IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

PRODUCT SUMMARY

EU Procedure number	IE/V/0398/001/DC
Name, strength and pharmaceutical form	PROBENCIL 300 mg/ml suspension for injection for cattle and pigs
Active substance(s)	Procaine benzylpenicillin
Applicant	MEVET S.A.U.
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of Authorisation/ completion of procedure	6th February 2019
Target species	Cattle and pigs (weighing more than 25 kg)
Indication for use	For the treatment ofsystemic infections in cattle and pigs (weighing more than 25 kg) causedby bacteria sensitive to penicillin.
ATCvet code	QJ01CE09
Concerned Member States	ES and PL

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 procaine benzylpenicillin and the excipients sodium methyl parahydroxybenzoate, sodium citrate, disodium edetate, povidone, lecithin, carmellose sodium, citric acid monohydrate and water for injections.
The container/closure system is 100 ml and 250 ml polyethylene terephthalate vials sealed with rubber stoppers and aluminium overseals.

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 procaine benzylpenicillin, 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(1) of Directive 2001/82/EC, as amended (a generic application). The reference product cited by the applicant is Norocillin 300 mg/ml Suspension for Injection marketed by Norbrook Laboratories Limited.

III.A Safety Testing
Pharmacological Studies
The applicant has conducted two *in vivo* bioequivalence studies, comparing the pharmacokinetic profile of the product with that of the reference product in cattle 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 10 mg procaine benzylpenicillin/kg bodyweight to cattle and pigs, and can be considered bioequivalent.
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of other pharmacological tests are not required.

Toxicological Studies
As this is a generic application according to Article 13(1), 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 in compliance with the relevant guideline 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 and pigs was below the trigger value of 100 µg/kg. In order to mitigate a potential risk to the environment following the treatment of pigs, the product is restricted to use in pigs weighing more than 25 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 residue depletion studies in pigs and cattle. The final formulation was administered at the recommended dose of 10 mg procaine benzylpenicillin/kg bodyweight for the maximum treatment period of 5 days. Samples of tissues were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period. The alternative approach was used to set the withdrawal period.
The analytical method was liquid chromatography-mass spectrometry. The method was fully validated.

No residue depletion studies were conducted for milk because the product:

is accepted as being bioequivalent to that of the reference product and consequently, the systemic bioavailability of the active substance is expected to be the same in all tissue matrices,
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.

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

	Cattle & 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 and pigs and 96 hours for milk in cattle are justified.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13(1) 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.