

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0125/001/MR
Name, strength and pharmaceutical form	Maymoxi 10 premix (IT) Maymoxi 100 g/Kg premezcla (ES)
Applicant	Laboratorios Maymó, S.A. Vía Augusta, 302 08017 Barcelona España
Active substance(s)	Amoxicillin trihydrate
ATC Vet code	QJ01CA04
Target species	Porcine (weaned pigs)
Indication for use	Prevention and treatment of respiratory infections caused by <i>Streptococcus suis</i> sensible to amoxicillin in weaned piglets

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	Mutual Recognition application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 27/02/2008
Date product first authorised in the Reference Member State (MRP only)	29/05/2007
Concerned Member States for original procedure	IT

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 amoxicillin trihydrate (100 mg/g) as the active substance and excipients (calcium stearate and hydrogenated vegetal oil).

The container/closure system consists of a 25 kg multi-layer bag of kraft paper with inner bag of low-density polyethylene, sealed with a plastic clamp. The bag is sewn with double thread and a kraft paper strip. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

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. The flow chart of the manufacturing process has been included.

The manufacturing process consists of a standardized blend at 70°C of the components of the product.

Process validation data on 4 industrial batches of the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is amoxicillin trihydrate, an established active substance described in the current edition of the European Pharmacopoeia monograph 0260. 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 certificate of suitability No. R0-CEP 2001-123- Rev 01 has been included.

Calcium stearate complies with the European Pharmacopoeia monograph 0882. A copy of the R1-CEP 2001-040-Rev 00 has been attached.

Hydrogenated vegetable oil complies with the British Pharmacopoeia 2007.

Certificates of analysis have been presented for each excipient.

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

Calcium stearate complies the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products according to the declaration of the supplier.

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 substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions (Do not store above 25°C, protect from light and store in a dry place). A retest period of 2 years has been established.

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 (3 years) under no special storage conditions.

The claim of 6 months stability after first broaching is based on the demonstration of stability for 3 batches broached and stored 6 months at 25±2°C/60±5% RH. One month stability after incorporation into medicated feed has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Amoxicillin trihydrate is an antibiotic that belongs to the β -lactam group of the therapeutic class of the aminopenicillins. Its antimicrobial activity has been demonstrated towards a broad spectrum of bacteria. The bibliographic documentation and the experimental studies that describe *in vitro* sensitive concentration of amoxicillin for clinical isolated strains of *Streptococcus suis* are addressed in Section IV I.A.1 Pharmacodynamics of the pre-clinical documentation.

The applicant has also provided a comprehensive package of pharmacokinetic studies in the target specie which show that the amoxicillin absorption by oral administration is independent of food ingestion and the maximum plasmatic concentrations are achieved rapidly in most animal species. Amoxicillin shows a low binding to plasmatic proteins and is rapidly distributed to the main body liquids and tissues. The diffusion is extended to synovial and expectoration fluids and lymphatic tissue. The diffusion is more satisfactory in liquids resulting of an inflammatory process. Amoxicillin is distributed essentially in extracellular fluids of the body. Its distribution to tissues is favoured by the weak index of plasmatic protein binding. Amoxicillin is almost entirely eliminated by the kidney, in active form. Low amounts are excreted through milk and bile. Amoxicillin metabolism is limited to beta-lactam ring opening by hydrolysis, what leads to the delivery of inactive penicilloic acid (20%). Biotransformations take place in liver. In porcine, after the administration of 20 mg/kg bw/day, through feed, the maximum plasmatic concentration of amoxicillin reached is $2.8 \pm 0.2 \mu\text{g/ml}$ 2 hours later, followed by a falling phase of the concentration and a slower elimination phase with a half-life of $5.76 \pm 0.82 \text{ h}$.

Toxicological Studies

The applicant has provided bibliographical data which show that penicillins have a low toxicity in the normal sense of the word; the therapeutic index is more than 100, and toxic effects have only been observed after extremely high doses.

