Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

PUBLIC ASSESSMENT REPORT
FOR VETERINARY MEDICINAL PRODUCTS

Cyclix Solution for Injection
(250 microgram/ml)
(Cloprostenol sodium)
Intervet Deutschland GmbH

Mutual Recognition Procedure
Generic application according to article 13 (a) iii of Directive 2001/82/EC of 6 November 2001

EU-Reference No.: DE/V/0111/001/MR
German Reference No.: 400793.00.00

Date: 13. February 2020

TABLE OF CONTENTS

I INTRODUCTION

Cyclix from Intervet Deutschland GmbH has been authorised in Germany on 30 May 2005 under the German reference number 400 793.00.00. It is a generic cloprostenol containing injection solution and is indicated for intramuscular injection to cows for the induction and synchronisation of the oestrus cycle, for the induction of abortion and parturition and for the treatment of diseases due to progesterone related cycle blockade. The national application in Germany followed Art. 13(a) iii of Directive 2001/82/EC of 6 November 2001 and was based on the proof of bioequivalence of Cyclix and the approved reference product Estrumate from ESSEX Pharma GmbH.

Following the national approval of the product in Germany, the applicant applied for mutual recognition of the marketing authorisation of Cyclix in Austria, Belgium, Czech Republic, Denmark, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Luxembourg, The Netherlands, Norway, Poland, Portugal, Slovenia, Slovakia, Sweden and the United Kingdom. The documentation submitted with this application consisted primarily of a bioequivalence study which confirmed the bioequivalence of Cyclix and the reference product Estrumate, which has been approved in all concerned member states. The mutual recognition procedure started on 25th of August 2005 and was terminated in January 2006 with the approval of the product in all concerned member states.

Cloprostenol has been included into Annex II of Council Regulation (EEC) No 2377/90 as amended by Commission Regulation (EC) No 1838/97 and Commission Regulation (EC) No 2232/2004 for edible tissues and milk from cattle, pigs and equidae.

II About the product

Mode of action:
Cloprostenol, the active ingredient of Cyclix Solution for Injection (250 microgram/ml), is a synthetic prostaglandin analogue with structural relation to prostaglandin F2α. In Cyclix, it is present as the sodium salt. PGF2α has luteolytic properties and is of major importance in the initiation of the sexual cycle and during parturition. PGF2α analogues such as cloprostenol are therefore used to initiate the sexual cycle in cows and for induction of abortion and parturition.

Pharmacological classification including ATC group:
Prostaglandin;
ATCvet code: QG02AD90

Target animal species:
Female cattle

Approved indications and recommendation for use (including a possible risk management strategy) and posology:
Induction of luteolysis allowing resumption of oestrus and ovulation in cyclic females when used during dioestrus, synchronisation of oestrus (within 2 to 5 days) in groups of cyclic females treated simultaneously, treatment of suboestrus and uterine disorders related to a functioning or persistent corpus luteum (endometritis, pyometra), treatment of ovarian luteal cysts, induction of abortion until day 150 of pregnancy, expulsion of mummified foetuses, induction of parturition.
For all indications, 2 ml of Cyclix Solution for Injection (250 microgram/ml) corresponding to 0,5 mg cloprostenol/animal should be injected intramuscularly. In order to synchronise

oestrus in groups of females, it is recommended that the product is administered on two occasions with a between treatment interval of 11 days.

Withdrawal times:
Meat and offal: 2days
Milk: zero days

III SCIENTIFIC OVERVIEW AND DISCUSSION

The application followed Art. 13(a) iii of Directive 2001/82/EC of November 2001 and was based on the proof of bioequivalence of Cyclix Solution for Injection (250 microgram/ml) and the approved reference product Estrumate from ESSEX Pharma GmbH. The latter has been authorised in Germany in 1978 under the German reference number 13764.00.00 and has been re-evaluated according to Council Directive 81/852/EEC in 1993. The reference product is also authorised in all concerned member states.
The documentation submitted with the present application consisted therefore primarily of a bioequivalence study which confirmed the bioequivalence of Cyclix and the reference product Estrumate in accordance with the requirements laid down in the CVMP Guidelines For The Conduct Of Bioequivalence Studies For Veterinary Medicinal products from July 2001. In addition, a summary of the efficacy and safety data on cloprostenol in cows was provided with the clinical expert report.
According to the generic application, the applicant has made full reference to the SPC of the reference product Estrumate granted in Germany. However, as this was not completely identical to the SPCs authorised for this product in other concerned member states, efforts have been made during the mutual recognition procedure to produce a harmonised overall accepted SPC for Cyclix Solution for Injection (250 microgram/ml).

III.1 Quality aspects

A. Composition

A.1 Composition of the Veterinary Medicinal Product

Cyclix is a colourless, sterile, aqueous solution for injection, containing the active substance Cloprostenol sodium (0,263 mg / ml) equivalent to 0.250 mg/ml cloprostenol in an isotonic citrate buffer. The excipients are benzyl alcohol (preservative), citric acid monohydrate, sodium citrate, sodium chloride, sodium hydroxide and water for injections.

A.2 Container/Closure System

The product is filled into injection vials made of white blow-moulded *glass* (hydrolytic class I) and closed by 20 mm *halogenated butyl* rubber stoppers (Ph. Eur.) fitted with aluminium caps. The declared filling volume is 20 and 50 ml respectively.

A.3 Clinical Trial Formula(e)

Not applicable.

A.4 Development Pharmaceutics

The product is an established injectable form of cloprostenol and its development is adequately described in accordance to the relevant European guidelines.

B. Method of Preparation

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.
The excipients are dissolved in water for injection. The bulk solution is completed by addition of the active substance. The pH of the bulk solution is measured and if necessary adjusted..
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post–authorisation.

