MINISTERIO
DE SANIDAD, POLÍTICA SOCIAL
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

SUBDIRECCIÓN GENERAL
DE MEDICAMENTOS
DE USO VETERINARIO

Agencia Española de Medicamentos y Productos Sanitarios

Parque Empresarial Las Mercedes
Edificio 8
C/Campezo 1,
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

ACTIONIS 50 mg/ml, suspension for injection for pigs and cattle

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0157/001/DC
Name, strength and pharmaceutical form	ACTIONIS 50 mg/ml, suspension for injection for pigs and cattle
Applicant	LABORATORIOS SYVA, S.A. Avda. Párroco Pablo Díez 49-57 León – Spain
Active substance(s)	Ceftiofur
ATC Vet code	QJ01D A90
Target species	Pigs and cattle
Indication for use	Infections associated with bacteria sensitive to ceftiofur: In pigs: -For the treatment of bacterial respiratory disease associated with Pasteurella multocida, Actinobacillus pleuropneumoniae and Streptococcus suis. In cattle: -For the treatment of bacterial respiratory disease associated with Mannheimia haemolytica, Pasteurella multocida and Histophilus somni. -For the treatment of acute interdigital necrobacillosis (panaritium, foot rot), associated with Fusobacterium necrophorum and Bacteroides melaninogenicus (Porphyromonas asaccharolytica). -For treatment of the bacterial component of acute post-partum (puerperal) metritis within 10 days after calving associated with Escherichia coli, Arcanobacterium pyogenes and Fusobacterium necrophorum, sensitive to ceftiofur.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23.02.11
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	BE; DE; FR; HU; IT; NL; PL; PT; UK

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 hydrochloride (50 mg/ml) and excipients (aluminium monoestearate, polysorbate 80 and medium chain tryglicerides).

The container/closure system are type II colourless glass vials of 100 and 250 ml with a bromobutyl stopper and an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are 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 and sterilised fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The manufacturing process is a non-standard one. Process validation for full-scale batches will be performed post-authorisation

C. Control of Starting Materials

The active substance is ceftiofur hydrochloride, an established active substance. The manufacturing authorisation holder certifies that 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.

A copy of the ASMF of the API manufacturer has been included.

D. 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.

E. Control on intermediate products

The tests performed during production are described and correspond to those carried out after primary packaging before terminal sterilization.

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 site have been provided demonstrating compliance with the specification. Analytical data from full-scale batches will be provided post-authorisation.

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 when stored under the approved conditions.

The claim of 28 days stability after broaching is based on the demonstration of stability for two batches broached and stored 28 days at 30±2ºC/65±5% RH.

H. Genetically Modified Organisms

None of the starting materials used in the manufacture of the product contains genetically modified organisms.

J. Other Information

Not applicable

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

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

The safety profile of the product is identical to the reference product.

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, the environment and consumers.

III.A Safety Testing

Pharmacological Studies

Since this is a generic application and the bioequivalence with the reference product has been demonstrated the applicant is not required to provide the results of pharmacological trials.

Bioequivalence with the reference medicinal product, Excenel RTU, has been demonstrated in the target species with cross-over bioequivalence studies in cattle after single-dose subcutaneous administration and in pigs after single-dose intramuscular administration.

Toxicological Studies

Since this is a generic application and the bioequivalence with the reference product has been demonstrated, the applicant is not required to provide the results of toxicological trials.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that, implementing the indicated protective measures, the use of the product poses an acceptable risk.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product has an acceptable risk for the environment.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

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.B Residues documentation

Residue Studies

According to the requirements established in Title III of the Commission Directive 2009/09/EC for generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, a residue depletion study in the administration site has been performed with ACTIONIS in the target species.

A residue depletion study using the final formulation has been conducted in calves. Samples of liver, kidney, muscle, fat and injection site, were taken from animals at several time points. Results show that residues depleted below the MRL in all tissues before the end of the withdrawal period. Analysis by alternative approach of the results was used to set the withdrawal period.

A residue depletion study using the final formulation has been conducted in pigs. Samples of injection site were taken from animals at several time points. Results show that residues depleted below MRL in all samples before the end of the withdrawal period. Analysis by alternative approach of the results was used to set the withdrawal period.

The analytical method was HPLC-UV. The method was fully validated.

MRLs

Ceftiofur is included in the table 1 of the Annex of the Regulation 37/2010 as a pharmacological active substance with the following MRLs:

Active substance	Marker residue	Animal specie	MRL (µg/kg)	Target tissue
Ceftiofur	Sum of all residue retaining the betalactam structure expressed as Desfuroylceftiofur	All mammalian food producing species	1000 2000 2000 6000 100	Muscle Fat Liver Kidney milk

Withdrawal Periods

Based on the data provided above, a withdrawal period of 6 days for meat in pigs and cattle and zero hours for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, 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.
However, according to what is established in Title III (Requirements for specific marketing authorisation applications) of the Commission Directive 2009/09/EC for generic veterinary medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes – ACTIONIS is administered by intramuscular route in porcine and by subcutaneous route in bovine –, studies on target animal tolerance at the administration site.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted two controlled target animal tolerance studies in the injection site using the recommended dose for the highest recommended duration in the target species. A placebo was used as a control. All doses were administered by im route in porcine on 3 occasions. All doses were administered by sc route in bovine on 5 occasions.
Parameters evaluated were: General parameters: Local parameters: Blood sampling: Tissue sampling
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

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).