ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Synuclav Suspension for Injection (UK)
Clavobay Suspension Injectable (FR)
Noroclav Suspension for Injection (PT)
Noroclav 175 mg Suspension for Injection (ES)
Noroclav Injection (BE, IT)
Combisyn Injection (IS)

PuAR correct as of 30/01/2019 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0200/001/E/001
Name, strength and pharmaceutical form	Synuclav Suspension for Injection
Applicant	Norbrook Laboratories Limited Station Works Newry Co. Down BT35 6JP Northern Ireland
Active substance(s)	Amoxicilin, clavulanic acid
ATC Vetcode	QJ01CR02
Target species	Cattle and Dogs
Indication for use	In Cattle: Treatment of respiratory infections due to *Pasteurella multocida* and *Mannheimia haemolytica*. In Dogs: Respiratory tract infections, urinary tract infections, skin and soft tissue infections (e.g. abscesses, pyoderma, anal sacculitis and gingivitis

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) (a) (iii) of Directive 2001/82/EC.
Date of completion of the original mutual recognition procedure	20th July 2004.
Date product first authorised in the Reference Member State (MRP only)	13th January 2003
Concerned Member States for original procedure	Belgium, France, Italy, Portugal, Spain.

I. SCIENTIFIC OVERVIEW

This was a generic application submitted under Article 13 (1) (a) (iii) of Directive 2001/82/EC. The reference product was Synulox Ready-To-Use Suspension for Injection, (previously Synulox Ready-To-Use Injection). The global reference product used for Safety and Efficacy studies was Noroclav Injection. Synuclav Suspension for Injection is a suspension containing 14.0% w/v amoxicillin as amoxicillin trihydrate and 3.5% w/v clavulanic acid as potassium clavulanate. The product maybe used in cattle and in dogs, for the following indications: cattle, treatment of respiratory infections due to *Pasteurella multocida* and *Mannheimia haemolytica*. In dogs, the product may be used for respiratory and urinary tract infections and soft tissue and skin infections. The recommended dosage via the intramuscular route for cattle and the subcutaneous route for dogs is 8.75 mg/kg bodyweight (7 mg/kg bodyweight amoxicillin and 1.75 mg/kg bodyweight clavulanic acid), equating to 1 ml/20 kg bodyweight, once daily for 3-5 days. In cattle, the maximum volume administered should not exceed 10 ml. This product underwent a Renewal procedure in 2009, a Repeat Use procedure in 2010, and a variation in 2011, in which dogs were added as an additional target species.

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.[1] The product is safe for the user, the consumer of foodstuffs from treated animals, (cattle only), 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 benefit/risk analysis is in

[1] SPC – Summary of Product Characteristics.

favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains amoxicillin and clavulanic acid and the excipients butylatedhydroxyanisole (E320) 0.08 mg, butylated hydroxytoluene (E321) 0.08 mg, and propylene glycol dicaprylate/dicaprate.

The container system consists of clear, colourless Type II glass vials of 50 ml and 100 ml, closed with nitryl bungs and aluminium caps. The particulars of the containers and controls performed are provided and conform to the regulation.
The absence of a preservative 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. A proportion of the excipients are dissolved in propylene glycol dicaprylate/dicaprate and the solution sterilised. The active substances are added and the batch made up to volume with remaining excipients. In-process checks are made as appropriate, and the product is then filled into vials.

C. Control of Starting Materials

The active substances are amoxicillin and clavulanic acid, established active substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice. Appropriate Certificates of Suitability were provided. All excipients apart from propylene glycol dicaprylate/dicaprate are monographed in the Ph. Eur, an in-house specification was drawn up for propylene glycol dicaprylate/dicaprate.

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

A Format 2 declaration covers the use of the starting material lactose for legitimate use in this product.

E. Control on intermediate products

There are no intermediate products.

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. Tests include those for appearance, resuspendability, identity and assay of active substances and impurities, particle size, sterility, syringeability, fill volume and relative density.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances and finished product when stored under the approved conditions. The stability data indicated that the product had a shelf-life as packaged for sale of 1 year, and once broached, vials should be used within 28 days.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life as packaged for sale: 1 year.
Do not store above 25^{o}C. Once vial has been broached the contents should be used within 28 days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

The product is qualitatively and quantitatively identical to the global reference product Noroclav Injection, and therefore, the results of pharmacological and toxicological studies are not required. However, relevant depletion studies were required to ensure bioequivalence with a reference product, as the product is delivered intramuscularly to cattle.