The applicant has submitted published papers of studies in rats, mice and humans. The toxicological conclusion was that amoxicillin modified the *in vitro* renal development at dose of 100 $\mu\text{g/ml}$. Young animals exposed to intrauterine penicillin showed benign oligonephronia; no ontogenic effects were observed in nephrons after the intrauterine exposure. In mice, a NOEL of 400 mg/kg was established based on the effects on the reabsorption number. Penicillins, as a group are considered safe in humans during gestation.

The penicillins group is regarded as being devoid of mutagenic and carcinogenic potential.

Other Studies

The applicant has provided bibliographical data in relation with the immunotoxic effects. In connection with therapeutic use of penicillins hypersensitivity reactions are by far the most commonly encountered side-effects. The bibliographic studies enclosed by the applicant demonstrated the skin hypersensitivity of amoxicillin, similar to other penicillins, which may vary from a simple urticaria to an anaphylactic shock. Other cases have also been described of neurophathy due to induced autoimmune reaction after direct application of antibiotic on brain surface or cerebral cisterns. These kind of adverse effects are not expected if amoxicillin is administered by oral route.

Observations in Humans

The applicant has provided bibliographical data which show that the most important adverse effects in humans are described as hypersensitivity reactions, gastrointestinal disturbances, interstitial nephritis, haematological disturbances, hypopotasemia, reversible increase of transaminases and encephalopathy.

There is no convincing evidence that any single penicillin differs from the group in its potential for causing true allergic reactions, i.e. all penicillins are assumed to be cross-sensitizing and cross-reacting. The incidence of allergic reactions in connection with penicillin therapy varies from 0.7% to 10% in different studies. The major adverse effects of penicillins are acute anaphylaxis and collapse. Their incidence is thought to be 0.015 to 0.04% in humans treated with penicillin. Milder hypersensitivity reactions (urticaria, fever, angioneurotic edema) are more common. The overall prevalence of penicillin allergy in humans has been estimated to be between 3% and 10%.

Microbiological Studies

The applicant has provided data of MIC distribution values and resistance level for isolates from pigs of slaughterhouse of intestinal zoonotic bacteria and commensal indicator bacteria in order to assess the effect of resistance on public health. A decreasing evolution in amoxicillin resistance level has been observed through the studied period, reaching the 30% in the case of *Salmonella enterica*.

Excipients are commonly used in oral veterinary pharmaceuticals

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product should not be handled by people with hypersensitivity to penicillins and/or cephalosporin.

In the light of the knowledge of the molecule, hypersensitivity reactions are undoubtedly the most serious risk for the user. Skin sensitisation and inhalation toxicity may occur due to dermal hypersensitivity (Type IV) and hypersensitivity Type I for

penicillin respectively. In addition, cross-hypersensitivity have been observed with other penicillins and sometimes also with cephalosporins.

Exposure to amoxicillin from the product is possible by skin contact, inhalation during incorporation into feed or deliberate ingestion. For these cases, the following safety measures are recommended: a dustproof mask, gloves, overalls and safety glasses should be worn and contact with the skin and eyes avoided. Advice has been included regarding accidental skin or eye contact. General warnings, do not smoke, eat or drink while handling the product, have also been agreed.

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 PEC in soil was calculated by applying Spaepen's formula when the degradation half-life in excreta (DT_{50E}) is available and the value obtained is much lower than 100 µg/kg. The assessment concluded that there is no need to carry out studies on environmental effects. No warnings regarding amoxicillin are therefore required.

The SPC contains a standard phrase in section 6.6 as required.

III.B Residues documentation

Residue Studies

Residue depletion study using the final formulation has been conducted in pigs. Samples of tissues were taken from animals at several time points. Results show that residues depleted to below the MRL, in all tissues, before the end of the withdrawal period. Based on the result of the residue depletion study, the longest calculated withdrawal period is 8 days (by statistical approach). This withdrawal period is based on depletion from kidney and skin+fat.

The analytical method was HPLC with fluorescence detection. The method was fully validated.

MRLs

Currently, amoxicillin is included in Annex I of Council Regulation (EEC) No 2377/90 by the Regulation 675/1992. The marker substance is amoxicillin.

