IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

---

Lutalyse

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Lutalyse 12.5 mg/ml solution for injection for cattle
Active substance	Dinoprost (as tromethamine salt)
Marketing Authorisation Holder	Zoetis Belgium S.A.
Legal basis of application	Line extension application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of Authorisation:	
Target species	Cattle
Indication for use	Indicated for its luteolytic and/or oxytocic effects in cattle. The indications for use are: -To more effectively control the time of oestrus in cycling cows. -To treat cows which have a functional corpus luteum, but do not express behavioural oestrus (sub-oestrus or silent heat). -To induce abortion. -To induce parturition. -For treatment of chronic metritis and pyometra. -For controlled breeding in normally-cycling dairy cows: - oestrus synchronisation - ovulation synchronisation in combination with GnRH or GnRH analogues as part of fixed time artificial insemination protocols.
ATCvet code	QG02AD01

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 16.77 mg/ml of the active substance dinoprost trometamol and the excipients benzyl alcohol, sodium hydroxide, hydrochloric acid and water for injections.

The container/closure system is 10 ml, 20 ml or 100 ml Type I clear glass vials with chlorobutyl rubber stoppers and aluminium seals with a flip-off disc.

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 dinoprost trometamol, an established 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 has been provided.

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

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 has 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

An *in vivo* bioequivalence study comparing the formulation of Lutalyse 12.5 mg/ml solution for injection with that of Lutalyse 5 mg/ml has been provided. The applicant specified *a priori* in the study protocol that bioequivalence may be concluded if the 90% confidence interval for the ratio of the means of the parameter AUC was included within the limits 80-125%. For C_{max} the wider limits of 70-143% were specified. The results of the study indicated that the 90% confidence intervals for both AUC and C_{max} lie within the narrower limits of 80-125%. Based on the study presented it is accepted that there are comparable rates and extent of PGFm absorption/systemic exposure for the test and control items following IM administration at a dose rate of 25 mg dinoprost/head to cattle. For plasma PGFm, the products can be considered bioequivalent with respect to AUC and C_{max}. It is accepted that the safety profile will be the same as that of the reference product.

The applicant has submitted a bioequivalence study demonstrating that Lutalyse 5 mg/ml is bioequivalent to Lutalyse 12.5 mg/ml when administered by intramuscular injection at a dose of 25 mg dinoprost per animal. As this is a line extension for a new strength as referred to in Annex I of Regulations (EC) No 1234/2008 and bioequivalence is demonstrated it is accepted that no new information on pharmacology is required.

The pharmacological aspects of this product are identical to the reference product.

Toxicological Studies

As this application is a change to the applicant's existing marketing authorisation leading to an extension as referred to in Annex I of Regulations (EC) No 1234/2008 no new information or studies have been presented.

The toxicological aspects of this product are identical to the reference product.

User Safety

The applicant has provided a user risk assessment broadly in accordance with the current guideline. The warnings and precautions listed on the product literature reflect those authorised for Lutalyse 5 mg/ml and are considered to adequately mitigate any risk to the user from exposure, taking into account the increased concentration of the active substance.

Environmental Risk Assessment

Phase I

The environmental risk assessment can stop in Phase I because exposure to the environment will be negligible.

Conclusion

Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

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 the environment.

III.B Residues Documentation

Residue Studies

No residue depletion studies were conducted because the rate and extent of absorption are bioequivalent to that of the reference product Lutalyse 5 mg/ml. In addition, as this is an aqueous solution and dinoprost is included in Table 1 of the Annex of Commission Regulation (EU) No. 37/2010 as 'No MRL required' the extrapolation of the withdrawal periods are not considered to pose a consumer safety concern and thus can be accepted.

MRLs

Dinoprost tromethamine is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as 'No MRL required.'

Withdrawal Periods

Based on the information provided above, a withdrawal period of 1 day for meat in cattle and zero hours for milk are justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant provided a target animal safety study investigating the effect of the increased strength on animal tolerance. Based on the results of the study and taking into account the results of the bioequivalence study the proposed adverse effects are the same as for Lutalyse 5 mg/ml solution for injection.

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

IV.B Clinical Studies

As this application is a change to the applicant's existing marketing authorisation leading to an extension as referred to in Annex I of Regulations (EC) No 1234/2008 no new information or studies have been presented. The efficacy claims for this product are equivalent to those of the reference product.

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.