ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Cefenil 50mg/ml Powder and Solvent for Solution for Injection for Cattle, Pigs and Horses
Applicant	Norbrook Laboratories Limited Station Works, Camlough Road Newry County Down BT35 6JP
Active substance(s)	Ceftiofur (as ceftiofur sodium)
ATC Vetcode	QJ01DD90
Target species	Cattle, pigs and horses
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 interdigitial 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 to ceftiofur are involved. Horses: Treatment of horses with bacterial respiratory disease in which *Streptococcus spp* including *Streptococcus zooepidermicus* and *Streptococcus equi., Staphylococcus spp* and/or *Pasteurella spp* are involved.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

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.

I. SCIENTIFIC OVERVIEW

This was a generic application submitted in accordance with Article 13(1) of Directive 2001/82/EC. The reference product for Cefenil 50mg/ml Powder and Solvent for Solution for Injection for Cattle, Pigs and Horses is Excenel Sterile Powder 1g and 4g which were originally authorised in the UK in 1991. The applicant claimed exemption from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products.

In cattle, Cefenil Powder and Solvent for Solution for Injection is intended for the treatment of acute bacterial respiratory disease in which *Mannheimia haemolytica, Pasteurella multocida* or *Histophilus somni* sensitive to ceftiofur are involved, as well as for the treatment of cattle with acute interdigitial necrobacillosis (foul in the foot) in which *Fusobacterium necrophorum* and *Bacteroides melaninogenicus* are involved. In pigs, the product is intended for the treatment of bacterial respiratory disease in which *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida* and/or *Streptococcus suis* sensitive to to ceftiofur are involved. In horses, the product is intended for the treatment of bacterial respiratory disease in which *Streptococcus spp* including *Streptococcus zooepidermicus* and *Streptococcus equi., Staphylococcus spp* and/or *Pasteurella spp* are involved.

The product is for intramuscular injection use only. It comes in a 1g vial and a 4g vial. The 1g vial should be reconstituted by adding 20ml of water for the injection and the 4g vial by adding 80ml of water for injection, resulting in 50 mg of ceftiofur per ml. In cattle the recommended dose rate is 1 mg/kg (equivalent to 1ml/50kg reconstituted product) to be administered in 24 hour intervals for 3-5 days for respiratory disease and 3 days for foul in the foot. In pigs the recommended dose rate is 3 mg/kg (equivalent to 1ml/16kg) at 24 hour intervals for 3 days. In horses the recommended dose rate is 2 mg/kg (equivalent to 2ml/50kg) at 24 hour intervals for up to 10 days (or 48 hours after clinical signs have disappeared). In pigs, an appropriately-graduated syringe must be used to allow accurate administration of the required dose volume (particularly when injecting piglets weighing less than 16 kg). For all species, do not administer more than 10 ml per injection site.

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 product is safe for the user and for the environment when used as recommended. Suitable warnings and precautions are indicated in the SPC[1].

II. QUALITY ASPECTS

A. Composition

Cefenil 50mg/ml Powder and Solvent for Solution for Injection contains 50mg of ceftiofur (as ceftiofur sodium). The excipients are potassium dihydrogen phosphate and sodium hydroxide, with water for injections as the solvent. The absence of preservative is justified.

The sterile powder for reconstitution comes in a clear glass vial with a bromobutyl stopper and aluminium seal with a cool green (1g) or yellow (4g) flip-off plastic disc. The solvent comes in a clear glass vial sealed with a bromobutyl stopper and aluminium cap. One vial of Cefenil Sterile Powder (1g or 4g) comes with one vial of water for injection (20ml or 80ml) in a carton, in packs of 1, 6 and 12 presentations.

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 two batches of the product have been presented in accordance with the relevant European guidelines.

Manufacturing formulae for varying batch sizes were provided. The water for injections is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines and consists of deionisation and UV treatment of potable water followed by sterilization through a sterile filter and terminal heat sterilization. Manufacture of Cefenil powder for reconstitution is a relatively simple process. The sterile bulk powder is transferred aseptically into a sterile container in a sterile environment before being aseptically filled into sterilised clear glass vials, and sealed with a sterile bromobutyl bung and aluminium seal. During the product preparation process the product is checked for appearance, water content, pH, ceftiofur content, bacterial endotoxins and fill weight.