MRLs are listed below:

	all food producing species
Muscle	50 µg/kg
Liver	50 µg/kg

Kidney	50 µg/kg
Fat / skin	50 µg/kg
Milk	4 µg/kg

Withdrawal Periods

Based on the data provided above, a withdrawal period of 8 days for meat in pigs is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

A large amount of data has been presented to support the pre-clinical and clinical aspects of this application. Antibacterial activity is supported by different bibliographic studies those revise the activity of the amoxicillin against different microorganisms. Furthermore, the applicant carries out a study in order to assess the degree of sensitivity of different strains of *S.suis*. and *H. parasuis*. The study was performed with 60 swine isolates belonging to the *S. suis* (30) species and *H. parasuis* (30). All strains were isolated in Spain from pigs. The method used and the break points were adequate, based on the NCCLS recommendations. In the case of *S. suis*, the corresponding MIC₅₀ value was $\leq 0.03 \mu\text{g/ml}$ and the MIC₉₀ was $0.06 \mu\text{g/ml}$. According to the sensitivity criteria established by the NCCLS for species of streptococci other than *Streptococcus pneumoniae*, an isolate is regarded as resistant when its MIC is the same as or higher than $8 \mu\text{g/ml}$ so all the isolates analysed in this study are susceptible to amoxicillin.

In the case of *H. parasuis* the corresponding MIC₅₀ value was $0.06 \mu\text{g/ml}$ and MIC₉₀ was $0.5 \mu\text{g/ml}$. For this bacterial species does not exist a break point established; therefore to evaluate an isolate susceptibility/resistance, the NCCLS values assigned to *H. influenzae* have to be used. Following this interpretation criteria most of the *H. parasuis* isolates studied are sensible to amoxicillin (MIC below $8 \mu\text{g/ml}$).

In order to reveal the pharmacokinetic of Maymoxi 10 Premix, the applicant submitted a study that provide information about the pharmacokinetics of the medicinal product Amoxicillin 10% Premix Maymó in swine following the administration of a single dose of amoxicillin of 20 mg/kg b.w. by the intravenous and oral route, and following a multiple oral dose of 20 mg/kg b.w./day in feed for 15 days.

Tolerance in the Target Species of Animals

One study is carried out to assess the safety of the product. The design of the target animal safety study was appropriate to examine the tolerance of the product at elevated dose. The selected parameters used to analyse the tolerance (blood analyses, zootechnical parameters and external pathological signs) and the data analysis were adequate to identify amoxicillin specific effects in the target animals. The different results of the parameters defined for the analysis were assessed and, in summary, no clinical symptomatology associated to one or the other treatment is observed. Tolerance to the product has been shown good

Resistance

According to the sensitivity criteria established by the NCCLS for species of streptococci other than *Streptococcus pneumoniae*, an isolate is regarded as resistant when its MIC is the same as or higher than $8 \mu\text{g/ml}$ so all the isolates analysed in this study are susceptible to amoxicillin.

In the case of *H. parasuis* the corresponding MIC₅₀ value was $0.06 \mu\text{g/ml}$ and MIC₉₀ was $0.5 \mu\text{g/ml}$. For this bacterial species does not exist a break point established; therefore to evaluate an isolate susceptibility/resistance, the NCCLS values assigned to *H. influenzae* have to be used. Following this interpretation criteria most of the *H. parasuis* isolates studied are sensible to amoxicillin (MIC below $8 \mu\text{g/ml}$).

IV.B Clinical Studies

Field Trials

The efficacy of the product has been supported by bibliography references and a clinical trial carried out in Spain with the product. The design of the study is considered suitable for the efficacy assessment of the test product at the recommended dose. The product intended for marketing was administered by oral route in feed. The monitored parameters were the first-order parameter (rectal temperature, dyspnoea, cough, depression, nervous signs nasal mucosity) and the second-order (bacteriological healing, mortality, body weight, feed intake) . Numerical scores of 0 to 1 (0 = Absence and 1 = Presence) were used to describe each of the clinical parameters.

The statistical method was an unilateral comparison between two treatment (experimental and control groups) for checking the non-inferiority of the experimental product; the principal variable was treatment success [provided by the first-order variables (rectal temperature, dyspnoea, cough, depression, mucosity)] The results confirm the non-inferiority of the experimental product in relation to control.

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).