ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Octacillin Water Soluble Powder for Chickens 697mg/g

PuAR correct as of 09/10/2018 when RMS was transferred to BE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0214/001
Name, strength and pharmaceutical form	Octacillin Water Soluble Powder for Chickens 697mg/g
Applicant	Eurovet Animal Health B.V. Handelsweg 25 5531 AE Bladel (PO BOX 179, 5530 AD Bladel) The Netherlands
Active substance	Amoxicillin Trihydrate
ATC Vetcode	QJ01CA04
Target species	Chickens (excluding laying birds)
Indication for use	For the treatment of primary infections in chickens and secondary infections, which arise following viral or mycoplasmal infection or following the use of some live viral vaccines. Amoxicillin is active against some Gram-negative and most Gram-positive bacteria. Not effective against beta-lactamase producing organisms.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (**WWW.HEVRA.ORG**).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Essential similarity application in accordance with Article 13.1.a.iii of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	21st December 2005
Date product first authorised in the Reference Member State (MRP only)	Not Applicable
Concerned Member States for original procedure	Belgium Czech Republic Greece Hungary Ireland Italy Poland Portugal Slovakia

I. SCIENTIFIC OVERVIEW

Octacillin Water Soluble Powder for Chickens 697 mg/g is a powder containing amoxicillin (in the form of amoxicillin trihydrate), which is intended to be dissolved in the drinking water and given to chickens suffering from infections caused by bacteria susceptible to amoxicillin. For ease of reading, the product will be referred to simply as "Octacillin" throughout this document.

Amoxicillin is an antibiotic of the penicillin family. Antibiotics in this family contain the chemical structure known as a beta-lactam ring and they work by inhibiting the synthesis of the cell walls of certain types of bacteria; without an intact cell wall the bacteria cannot survive. In order to affect cell wall synthesis, the antibiotic must first attach to it, and some bacteria have a cell wall that prevents this. Such bacteria are thus resistant to the effects of penicillin. Other bacteria may produce enzymes which destroy the beta-lactam ring of the antibiotic, and this too means that the antibiotic will not work.

The recommended dose of Octacillin is 10 – 20 mg of Octacillin per kilogram bodyweight.

The application for a Marketing Authorisation for Octacillin was made on the basis of its essential similarity[1] to the established product Amoxypen SP, first authorised in the UK in September 1992 and marketed by Intervet UK Ltd. For this type of application, applicants are exempted from the usual requirement to produce evidence of safety and efficacy, if they show that the composition of the product is essentially similar to, i.e. closely resembles, that of an established product, i.e. one authorised in the EU for more than 10 years.

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[2].
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 amoxicillin trihydrate 697 mg/g and the excipients sodium carbonate monohydrate, sodium citrate (dihydrate) and silica colloidal anhydrous.

The container/closure system are aluminium foil sachets which comply with the requirements of Directive 90/128EC, concerning articles intended to come into contact with foodstuffs, and the

[1] This means that the application was made under the provisions of Article 13.1.a.iii of Directive 2001/82/EC.
[2] Summary of Product Characteristics

control of heavy metals is in accordance with the requirements of Directive 94/62 for packaging articles.

The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The product is a powder which is administered in drinking water. Since amoxicillin trihydrate is only slightly soluble and has poor long-term stability in water, the product is formulated to improve solubility. This is achieved partly by using amoxicillin trihydrate with a small particle size and partly by the addition of sodium carbonate which makes the solution more alkaline and thus accelerates dissolution. Sodium citrate is also added to counteract the effects of hard water and it may also help dissolution. Colloidal anhydrous silica is included as a flow agent to minimise agglomeration of particles in the product, and to improve flow.

The product is supplied in aluminium sachets with a polyethylene lining and these may contain 100, 250, 500 or 1000 grams of the product. It is intended that the entire contents of a pack would be used at the same time and the pack sizes were designed to facilitate this by providing the correct amount of product to treat all the birds in a broiler house containing a given number of birds of a specific developmental stage.

In justifying essential similarity, the applicant has pointed to the comparability of the following characteristics of Octacillin with the established product: dissolution characteristics, appearance, pH of solution, amoxicillin content after 24 hours, and degradation.

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.

The product is manufactured in accordance with GMP[3]. The manufacturing process consists of sieving each ingredient to eliminate agglomerated particles, followed by mixing and filling of sachets. Data show that a homogeneous product of the expected potency is consistently produced.

