IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Cefenil 50 mg/ml Powder and Solvent for Solution for Injection for Cattle and Pigs

PRODUCT SUMMARY

EU Procedure number	IE/V/0220/001/DC
Name, strength and pharmaceutical form	Cefenil 50mg/ml Powder and Solvent for Solution for Injection for Cattle and Pigs
Active substance(s)	Ceftiofur
Marketing Authorisation Holder	Norbrook Laboratories (Ireland) Limited, Rossmore Industrial Estate, Monaghan, Ireland
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of Authorisation	1st July 2009
Target species	Cattle and Pigs
Indication for use	Cattle Treatment of cattle with acute bacterial respiratory disease in which *Mannheimia haemolytica, Pasteurella multocida or Histophilus somni* sensitive to ceftiofur are involved. Treatment of cattle with acute interdigital necrobacillosis (foul in the foot) in which *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* are involved. Pigs Treatment of pigs with bacterial respiratory disease in which *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida* and/or *Streptococcus suis* sensitive to ceftiofur are involved.
ATCvet code	QJ01DD90
Concerned Member States	AT, BE, CY, CZ, DE, EE, EL, ES, FI, FR, HU, IT, LT, LV, NL, PL, PT, RO, SE, 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 is a sterile powder for solution for injection that is to be presented in vials containing 1 g or 4 g.Vials containing 1 g of product are to be reconstituted with 20 ml water for injection and vials containing 4 g of product are to be reconstituted with 80 ml water for injection to give a 50 mg/ml solution of the active substance in each case.On reconstitution the product contains 50 mg/ml ceftiofur (as ceftiofur sodium) and the excipients potassium dihydrogen orthophosphate, sodium hydroxide and water for injection.

The container/closure systems are as follows:
Powder:Type II clear glass vials sealed by bromobutyl stoppers and an aluminium seal with a cool green flip-off plastic disc.

Diluent:Type I clear glass vials sealed with bromobutyl stoppers and aluminium caps.

One vial with 1 g Cefenil Sterile Powder with one vial with 20 ml Water for Injections per carton in packs of 1, 6 and 12 presentations.

One vial with 4 g Cefenil Sterile Powder with one vial with 80 ml Water for Injections per carton in packs of 1, 6 and 12 presentations.

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 on the product have been presented in accordance with the relevant European guidelines.

C.Control of Starting Materials

The active substance is ceftiofur, 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.

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 have been provided.
Batch analytical data from the proposed production site have 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 and in-use shelf life when stored under the approved conditions.

G.Other Information

None.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.ASafety Testing

Pharmacological Studies
The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application and therefore data on pharmacodynamics are not required.

The applicant claims exemption from bioequivalence studies in accordance with paragraph 4(b) of the Guideline for Conduct of Bioequivalence Studies (EMEA/CVMP/016). Paragraph 4(b) of the guideline permits exemption from the requirement for bioequivalence studies where 'the product is to be parenterally or orally administered as a solution and contains the same active substance(s) and excipients in the same concentrations as a veterinary medicinal product currently approved for use in the target species which is the subject of the new application.' Based on the argumentation and chemical data provided by the applicant, the claimed exemption is accepted. Consequently, systemic availability of the active substance following administration of 'Cefenil' is assumed to be equivalent to that achieved following administration of the reference product, with the result that 'Cefenil' and the reference product will have a similar safety and efficacy profile.

Information included in the section 5 of the SPC reflects the text approved in the SPC for the reference product, Excenel Sterile Powder, in the RMS. In addition, section 5.1 has been updated to include MIC data for the target pathogens.

Toxicological Studies

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application and therefore data on toxicological studies are not required.

No data were presented and this is accepted.

Studies on Metabolites, Impurities, Other Substances and Formulation.

The applicant has provided information regarding impurities.Studies have been conducted to determine the comparative impurity profile of this product compared with the reference product and the results are satisfactory.
Excipients included in the product are commonly used in injectable veterinary pharmaceuticals.

User Safety

The applicant has provided a user safety assessment which shows thatthat the product does not present any greater risk to the user than the reference product.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The PEC_{soil} value for all relevant scenarios was found to be less than 100 µg/kg.No specific warnings in respect of environmental risk are therefore required.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.BResidues documentation

Residue Studies

Residue depletion studies using the final formulation were conducted in accordance with Good Laboratory Practice in both cattle and pigs.Samples of injection site tissue were taken from animals at several time points following treatment. Results confirm that residues depleted to below the maximum residue limit (MRL) in injection site tissue before the end of the proposed withdrawal period.

The analytical method was based upon a HPLC assay using UV detection. The method was fully validated.

MRLs

Ceftiofur is listed in Annex I of Council Regulation 2377/90 (O.J L225 17/08/2006 page 3).The marker substance is the sum of all residues retaining the betalactam structure expressed as desfuroylceftiofur.

MRLs are listed below:

	Bovine	Porcine
Muscle	1000 µg/Kg	1000 µg/Kg
Liver	2000 µg/Kg	2000 µg/Kg
Kidney	6000 µg/Kg	6000 µg/Kg
Fat/ skin	2000 µg/Kg	2000 µg/Kg
Milk	100 µg/Kg	100 µg/Kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 2 days for meat in cattle and pigs is justified.

Given that the test product and the reference product can be considered bioequivalent, the cattle milk withdrawal period as approved for the reference product (zero days) can be applied to the proposed ‘Cefenil’ product

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13, and exemption from the demonstration of bioequivalence with a reference product has been accepted, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and exemption from the demonstration of bioequivalence with a reference product has been accepted, no tolerance studies have been provided. It is argued that the safety profile of the test product will be the same as that for the reference product.

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

Adequate warnings and precautions appear on the product literature.

Resistance

The SPC has been updated with appropriate prudent use warnings as recommended in the relevant guidelines.

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.