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.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product is suitable for use when used as directed on the SPC. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- 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 know you are sensitised, or if you have been advised not to work with such preparations.
- In case of contact with eyes, rinse immediately with plenty of water.
- 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 or difficulty with breathing are more serious symptoms and require urgent medical attention.
- Wash hands after use.

Ecotoxicity

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

Pharmacokinetic data were provided in order to demonstrate bioequivalence with the reference product. For cattle, this was submitted for the original application. A series of tissue residue depletion studies were also submitted in order to determine depletion of residues from the injection site. Post-mortem, levels of the active substances were measured via HPLC[2] No residue studies were submitted for milk, because as Synuclav Suspension for Injection was considered to be bioequivalent to the reference product, milk withdrawal data already obtained for Synulox Ready-To-Use Suspension for Injection was considered relevant for this product.

[2] HPLC – High performance liquid chromatography.

MRLs

Amoxicillin is entered into Annex I of Council Regulation (EEC) No. 2377/90 in accordance with the following table:-

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
AMOXICILLIN	Amoxicillin	All food producing species	50 µg/kg 50 µg/kg 50 µg/kg 50 µg/kg 4 µg/kg	Muscle Fat Liver Kidney Milk	

Clavulanic acid is entered into Annex II of Council Regulation (EEC) No. 2377/90 in accordance with the following table:-

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Clavulanic acid	Clavulanic acid	Bovine	100 µg/kg 100 µg/kg 200 µg/kg 400 µg/kg 200 µg/kg	Muscle Fat Liver Kidney Milk	
		Porcine	100 µg/kg 100 µg/kg 200 µg/kg 400 µg/kg	Muscle Fat Liver Kidney	

Withdrawal Periods

Based on the data provided, a withdrawal period of 42 days for meat and offal and 60 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 via a pharmacokinetic study, further efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

Pharmacology

Pharmacodynamics

Amoxicillin is a semi-synthetic penicillin having activity against a range of Gram-positive and Gram-negative bacteria. The mode of action is interference with peptidoglycan synthesis, compromising the formation of the bacterial cell wall. Clavulanic acid is similar to penicillin, having effect against some beta-lactamases produced by Gram-negative bacteria. In combination, clavulanic acid prevents the amoxicillin from breakdown by bacterial beta-lactamases, creating a broader spectrum of activity.

Pharmacokinetics

Literature reviews were used to provide evidence that the two active substances do not interfere with each other when given in conjunction. A bioequivalence study in cattle, carried out to Good Laboratory Practice (GLP) requirements was provided comparing the product with the reference product, Synulox Ready-To-Use Suspension for Injection. A suitable number of cattle were given either product or reference product at the recommended dose, via the recommended route of administration for 5 consecutive days, in a cross-over study with two treatment periods, with a washout period of 24 days.

Blood samples were taken at relevant time points, and results analysed via ANOVA[3] of C_{max}[4], T_{max}[5], AUMC[6] and t 0.5[7]. Relevant analysis of the data, including observations on t>MIC[8] established bioequivalence between product and reference product.

For the variation procedure utilised to include dogs as a new target species, the product was compared to Synulox Ready-To-Use Suspension for Injection. A suitable number of animals were given either the product or the reference product in a GLP-compliant cross-over study, with a 35 day wash-out period, using the products at the recommended dose and via the specified administration route. Blood samples were taken at relevant time points, and results analysed via ANOVA of C_{max}, and AUMC. Relevant analysis of the data established bioequivalence between product and reference product.

[3] ANOVA – Analysis of variance.

[4] C_{max} – Maximal plasma concentrations of the active substances.
[5] Tmax – Time at which maximum concentration of the active substances is reached.
[6] AUMC – Area under the concentration versus time curve.
[7] t 0.5 – Time for concentrations of the active substances to fall to half of the maximum.
[8] T>MIC – Time that the concentration of antibiotic remains above the minimum inhibitory concentration.

A further study analysed repeat dosing of dogs with the product or a placebo at the recommended dose, once a day over a six day period. On analysis of ANOVA, No significant adverse reactions were seen associated with use of the product.

Tolerance in the Target Species of Animals

Tolerance studies for cattle were carried out for the original application. Minor, local reactions were seen, appropriate information is cited in the SPC. A suitable number of cattle were also given Synuclav Suspension for Injection at the recommended dose rate for five days, no adverse reactions were seen. Relevant studies in the dog showed that the product was well-tolerated.

Laboratory Trials

As this was a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated via a pharmacokinetic study, clinical studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Field Trials

As this was a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated via a pharmacokinetic study, clinical studies are not required. The efficacy claims for this product are equivalent to those 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.

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)