The specification for the finished product controls appropriate parameters, including appearance, weight, loss on drying, amoxicillin content and microbiological quality. In addition, when made into a solution, checks are made of rate of dissolution, clarity of solution, colour and pH.

Data have been provided showing that a product can be produced that consistently meets this specification.

[3] GMP = Good Manufacturing Practice

C. Control of Starting Materials

The active substance is amoxicillin trihydrate, an established active substance described in the European Veterinary Pharmacopoeia. 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.

The company uses sources of amoxicillin trihydrate that have certificates of suitability. These certificates include requirements that are additional to the tests of the European Pharmacopoeia, and the company routinely tests all incoming batches of amoxicillin trihydrate for amoxicillin content and particle size.

The other ingredients all comply with the tests specified in the relevant monograph of the European Pharmacopoeia.

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 the results of 3 consecutive runs, conforming to the specifications, are provided.

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 sites have been provided demonstrating compliance with the specification.

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 have been provided on several batches of the active substance, including at least one from each source. These demonstrate adequate stability when the agreed retest intervals and checking regimes for each source are used.

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. Studies have been performed in which the stability of six batches of Octacillin was compared with the established product, Amoxypen SP. Samples of the Octacillin batches were stored in three of the approved pack sizes, including the smallest and largest, and were subjected to accelerated testing and to long-term testing under standard test conditions. The results justified a shelf-life of 24 months without special storage precautions, the degradation profile over this time being at least as good as that of the established product.

Stability of the product when dissolved in hard and soft water was demonstrated to be at least as good as the reference product.

Although the size of the sachets has been chosen with the intention that part sachets will not need to be used, data have also been submitted on the stability of the product when stored in a sachet that has been opened and the cut edge folded over and secured with a clip. These demonstrated that the powder is stable for 3 months under such conditions.

H. Conclusions on Quality

The data submitted by the company demonstrate that Octacillin is suitably formulated and quality-controlled. Data also show that it is essentially similar to the established product, Amoxypen SP. Shelf-lives have been justified as follows:

Product as supplied (no special storage requirements)	2 years
Product remaining in original packing after opening (subject to folding over the cut edge and securing with a clip)	3 months
Product dissolved in water	12 hours

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

The application was based on the essential similarity of Octacillin to the established product Amoxypen SP. The company demonstrated that the products were essentially similar by providing data comparing the physico-chemical characteristics of both products, including rate of dissolution and stability. This was considered satisfactory because solutions for administration by mouth are generally accepted as being essentially similar, provided the amount of the active ingredient is the same. Thus, if two powders containing the same amount of the same active ingredient dissolve at the same rate, they too can be considered essentially similar. The company therefore did not need to submit further information to demonstrate the safety of the product for humans or the environment.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that Octacillin and Amoxypen SP are essentially similar, and the user warnings that apply to Amoxypen SP are therefore also applicable to Octacillin. These warnings relate to the possibility that people handling the product may be allergic to amoxicillin. They are detailed in full in the SPC.

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

Consumer Safety

The withdrawal period[4] for Amoxypen SP is 24 hours. Under the rules for essentially similar products, the withdrawal period for Octacillin may not be less than the withdrawal period for Amoxypen SP. Therefore the approved withdrawal period for Octacillin must be 24 hours.

The product is not permitted for use in birds laying eggs for human consumption and no egg withdrawal period is therefore required.

Ecotoxicity

Since the application was made on the basis of essential similarity to an established product, it is exempt from the requirement for ecotoxicity testing because environmental safety aspects of the established product have already been considered. Disposal advice, as shown on the SPC, is the same for the two products.

Any unused product or waste material should be disposed of in accordance with national requirements.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

The application was based on the essential similarity of Octacillin to the established product Amoxypen SP. The company demonstrated that the products were essentially similar by providing data comparing the physico-chemical characteristics of both products, including rate of dissolution and stability. This was considered satisfactory because solutions for administration by mouth are generally accepted as being essentially similar, provided the amount of the active ingredient is the same. Thus, if two powders containing the same amount of the same active ingredient dissolve at the same rate, they too can be considered essentially

[4] The withdrawal period is the period between the time when drinking water containing Octacillin is no longer available to the birds and the time when the birds may be killed for human consumption.

similar. The company therefore did not need to submit further information to demonstrate the efficacy of the product or its safety for chickens.

The company demonstrated that Octacillin is essentially similar to the established product Amoxypen SP and the safety warnings and claims made are the same as those for the established product. Safety and efficacy in chickens are therefore considered to be satisfactory.

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 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.

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