IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

EFICUR 50 mg/ml suspension for injection for pigs and cattle

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PRODUCT SUMMARY

EU Procedure number	IE/V/0190/001/DC
Name, strength and pharmaceutical form	EFICUR 50 mg/ml suspension for injection for pigs and cattle
Active substance(s)	Ceftiofur (as ceftiofur hydrochloride)
Applicant	Laboratorios Hipra S.A. Avda la Selva 135 - 17170 Amer (Girona) Spain
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original procedure Date of completion of the repeat use procedure	Wed 28 February 2007 29 October 2008
Target species	Pigs and cattle
Indication for use	Infections associated with bacteria sensitive to ceftiofur
ATCvet code	QJ01DA90.
Concerned Member States for original procedure	CZ, EL, LT, PT, ES and AT. BE, BG, CY, DE, DK, EE, IS, IT, LV, PL, NL, FR, HU, SI, 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 included 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 included in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains
Active substance Excipients
Ceftiofur (as ceftiofur hydrochloride) 50 mg/ml
Aluminium Monostearate
Sorbitan oleate
Triglycerides medium-chain

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The product is supplied in 50, 100 ml and 250 ml colourless, type II glass multidose bottles and PET bottles. Closures are bromobutyl bungs and aluminium overseal. The particulars of the containers and controls performed are provided and conform to the regulation.
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 ceftiofur 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.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

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The applicant provided bibliographical data detailing that ceftiofur is a late generation cephalosporin, which is active against Gram-positive and Gram-negative bacteria. Like all beta-lactam antibiotics, ceftiofur inhibits bacterial cell wall synthesis, thereby exerting bactericidal properties. Cell wall synthesis is dependent on enzymes that are called penicillin-binding proteins

(PBP´s). Bacteria may develop resistance to cephalosporins by 1) having penicillin binding proteins insensitive to an otherwise effective β-lactam; 2) altering cell permeability to β-lactams; 3) producing β-lactamases that cleave the β-lactam ring of the antibiotic or 4) active efflux.

Some β-lactamases, documented in Gram-negative enteric organisms, may lead to varying degrees of cross resistance between cephalosporins, as well as with penicillins, ampicillins and β-lactam inhibitor combinations.

Ceftiofur is active against the following microorganisms which are involved in respiratory diseases in pigs: *Pasteurella multocida, Actinobacillus pleuropneumoniae* and *Streptococcus suis. Bordetella bronchiseptica* is intrinsically non-susceptible to ceftiofur.

It is also active against bacteria involved in respiratory disease in cattle: *Pasteurella multocida, Mannheimia haemolytica, Haemophilus somnus*; bacteria involved in acute bovine foot rot (interdigital necrobacillosis): *Fusobacterium necrophorum, Bacteroides melaninogenicus* (*Porphyromonas asaccharolyitica*); and bacteria associated with acute post-partum (puerperal) metritis in cattle: *Escherichia coli, Arcanobacterium pyogenes and Fusobacterium necrophorum*.

The following Minimum Inhibitory Concentrations (MIC) have been determined for ceftiofur in European isolates of target bacteria::

PIGS		
Organism (number of isolates)	MIC range (microgram/mL)	MIC_{90} (microgram/mL)
A. pleuropneumoniae (28)	≤0.03*	≤0.03
Pasteurella multocida (37)	≤0.03-0.13	≤0.03
Streptococcus suis (495)	≤0.03-0.25	≤0.03
Haemophilus parasuis (16)	≤0.03-0.13	≤0.03
CATTLE		
Organism (number of isolates)	MIC range (microgram/mL)	MIC_{90} (microgram/mL)
Mannheimia spp. (87)	≤0.03*	≤0.03
P. multocida (42)	≤0.03-0.12	≤0.03
H. somnus (24)	≤0.03*	≤0.03
Arcanobacterium pyogenens (123)	≤0.03-0.5	0.25
Escherichia coli (188)	0.13 - >32.0	0.5
Fusobacterium necrophorum (67) (from cases of foot rot)	≤0.06-0.13	ND
Fusobacterium necrophorum (2) (from cases of acute metritis)	≤0.03-0.06	ND
* No range; all isolates yielded the same value. ND: not determined.		
The following breakpoints are recommended by NCCLS for bovine and porcine respiratory pathogens:		
Zone Diameter (mm)	MIC (microgram/mL)	Interpretation

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≥21	≤2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≥17	≥8.0	(R) Resistant

No breakpoints have been determined to date for the pathogens associated with foot rot or cute post-partum metritis in cows.

Pharmacokinetics

The applicant has conducted single dose pharmacokinetic studies in cattle and pigs which show that Eficur is bioequivalent to the authorised product Excenel RTU.
The applicant also provided bibliographical data which describes the main pharmacokinetic features of Ceftiofur. After administration, ceftiofur is quickly metabolised to desfuroylceftiofur, the principal active metabolite.
Desfuroylceftiofur has an equivalent anti-microbial activity to ceftiofur against the bacteria involved in respiratory disease in animals.It is reversibly bound to plasma proteins and as a result, the metabolite concentrates at sites of infection. It remains active in the presence of necrotic tissue and debris.

Pigs

A single intramuscular dose of the product at 3 mg ceftiofur/kg body weight resulted in mean C_{max} of approximately 9 microgram/mL after about 1 hour. The terminal elimination half-life ($t_{1/2}$) of desfuroylceftiofur was about 23 hours. No accumulation of desfuroylceftiofur has been observed after a dose of 3 mg ceftiofur/kg bw/day administered daily over 3 days.

