for cattle, horses and pigs

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

PRODUCT SUMMARY

EU Procedure number	IE/V/0228/001/MR
Name, strength and pharmaceutical form	Genestran 75 microgram solution for injection
Active substance	75 microgram (+)-cloprostenol
Applicant	aniMedica GmbH Im Südfeld 9 48308 Senden-Bösensell Germany
Legal basis of application	Bibliographic application in accordance with Article 13(a) of Directive 2001/82/EC, as amended.
Date of completion of procedure	01/10/2008
Target species	Cattle, horses and pigs
Indication for use	Luteolysis
ATCvet code	QG02AD90
Concerned Member States	AT, BE, CZ, DE, EE, ES, FR, IS, IT, LT, LU, LV, NO, PL, PT, RO, SI, SK, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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, 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains:

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

Active substance
75 microgram (+)-cloprostenol

Excipients
Chlorocresol (as preservative)

Citric acid monohydrate
Sodium hydroxide
Water for injections

The container/closure system is Type I glass containing 20 ml of solution for injection with a chlorobutyl rubber stopper and aluminum overseal. 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 at a licensed manufacturing site.

Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is (+)-cloprostenol which is an established active substance. 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.

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.

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. 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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. 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.

An in-use shelf life as detailed on the SPC has been supported by appropriate data.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Precise Identification of the Product concerned by the Application

The product is a solution containing 75 micrograms of (+)-cloprostenol per ml.

III.A Safety Testing

Pharmacological Studies

The product is a synthetic prostaglandin.

Pharmacodynamics:

The applicant has conducted pharmacodynamic studies / has provided bibliographical data which show that cloprostenol acts similarly to the naturally occurring endogenous PGF_2 . Since Genestran contains only the biologically active component (+) – cloprostenol, low doses are sufficient to produce luteolytic and/or stimulatory effects on the myometrium.

Pharmacokinetics

The applicant has conducted pharmacokinetic studies and has provided bibliographical data which show that Cloprostenol is reabsorbed rapidly. Elimination occurs in the urine and faeces.

Toxicological Studies

The applicant has conducted laboratory studies and provided bibliographical data which show that the acute toxicity of cloprostenol is low. No teratogenic properties of cloprostenol were reported while the compound was devoid of mutagenic activity in the tests conducted.

Observations in Humans

The applicant has provided information which shows systemic exposure may occur following accidental spillage or self-injection. Such exposure may lead to adverse gastro-intestinal events such as nausea, vomiting or abdominal pain. Bibliographical information from exposure of humans show that prostoglandins may induce hypotension and bradycardia. Asthmatics are more sensitive to bronchoconstrictor effects induced by PGF_2 .

Studies on Metabolites, Impurities, Other Substances and Formulation

The applicant has provided bibliographical information regarding metabolites which shows that cloprostenol is extensively metabolised to substances without pharmacological activity.

Excipients are commonly used in injectable veterinary pharmaceuticals/human medicines.

User Safety

The applicant has provided a user safety assessment which shows that the product is safe to use when the recommended use conditions are followed.

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

Environmental Risk Assessment

Phase I

The applicant has provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which shows that no further assessment is required. The assessment concluded that use of the product will result in environmental exposures well below the PEC_{soil} concentrations of 100µg/kg. No special warnings regarding disposal of dung are therefore required.

Warnings and precaution 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 Studies

Precise Identification of the Product concerned by the Application

The product is intended for use in cattle, pigs and horses. It contains cloprostenol and is to be administered by the intramuscular route as a single dose.

Residue Studies

The applicant has provided bibliographical data which show that by 24 hours after treatment, the maximum amount of residues which might be ingested from pig or cattle meat and cows milk amounts to less than 7% (including 300g injection site) of the ADI for cloprostenol. The available pharmacokinetic data do not indicate any significant variability between mammalian species, therefore any possible difference in pharmacokinetics in horses would not be expected to have a significant impact on this percentage.

MRLs

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

Withdrawal Periods

Based on the data provided above, a withdrawal period of 1 day for meat and 0 hours for milk are justified.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data to show that the pharmacological action of cloprostenol is qualitatively similar to the action of endogenous PGF_2 . Concerning pharmacokinetics, bibliographic data are provided in respect of cows. The compound is rapidly eliminated as evidenced by radiolabel studies. The applicant has also conducted a GLP study on cows treated with 150µg of d-cloprostenol both intravenously and, after a nine day washout period, by intramuscular injection.

Tolerance in the Target Species of Animals

The applicant has conducted target animal tolerance studies using the recommended dose or a multiple thereof in horses, pigs and cattle. All doses were administered by the recommended route of administration.

Parameters evaluated were general clinical signs, including temperature, heart rate and respiratory rate.

No clinically relevant side effects were seen. Some treated horses showed signs of restlessness, increased intestinal activity (diarrhoea) and sweating; these signs were moderate and transient.

Bibliographical data has also been provided which shows that at doses of 50-100 times those recommended cattle may show signs of uneasiness, slight frothing and milk let-down. Post marketing information has also been provided which shows that there has been a single suspected adverse reaction reported despite widespread use of the product in many EU member states as well as elsewhere in the world over several years. The reaction reported is not thought to be related to treatment with the product.

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

Resistance

Not applicable.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted dose determination and confirmation studies which show that the doses recommended are appropriate.

Field Trials

The applicant has conducted field studies and provided bibliographical data which show that the indications for use are adequately justified.

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 benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI 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 HPRA website.

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.

Changes:
None.