IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Primopen

"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/0640/001/DC
Name, strength and pharmaceutical form	Primopen
Active substances(s)	Benzylpenicillin (procaine) monohydrate
Applicant	FATRO S.p.A. Via Emilia, 285 - 40064 Ozzano Emilia Bologna Italy
Legal basis of application	Generic hybrid application (Article 13(3) of Directive No 2001/82/EC)
Date of completion of procedure	29/07/2020
Target species	Cattle, Horses, Pigs
Indication for use	For the treatment of infections caused by penicillin-sensitive bacteria
ATCvet code	QJ01CE09
Concerned Member States	DK, EL, IT, NO,PL, 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 300 mg/ml benzylpencillin (procaine) monohydrate and the excipients sodium formaldehyde sulfoxylate, sodium methyl parahydroxybenzoate (E219), sodium citrate, disodium edetate, povidone K30, lecithin, hydrochloric acid dilute and water for injections.
The container/closure system is 100 ml and 250 ml Type II glass bottles and polyethylene terephthalate (PET) bottles, closed with rubber stoppers and flip-off aluminium collars.
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 benzylpencillin (procaine) monohydrate, is 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 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 sites 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)

The application was made in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a generic hybrid application).
The reference product cited by the applicant is Depocillin 300 mg/ml Suspension for Injection marketed by Intervet Ireland Ltd.

III.A Safety Testing

Pharmacological Studies

The applicant has conducted three *in-vivo* bioequivalence studies, comparing the pharmacokinetic profile of the product with that of the reference product in cattle, horses and pigs when administered by the intramuscular route. It is accepted on the basis of these studies that the product and reference product exhibit comparable rates and extent of absorption following intramuscular administration at a dose rate of 12 mg benzylpenicillin procaine/kg bodyweight to cattle, horses and pigs, and can be considered bioequivalent.
As this is a generic hybrid application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, results of other pharmacological tests are not required.

Toxicological Studies

As this is a generic hybrid application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

User Safety

The applicant has provided a user safety assessment which shows that penicillin may cause allergic reactions following injection, ingestion or skin contact.
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 users.

Environmental Risk Assessment Phase I

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the Predicted Environmental Concentration (PEC) for soil for cattle, horses and pigs was below the trigger value of 100 µg/kg.

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.

III.B Residues Documentation

Residue Studies

The applicant has conducted tissue residue depletion studies in pigs and cattle and a milk residue depletion study in cattle. The final formulation was administered at the recommended dose of of 12 mg benzylpenicillin procaine/kg bodyweight for the maximum treatment period of 5 days. Samples of tissues and milk were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues and milk before the end of the withdrawal period. The analytical method was a fully validated HPLC-MS/MS method.

The alternative approach was used to set the withdrawal period for tissues and the Time-To-Safe-Concentration (TTSC) approach to calculate the withdrawal period in milk.
No tissue residue depletion studies were conducted in horses because the candidate formulation:

- is accepted as being bioequivalent to that of the reference product in horses,
- has the same qualitative and quantitative composition in terms of active substance,
- is to be administered to the same food-producing target species,
- uses the same route of administration, intramuscular,
- has the same posology as already approved for the reference product.

No milk residue data in equidae was submitted.

MRLs

Procaine benzylpenicillin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	Cattle, horses & pigs
Muscle	50 µg/kg
Liver	50 µg/kg
Kidney	50 µg/kg
Fat / skin	50 µg/kg
Milk	4 µg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 6 days for meat in cattle, 4 days for meat in pigs, 6 months for meat in horses and 4 days for milk in cattle are justified. The product should not be used in horses intended to produce milk for human consumption.

IV. CLINICAL ASSESSMENT

As this is a generic hybrid application according to Article 13(3) of Directive 2001/82/EC as amended, 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 applicant has conducted target animal local tolerance studies using the recommended dose in the target species. No adverse effects were seen following the recommended dose.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Adequate warnings and precautions appear on the product literature.

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.