FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CURACEF DUO, 50 mg/ml / 150 mg/ml, Suspension for injection for cattle

Date: 09 Septemberly 2014

French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0258/001/DC
Name, strength and pharmaceutical form	CURACEF DUO, 50 mg/ml / 150 mg/ml, Suspension for injection for cattle
Applicant	VIRBAC 1ère avenue – 2065m – L.I.D. 06516 Carros FRANCE
Active substance(s)	Ceftiofur (as hydrochloride) and Ketoprofen
ATC Vetcode	QJ01DD99
Target species	Cattle
Indication for use	For the treatment of bovine respiratory disease (BRD) caused by *Mannheimia haemolytica* and *Pasteurella multocida* susceptible to ceftiofur and the reduction of associated clinical signs of inflammation or pyrexia

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the websitehttp://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Fixed combination application in accordance with Article 13 (b) of Directive 2001/82/EC as amended.
Date of completion of the original decentralisedprocedure	19/06/2014
Concerned Member States for original procedure	AT – BG – CY – CZ – DE – EE – EL – ES – HU – IE – IT – LT – LV – 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 50 mg/ml ceftiofur (as hydrochloride), 150 mg/mlketoprofen as active substances, and excipientssorbitan oleate, hydrogenated soya lecithin and cottonseed oil.
The container is a glass vial or a plastic vial with bromobutyl rubber stopper.The particulars of the container 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 substances are ceftiofur (as hydrochloride) and ketoprofen, established active substances. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are 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

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

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 site have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances 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.
An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

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 applicant has provided bibliographical data about pharmacological features of ceftiofur and ketoprofen.

Ceftiofur is a third generation cephalosporin, which is active against many Gram-positive and Gram-negative bacteria. Ceftiofur, as other beta-lactams, inhibits the bacterial cell wall synthesis, thereby exerting bactericidal properties.

Ketoprofen is a derivative of phenylpropionic acid, and belongs to the non-steroidal anti-inflammatory group of drugs. The mechanism of action is related to the ability of ketoprofen to interfere with the synthesis of prostaglandins from precursors such as arachidonic acid.

The applicant has provided two pharmacokinetic studies in the target species.

As regards ceftiofur pharmacokinetic, one bioequivalence cross over study after administration of the test product and a monoproduct (Excenel RTU) was presented. The bioequivalence was not demonstrated. Higher systemic exposure of ceftiofur is obtained with the test product mainly during the first hours (higher Cmax).

As regards ketoprofen phamacokinetic, one parallel study assessed the bioavailabilty of ketoprofen and compared ketoprofen kinetics in the combination product *vs.* in a monoproduct (Ketofen 10%). It can be concluded that ceftiofur likely enhances the systemic bioavailability of ketoprofen.

Despite both active ingredients show higher systemic exposure when administered together by intramuscular route in the combination than in the monoproduct, the pivotal TAS study presented gives reassurance on the well tolerance of the combination.

Toxicological Studies

The applicant has provided relevant bibliographical data to characterise acute and chronic toxicity, reproductive toxicity and mutagenicity/ carcinogenicity for each of the active ingredients of the product.

The results of two specific studies have been presented. The combination does not display eye or skin irritations.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

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 was required.

III.B Residues documentation

Residue Studies

The applicant has provided one ceftiofur residue study in meat and offal and 2 confirmatory studies at the injection site for ketoprofen.

The applicant has provided two ceftiofur residue studies in milk.

MRLs

b. active substances

The two active substances are included in table 1 of the MRL regulation 37/2010, as follows:

CEFTIOFUR						
Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**
Sum of all residues retaining the betalactam structure expressed as desfuroylceftiofur	All mammalian food producing species	1 000 µg/kg 2 000 µg/kg 2 000 µg/kg 6 000 µg/kg 100 µg/kg	Muscle Fat Liver Kidney Milk	For porcine species the fat MRL relates to "skin and fat in natural proportions"	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009

KETOPROFEN						
ADI = 5 µg/kg						
Marker residue	**Animal Species**	**MRL**	**Target Tissues**	**Other Provisions**	**Therapeutic Classification**	**Regulation**
Not applicable	Bovine, porcine, Equidae	No MRL required	Not applicable	No entry	No entry	37/2010 of 22.12.2009
As trace levels of residues are detected at the injection site 96 hours after treatment, the Commitee recommends a withdrawal period of 4 days for edible tissues.						

b. excipients

The MRL status of excipients of the product is indicated in the following table:

Excipient	MRL status	ADI
Sorbitan oleate	Table 1, no MRL required	-
Hydrogenated phosphatidylcholine	Table 1, no MRL required	-
Cottonseed oil	Out of scope	

Withdrawal Periods

Based on the data provided above, withdrawal periods of 8 days for meat and offal and 0 hours for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

A TAS study was performed under GLP conditions and according to the VICH Guideline on Target Animal Safety (EMEA/CVMP/VICH/393388/2006 - VICH GL43). The product was well tolerated up to five times the intended therapeutic dosage and three times the maximum therapeutic duration in ruminating calves.

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

Resistance

Minimum Inhibitory Concentrations (MICs) have been determined for ceftiofur in European isolates of target bacteria, isolated from diseased animals between 2009 and 2012.

Species (number of isolates)	MIC range (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)
Mannheimia haemolytica (104)	0.002 - 0.06	0.015	0.03
Pasteurella multocida (172)	0.002 - 0.5	0.008	0.03

MICs of respiratory target pathogens showed mono-modal distribution profiles with good susceptibility towards ceftiofur. Clinical breakpoints (CLSI document Vet 01-S2) for ceftiofur are established for bovine respiratory disease and *M. haemolytica*, *P. multocida*: susceptible: ≤2 µg/ml; intermediate: 4 µg/ml; resistant: ≥8 µg/ml. According to these breakpoints no clinical resistant strains of respiratory target pathogens were observed.

IV.B Clinical Studies

The justification of the combination is based on:
- The fact that bovine respiratory disease (BRD) is very frequently associated with inflammation signs and hyperthermia.
- The benefit of the development of an association for which quality is warranted in comparison of association that may be seen on field sometimes in the same syringe without guaranty in terms of quality matters.
- The superiority of the combination above the antibiotic alone has been demonstrated in the treatment of BRD caused by *Mannheimia haemolytica* and *Pasteurella multocida.*

One laboratory trial (challenge model) and one field trial were provided to support the efficacy of CURACEF DUO for the treatment of bovine respiratory disease (BRD).

The laboratory study was a challenge model conducted according to the Good Laboratory Practices. This study showed that the same dose rate of the combined product and of the reference ketoprofen product, gives similar results in reducing hyperthermia and Thromboxanes B2 concentration.

The clinical field trial was GCP compliant, multicentered, controlled, randomised and blinded. The control product was a marketed ceftiofur HCl-based product already registered for the treatment of BRD (Excenel RTU). The dose rate was the same for both products (1 mL/50 kg at each injection) but the route of administration was different (intramuscular for CURACEF DUO and subcutaneous for Excenel RTU). The combined product was administered for one to 5 days with a switch to Excenel RTU when NSAID treatment was no longer needed. The control product (Excenel RTU) was administered for 3 to 5 days if required.
In this trial, CURACEF DUO was shown to be superior to Excenel RTU for the treatment of BRD caused by *Mannheimia haemolytica* and *Pasteurella multocida* since it showed a faster reduction in fever and a higher clinical success rate.

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.