C. Control of Starting Materials

C.1 Active Substance

The active substance *Cloprostenol* sodium complies with the monograph of the current British Pharmacopoeia Veterinary (BP Vet). An ASMF has been provided by the supplier. 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.

C.2 Other Substances

Excipients used in the manufacture of the finished product comply with the current monographs of the European Pharmacopoeia.

C.3 Packaging Materials

The product is packaged in 20 and 50 ml colourless glass (Type I) vials fitted with bromobutyl rubber stoppers. The packaging materials comply with relevant EU standards.

D. Specific Measures Concerning The Prevention Of The Transmission Of Animal Spongiform Encephalopathies

There are no substances of ruminant animal origin present or used in the manufacture of this product.

E. Control Tests 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

G.1 Stability of the Active Substance

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 for 3 years.

G.2 Stability of the Finished Product

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the product. At present a shelf life of 3 years has been established. Stability studies are ongoing. The product should be stored protected from light. Broached vials have to be used within 28 days.

Conclusion on quality

The manufacture of the dosage form is adequately described and controlled. Methods and specifications for active substance, excipients and packages are acceptable. The RMS has been assured that GMP standards are in place at all sites responsible for the manufacture and assembly of the product. The control tests and specifications for the finished product are adequately drawn up.
After the applicant has satisfactorily responded the questions related to some additional issues, approval was endorsed from the chemical/pharmaceutical point of view.

III.2 Preclinical aspects (Part III)

Due to the type of application, i.e. a generic application, a pre-clinical report is not necessary. The core document of the dossier, i.e. the study on bioequivalence, is reviewed under III.3 (Part.IV).

III.3 Clinical aspects (Part IV)

The documentation on bioequivalence of Cyclix Solution for Injection (250 microgram/ml) and the reference product Estrumate consisted of a pilot and of a pivotal bioequivalence study.

The exploratory (pilot) bioequivalence study was carried out in a limited number of cows with an Intervet cloprostenol injection solution corresponding to Cyclix and the approved original product Estrumate. The ratio of the mean AUCs from both products was 1.08 suggesting bioequivalence. A marked drop in plasma progesterone concentrations 2 hours after injection of both products served as an additional proof for their comparable pharmacological activity.

The GLP-compliant pivotal bioequivalence study followed the CVMP Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (July 2001) and was performed with cloprostenol injection solution from Intervet (Intervet generic) corresponding to Cyclix and the approved reference product Estrumate.
Rapid absorption of cloprostenol after injection of both products made an accurate determination of C_{max} difficult. It was agreed in line with the bioequivalence guidelines to use, therefore, the wider bounds of 70 to 143% for the 90 % confidence interval of this secondary bioequivalence parameter. For AUC_{last} which served as the key parameter of bioequivalence, the ratio of the test and the reference product was close to 100% and the 90% confidence limits were within the 80%-125% interval set for this parameter.
Both products are therefore bioequivalent in terms of AUC and $C_{max.}$

III.4 Residue aspects (Part III.B.2)

The application for Cyclix is abridged and follows Art. 13(a) iii of Council Directive 2001/82/EC of 6 November 2001 related to essentially similar veterinary medicinal products. A bioequivalence study confirms the essential similarity of Cyclix and the approved reference product Estrumate. The applied withdrawal periods are in compliance with the residue depletion profile in plasma, tissues and milk. New residue depletion studies with Cyclix for the target species cattle have not been provided.

Based on the toxicological evaluation cloprostenol has been included in Annex II of CR (EEC) No 2377/99 for bovine, porcine, equidae and caprine by CR (EEC) No 1838/97 at 24 September 1997 changed by CR (EEC) No 2232/04 at 23 December 2004. An ADI of 0.075 µg/kg bw/day was established and no MRLs were set. In view of Annex II entry for cloprostenol in CR (EEC) 2377/90 there is no need for a routine analytical method.

For the preservative excipient chlorocresol the CVMP recommended the inclusion in Annex II of CR (EEC) No. 2377/90 for all food producing species and no ADI was established. There is no risk for consumers because chlorocresol is rapidly metabolised and excreted. Chlorocresol has no potential to accumulate in tissues and is of low toxicity.

According to the CVMP summary report, 24 hours after treatment, the maximum amount of total residues which might be ingested from cattle meat and cows milk is less than 7 % of the ADI for cloprostenol (including 300 g of injection site). Furthermore, no residues were detectable after 48 hours post treatment in meat. In milk, no detectable cloprostenol residues were found.

Therefore, the precautionary withdrawal period of 2 days for edible tissues and a withdrawal time of zero days for milk are justified.

IV BENEFIT-RISK ASSESSMENT

Based on the long experience with cloprostenol in cows - the reference product Estrumate has been authorised in Germany in 1978 - , the safety of the treatment scheme recommended for Cyclix Solution for Injection (250 micrigram/ml) has to be considered as sufficiently proven in the target species. Special precautions for the animals to be treated and for the person administering the product to animals are adequately reflected in the SPC of the product.
Persons at particular risk such as pregnant women, asthmatics etc. should not use the product at all or handle it with great caution and avoid any contact with the skin, the mucous membranes or accidental self-injection.
Because of the stimulating effects of prostaglandin analogues on smooth muscle, cloprostenol may increase spasms of the bronchial or gastrointestinal tract and should therefore not be used under these circumstances in the target animals. Other serious side effects are not to be expected. Symptoms after overdosing of cloprostenol (diarrhoea) are based on the pharmacological characteristics of the substance.

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 Medicinal 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.

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Change in the composition of the finished product (DE/V/0112/II/014/G)	III. Quality aspects A.1 composition	13.02.2020