[1] Summary of Product Characteristics.

C. Control of Starting Materials

The active substance is ceftiofur sodium, an established active substance, and is manufactured in accordance with the principles of good manufacturing practice. The active substance is manufactured in accordance with an Active Substance Master File (ASMF). The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches of the active substance and all results were satisfactory. All excipients comply with the European Pharmacopoeia.

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

A declaration has been provided stating that the finished product complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. 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 on 3 batches of the product from the proposed production site have been provided demonstrating compliance with the specification. Tests include those for appearance, ceftiofur content and uniformity of dosage units for the powder for reconstitution, appearance and fill volume for the solvent, and appearance, ceftiofur content, and related substances for the reconstituted product.

G. Stability

Stability data on 3 batches of the active substance have been provided in accordance with the applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A re-test period of 2 years is acceptable.

Stability data on 9 batches of the water for injections and 9 batches of the powder for reconstitution have been provided in accordance with applicable European guidelines, demonstrating the stability of the product when stored under the approved conditions. Tests include those for pH, ceftiofur content,

syringeability of the reconstituted solution, sterility and endotoxins. All results were satisfactory.

J. Other Information

The shelf life of the powder for reconstitution as packaged for sale is 3 years and the shelf life of the solvent (water for injections) as packaged for sale is 3 years. After reconstitution the product should be used within 24 hours. Any reconstituted product remaining after the stated periods should be discarded.

The unreconstituted powder and solvent, and the reconstituted product should be stored in a refrigerator (2°C - 8°C). The containers should be kept in the outer carton to protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines' for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of pharmacological and toxicological studies are not required.

III.A Safety Testing

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is safe for the user under normal conditions of use. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The following safety warnings are in place:

- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and *vice versa.* Allergic reactions to these substances may occasionally be serious.
- Do not handle this product if you are sensitised or if you have been advised not to work with such preparations.
- Handle this product with great care to avoid exposure, taking all recommended precautions.
- If you develop symptoms following exposure such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes of difficulty with breathing are more serious symptoms and require urgent medical attention.

- Wash hands after use.

Ecotoxicity

The applicant has 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 is not expected to pose a risk to the environment when used in accordance with the SPC. 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

As this is a generic application according to Article 13, on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines' for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of residues studies are not required.

Withdrawal Periods

The withdrawal periods for this product are identical to that of the reference product as follows:

Cattle: Meat and offal:1 day
Milk: zero hours

Pigs: Meat and offal: 2 days

The product is not for use in horses intended for human consumption and therefore the following warnings are proposed in the product literature:

- Not to be used in horses intended for human consumption.
- Treated horses may never slaughtered for human consumption.
- The horse must have been declared as not intended for human consumption under the national horse passport legislation.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines' for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Resistance

As this is a generic application according to Article 13, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of resistance studies are not required.

However, in order to minimise the risk of development of antimicrobial resistance, the applicant has included appropriate additional advice in section 4.5 (i) of the SPC 'Special precautions for use in animals' to facilitate prudent use of the product as prescribed in the CVMP[2] guidance document 'Revised guideline on the SPC for Antimicrobial Products' (EMEA/CVMP/SAGAM/383441/2005).

IV.B Clinical Studies

As this is a generic application according to Article 13, on the basis of essential similarity, the applicant is exempt from providing bioequivalence studies in accordance with exemption 4.b) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The product is qualitatively and quantitatively identical to the reference product, and therefore, the results of clinical studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

An additional suitable warning has been added to section 4.5 (i) of the SPC 'Special precautions for use in animals' in line with the recommended additional statements for all 3rd and 4th generation cephalosporins, as stated in the CVMP 'Revised reflection paper on the use of 3rd and 4th generation cephalosporins in food producing animals in the European Union: Development of resistance and impact on human and animal health:

- In the pig, particular care must be taken to avoid injection into the fat tissue. See section 4.9.

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.

[2] Committee for Medicinal Products for Veterinary Use.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)