Elimination occurs mainly via the urine (more than 70%); 12-15 % is eliminated via faeces.
Ceftiofur is completely bioavailable following intramuscular administration.

Cattle

A single subcutaneous dose of the product at 1 mg ceftiofur/kg resulted in mean C_{max} of approximately 2 microgram/mL after about 2.5 hours. After administration of the product, the terminal elimination half-life ($t_{1/2}$) of desfuroylceftiofur in cattle is approximately 18 hours.

In other studies in healthy cows, a mean C_{max} of approximately 2.25 microgram/mL was reached in the endometrium about 5 hours after a single administration of cefiofur. Maximum mean concentrations reached in caruncles and lochiae of healthy cows were about 1 microgram/mL.
No accumulation of desfuroylceftiofur has been observed after a daily treatment of ceftiofur over 5 days. Elimination occurs mainly via the urine (more than 55%). 31% is eliminated in the faeces. Ceftiofur is completely bioavailable following subcutaneous administration.

Toxicological Studies

As this is a generic product submitted in accordance with Article 13 of Directive 2001/82 as amended, and is based on bioequivalence with the reference product, no toxicological studies have been conducted by the applicant.The applicant has included a summary of toxicological characteristics and has provided some bibliographic information as supplementary data

Observations in Humans

Ceftiofur has been developed exclusively for veterinary use.There appears to be no studies in humans.

Microbiological Studies (if relevant – or delete)

Bibliographical information is provided with respect to the activity of ceftiofur and its metabolites against various bacteria. Tables of MIC values are presented, relating to human strains of GI bacteria and various organisms of veterinary importance.

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All three excipients are commonly used in pharmaceutical products. Medium chain triglycerides and sorbitan esters are generally regarded as essentially non-toxic and non-irritant. Sorbitan esters are also widely used in cosmetics and food products and have an ADI of 25 mg/kg (WHO). Aluminium compounds similarly are widely used in the food and beverage industry and have a long history of safe use by humans.
It is not considered likely that any excipient, metabolite or impurity that might be present would present any particular risk to humans or animals.

User Safety

The applicant points out that the Guideline on user safety (EMEA/CVMP/543/03) does not apply to generic applications.However a brief assessment of user safety has been provided.This also addresses the precautions taken during manufacturing for the safety of operators.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I assessment was conducted. The following PEC_{soil} were calculated:

Cattle – intensively reared: 14.57 microgram/kg
Cattle – pasture: 10.45 microgram/kg
Pigs – fattening: 26.52 microgram/kg
Pigs - weaner: 39.1 microgram/kg

The calculations were conducted in line with current guidance and are based on the recommended treatment regimen for both target species. Given that the PEC values do not exceed the trigger of 100 microgram/kg, the ERA can be concluded at Phase I.

III.B Residues Documentation

Residue Studies

The applicant has stated that the formulation of Eficur is very similar to that of the reference product, and has provided a comparative table relating to excipients, viscosity, density and particle size.Tissue residue depletion studies have been conducted in both target species using the finished formulation of Eficur: in the studies conducted by the Applicant, residues depleted below the respective MRLs in all tissues including the injection site 24 hours after administration. No studies on milk residues of Eficur were carried out.

In the applicant's method, ceftiofur is hydrolysed in the presence of dithioerythritol to obtain desfuroylceftiofur, which is derivatised using iodoacetamide.The derivative is used for determination and quantification of ceftiofur in tissues by HPLC, after pH adjustment and adsorption into a polymeric sorbent for purification.Solid phase extraction allows the production of a final extract free of interfering compounds at the retention time window of the desfuroylceftiofur derivative. Cefalexin is used as a quantitative internal standard.Both compounds were detected by UV absorption.

MRLs

Ceftiofur is listed in Annex I of Council Regulation 2377/90.The marker residue is the sum of all residues containing the betalactam structure expressed as desfuroylceftiofur.
MRLs are listed below: micrograms/kg

	Bovine	Porcine
Muscle	1000	1000
Liver	2000	2000

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Kidney	6000	6000
Fat/ skin	2000	2000
Milk	100	

Withdrawal Periods

Pigs:
- Meat and offal: 5 days.

Cattle:
- Meat and offal: 8 days - Milk: zero days.

The withdrawal periods agreed reflect those authorised for the reference product, Excenel RTU.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As this is a generic product submitted in accordance with Article 13 of Directive 2001/82 as amended, based on bioequivalence with the reference product, target animal tolerance studies are limited to assessment of local tolerance.

The applicant has conducted target animal tolerance studies in cattle and pigs with the finished formulation; the results support the safety of the product administered to both cattle and pigs.

A warning regarding the likelihood of mild injection site reactions has been included in Section 4.6 of the SPC.This warning is identical to that of the reference product.

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

Resistance

As this is a generic application, it can be assumed that the resistance aspects are similar to the reference product.The applicant states that ceftiofur has been used for the treatment of respiratory disease in pigs and cattle for many years and the target pathogens remain sensitive. Efficacy of β- lactam antibiotics is more time dependent that concentration dependent; concentrations remain several times higher than MIC for target organisms throughout the dosing period, and this is suggested to be the main reason why resistance has not developed.

IV.B Clinical Studies

No clinical studies have been presented, as this is a generic application in accordance with Article 13 of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been shown.The applicant has provided a bibliographical review of the efficacy of ceftiofur as supplementary information. The indications and recommended treatment regimes are based on the authorised indications and recommended treatment regimes of 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 benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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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.

Quality Changes

Summary of change	Approval date
Change in immediate packaging of the finished product (IE/V/0190/001/II/008/G)	

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