IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Huvamox

PRODUCT SUMMARY

EU Procedure number	IE/V/0642/001/DC
Name, strength and pharmaceutical form	Huvamox
Active substances(s)	Amoxicillin trihydrate
Applicant	HUVEPHARMA SA 34 RUE JEAN MONNET ZI D'ETRICHE SEGRE 49500 SEGRE-EN-ANJOU BLEU France
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Date of Authorisation	10/02/2021
Target species	Chickens, Ducks, Pigs, Turkeys
Indication for use	In chickens, turkeys and ducks: Treatment of infections caused by bacteria susceptible to amoxicillin. In pigs: For the treatment of pasteurellosis caused by Pasteurella multocida susceptible to amoxicillin.
ATCvet code	QJ01CA04
Concerned Member States	AT, BE, BG, HR, CY, CZ, DK, EE, FR, DE, EL, HU, IT, LV, LT, NL, PL, PT, RO, SK, SI, ES, UK(NI)

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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 reactions likely to be 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains the active substance amoxicillin 697 mg/g (as amoxicillin trihydrate 800 mg/g), and the excipients sodium carbonate, sodium citrate and silica colloidal hydrated.

The product is packaged in 100 g jars closed with a polypropylene screw cap, 100 g thermo-sealed bags, 500 g bags with a zipped closure, or 1 kg bags with a zipped closure.
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 at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance amoxicillin trihydrate is an established substance described in the European 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 has been provided.
Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on Intermediate Products

Not applicable.

E. 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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance has been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a hybrid application according to paragraph 3 of Article 13 of Directive 2001/82/EC and bioequivalence with a reference product has been demonstrated, results of safety and residue tests are not required.
The safety aspects of this product are the same as the reference product.
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.

III.A Safety Testing

Pharmacological Studies
Bioequivalence between the candidate formulation and the reference formulation was accepted in accordance with section 7.1.c of the CVMP Guideline for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.3).

Toxicological Studies
Given that bioequivalence with the reference product has been accepted, toxicological data was not required.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the product will not present an unacceptable risk for the user when handled, used, stored and disposed of in accordance with the recommendations included in the proposed SPC.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I
A Phase II ERA is required as the Phase I assessment showed that PEC soil intial values exceeded the trigger value of 100 µ/kg.
Phase II
A Phase II Tier A and B assessment was conducted. All laboratory studies were conducted in accordance with GLP and relevant OECD guidelines.

Physico-chemical properties of amoxicillin (AMOX) and amoxicillin penicilloic acid (APA)	
Study type	**Result**
Vapour pressure	AMOX: 6.24 x 10^{-15} Pa; APA: <6.4 x 10^{-4} Pa
Water solubility	AMOX: 3.43 g/l^{-1}; APA: 70.92 g/l^{-1}
Dissociation constants in water pKa	pKa = 2.64 (APA)
n-Octanol/Water Partition Coefficient logP_{ow}	logK_{ow} = 0.87 (AMOX);

Environmental fate	
Soil Adsorption/Desorption	Koc = 45.6 (AMOX) K_d = Not calculated as equilibrium not reached.
Transformation in Manure (species)	DT_{50} = 4.47 days in poultry litter and 134.3 days in pig slurry (APA).

Effect studies based on of amoxicillin (AMOX)			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *cyanobacteria Anabaena flos-aquae*	EC50	24.5 (APA)	mg/l
Daphnia sp. immobilisation	EC50	>94.61 (APA)	mg/l
Fish, acute toxicity/ *Danio rerio* (zebrafish).	LC50	>94.61 (APA)	mg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25% (AMOX)	
Terrestrial Plants, growth test	EC50	30 (AMOX)	mg/kg
Terrestrial Plants, growth test (Tier B)	NOEC	15 (AMOX)	mg/kg
Earthworm/*Eisenia andrei* reproduction	NOEC	240 (AMOX)	mg/kg

Risk characterisation
The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.
Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.
The risk characterisation resulted in risk quotients below 1 for the surface water, groundwater, soil and dung compartments indicating that the product will not pose a risk to those compartments when used as recommended.

PBT Assessment

An assessment of the compound in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.
The maximum log Kow of amoxicillin was demonstrated to be 1.347.
The compound is not considered to be either PBT or vPvB.

Conclusion
Based on the data provided, the product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies
Given that bioequivalence with the reference product has been accepted and given the route of administration (in drinking water), the omission of residue studies was accepted.

MRLs
Amoxicillin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

	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
As bioequivalence with the reference product was accepted and given the route of administration (in drinking water) and the fact that the candidate formulation was demonstrated to be rapidly dissolved in physiologically-relevant volumes and pH conditions across a physiologically-relevant pH range and therefore the excipients are unlikely to affect the rate of gastric transit of, or gastrointestinal permeability to amoxicillin trihydrate, the same withdrawal periods approved for the reference product were applied, namely, 1 day for meat & offal in chickens, 9 days for meat & offal in ducks, 5 days for meat & offal in turkeys and 2 days for meat & offal in pigs.
The product is not for use in laying birds producing eggs for human consumption.

IV. CLINICAL ASSESSMENT

IV. CLINICAL ASSESSMENT (EFFICACY)
As this is a hybrid application according to paragraph 3 of Article 13 and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals
As this is a hybrid application according to paragraph 3 of Article 13 and bioequivalence with a reference product has been demonstrated, target animal tolerance studies are not required. The efficacy claims for this product are equivalent to those of the reference product.
However, according to section 9 of the CVMP 'Guideline on the demonstration of palatability of veterinary medicinal products' (EMA/CVMP/EWP/206024/2011):
"For generic products for which no clinical efficacy and safety data is required, data on medicated feed or water uptake are necessary to demonstrate adequate consumption.
Palatability studies were conducted in pigs and chickens and which confirmed an acceptable level of uptake of the active substance.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
The concentration of amoxicillin trihydrate following dilution in drinking water (or in liquid feed for pigs) will be the same for both the candidate and reference product formulations; that is, the target species will be exposed to the same amount of amoxicillin trihydrate for the same duration irrespective of whether the candidate or reference products are used.

It was therefore accepted that use of the candidate formulation will not present any greater risk for the development of antimicrobial resistance than that which already exists for the reference product.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

As this is a hybrid application according to paragraph 3 of Article 13 and bioequivalence with a reference product has been demonstrated, 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.