Irish Medicines Board

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cefenil RTU, 50 mg/ml, Suspension for Injection for Swine and Cattle

MODULE 1

PRODUCT SUMMARY

EU Procedure number	IE/V/0284/001/DC
Name, strength and pharmaceutical form	Cefenil RTU, 50 mg/ml, Suspension for Injection for Swine and Cattle
Applicant	Norbrook Laboratories Limited Station Works Newry County Down BT35 6JP United Kingdom
Active substance(s)	Ceftiofur (as hydrochloride)
ATCvet code	QJ01DD90
Target species	Swine, cattle
Indication for use	Infections associated with bacteria sensitive to Ceftiofur: Swine: For the treatment of bacterial respiratory disease associated with *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Streptococcus suis* sensitive to ceftiofur. Cattle: For the treatment of bacterial respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* sensitive to ceftiofur. For the treatment of acute interdigital necrobacillosis (panaritium, foot rot), associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* (*Porphyromonas asaccharolytica*) sensitive to ceftiofur. For treatment of the bacterial component of acute post-partum (puerperal) metritis within 10 days after calving associated with, *Arcanobacterium pyogenes* and *Fusobacterium necrophorum*, sensitive to ceftiofur. The indication is restricted to cases where treatment with another antimicrobial has failed.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the veterinary Heads of Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25th April 2012
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, EE, EL, ES, FI, FR, HU, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK

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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains ceftiofur (as hydrochloride) 50 mg per ml and the excipients sorbitan oleate, aluminium monostearate and medium chain triglycerides.

The product is presented in Type I clear glass vials or high density polyethylene (HDPE) vials containing 50 ml, 100 ml and 250 ml of solution. Each vial is closed

with a nitryl bung and sealed with an aluminium cap. 100mL and 250mL Type I clear glass vials are presented in a protective plastic sleeve in order to minimise breakage.

The choice of the formulation is justified.

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 from 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 (as hydrochloride), 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. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and 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.

E. Control 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 sites have been provided demonstrating compliance with the specification.

G. 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 when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The application was made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The reference product for this procedure was Excenel RTU, 50 mg/ml suspension for injection for pigs and cattle.

The applicant conducted studies to investigate bioequivalence of the test and reference products in each of the target species and for each route of administration. Based on the data presented, bioequivalence was accepted for

the product when administered in pigs and therapeutic equivalence was accepted when administered to cattle (see Part IV).

As this is a generic application according to Article 13(1), and bioequivalence with a reference product for pigs, as well as therapeutic equivalence with a reference product for cattle has been claimed, results of pharmacological tests are not provided.

Toxicological Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been claimed, results of toxicological tests are not provided.

User Safety

The applicant provided a user safety assessment which showed that when used in accordance with label recommendations, the product will not pose any greater risk to the user than the risks associated with use of the reference product, Excenel RTU, 50 mg/ml suspension for injection for pigs and cattle.
Warnings and precautions as listed on the product literature are similar to those of the reference product and are adequate to ensure safety of the product to users.

Ecotoxicity

The applicant provided a phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. No warnings are therefore required.

III.B Residues documentation

Residue Studies

GLP residue depletion studies using the final formulation were conducted in cattle and pigs. Samples of tissues were taken from animals at several time points (4 animals per time point) following administration of the product in accordance with the recommended dosing regimen. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period.

The analytical method was HPLC with UV detection. The method was fully validated.

No residue depletion studies were conducted for milk given the legal basis of the application (Article 13(1), generic). Given the pharmacokinetic data provided, it was accepted that the rate of depletion of ceftiofur residues from milk following administration of the test product will be similar to, but not slower than, the rate of depletion of residues from milk following administration of the reference product. The authorised withdrawal period for the reference product can be accepted for the test product.

MRLs

Ceftiofur is listed in Table I of Commission Regulation (EU) No. 37/2010 (O.J. 20.1.2010, L 15/19). The marker substance is the sum of all residues retaining the betalactam structure expressed as desfuroylceftiofur.

MRLs are listed below:

	Pigs	Cattle
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	-	1000 µg/kg

Withdrawal Periods

Based on the information provided above, a withdrawal period of 5 days for meat in both cattle and pigs and zero hours for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The application was made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The reference product for this procedure was Excenel RTU, 50 mg/ml suspension for injection for pigs and cattle.

The applicant conducted studies to investigate bioequivalence of the test and reference products in each of the target species for each route of administration. The studies were conducted in accordance with GLP.

- Cattle subcutaneous study: the 90% confidence interval for AUC lay within the narrower limits of 0.8-1.25, with the 90% confidence interval for C_{max} marginally below the wider acceptance limit for C_{max} of 70%. It was accepted that the test (Ceftiofur HCl Injection) and reference products (Excenel RTU, 50 mg/ml Suspension for Injection for Pigs and Cattle) may be considered therapeutically equivalent when administered to cattle by the subcutaneous for the following reasons:

  - Bioequivalence was demonstrated in accordance with guideline requirements for AUC for ceftiofur in cattle and for both AUC and C_{max} for ceftiofur in pigs.

  - Based on the data presented, it was expected that the time for which the concentration of ceftiofur will be greater than any given MIC value (T>MIC) for target pathogens will be at least as long for the test article when compared with the reference product.

  - It was apparent that the only way to reduce the confidence interval for the estimate of C_{max} for ceftiofur was by the inclusion of an increased number of study animals. It was considered that there was inadequate scientific justification to request another study in this instance.

  It was concluded that this would not have a negative impact in terms of efficacy of the product or the possible development of resistance when compared with the reference product.

- Pig intramuscular study: the 90% confidence intervals for C_{max} lay within the wider limits of 0.70-1.43. For AUC, the lower 90% confidence interval was within the narrower limits of 0.8-1.25 but the upper confidence interval was marginally outside the upper limit. Notwithstanding the fact that the upper confidence interval for AUC, at 1.27, was marginally outside the pre-specified upper limit of 1.25, it was accepted that this finding will not impact negatively on the efficacy of the test product; that is, based on these data, it was expected that the test product will be at least as efficacious as the reference product. Recognising the fact that the higher C_{max} observed for the test product may have implications for safety, the applicant investigated both target animal safety and depletion of residues when the test product was administered by the intramuscular route to pigs.

Based on the data presented, bioequivalence was accepted for pigs and therapeutic equivalence for cattle.

Tolerance in the Target Species of Animals

The applicant conducted two target animal tolerance studies using multiples of the recommended dose in the target species. One investigated the tolerance of the test product in pigs when administered via the intramuscular route and the second investigated tolerance in cattle treated subcutaneously. In both studies, a placebo was used as a control.

Parameters evaluated were biochemical and haematological, with general clinical observations and physiological variables also evaluated.

In cattle, mild inflammatory reactions such as hardness at the injection site were observed in some animals, resolving by 21 days following the recommended dose. There were no reports of systemic effects in the cattle or pig studies.

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

Resistance

The warnings and precautions reflect those as prescribed in the European Commission decision on the referral under Article 35 of Directive 2001/82/EC, regarding all veterinary medicinal products containing systemically administered (parenteral and oral) 3rd and 4th generation cephalosporins intended for use in food-producing species.

IV.B Clinical Studies

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been claimed, efficacy studies are not provided. The efficacy claims for this product are equivalent to those of the reference product.

Based on the pharmacokinetic data presented, it is accepted that the test product will be at least as efficacious as 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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

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 veterinary Heads of 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.

None.