FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tudomax 10 mg/g powder for use in drinking water/milk

N° FR/V/0295/001/DC

Date: January 2017

French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0295/001/DC
Name, strength and pharmaceutical form	Tudomax 10 mg/g powder for use in drinking water/milk
Applicant	SP VETERINARIA SA Ctra Reus Vinyols km 4.1 Riudoms (43330) Spain
Active substance(s)	Bromhexine
ATC Vetcode	QR05CB02.
Target species	Cattle (Calves), pigs, chickens, turkeys and ducks.
Indication for use	Mucolytic treatment of congested respiratory tract.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	21/12/2016
Concerned Member States for original procedure	BG, CY, EL, ES, HU, IE, IT, MT, PL, PT, RO, UK

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 10 mg/g bromhexine (as bromhexine hydrochloride) and excipients citric acid anhydrous, silica, colloidal anhydrous and lactose monohydrate.

The containers are bags. The particulars of the containers and controls performed are provided and conform to the regulation.

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.

C. Control of Starting Materials

The active substance is bromhexine hydrochloride, 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 have been provided.

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

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

Re-test periods for the active substance is set in the certificates of suitability issued by EDQM.
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.
An in-use shelf-life after first opening and an in-use shelf-life after dilution as detailed on the SPC have been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The application is submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application). The reference product, QUENTAN POUDRE, oral powder, marketed by BOEHRINGER INGELHEIM, has been registered in France for more than 10 years.
No *in vivo* bioequivalence studies in calves, pig, poultry, dogs and cats are provided.

The applicant performed a dissolution study showing comparable dissolution profiles between the test and the reference products, and the very quick dissolution of the powder in water and milk.
The test and the reference product are considered bioequivalent accordingly to exemption 7.1.c) of the guideline EMEA/CVMP/016/00-rev 2. “Guideline on conduct of bioequivalence studies for veterinary medicinal products ».

As this is a hybrid application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

The pharmacological aspects of this product are identical to the reference product.

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, results of toxicological tests are not required.

The toxicological aspects of this product are identical to the reference product.

User Safety

The applicant has provided a user safety assessment.
Main route of exposures are dermal contact and inhalation
The total calculated dermal exposure is 2.86 mg/kg/day and the total calculated inhalatory exposure is 0.0442 mg/kg/day.
The MOE (margin of exposure) for both exposures are lower than 1. Therefore, protective measures are applied to diminish exposure risks.

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

- This product may cause hypersensitivity reactions (allergy). People with known hypersensitivity to bromhexine or lactose should avoid contact with the product.
- During preparation and administration inhalation of dust particles should be avoided. Wear an appropriate dust mask (either a disposable half-mask respirator conforming to European Standard EN149) or a non-disposable respirator to European Standard EN 140 with a filter to EN 143), when handling the product. If respiratory symptoms develop following exposure, seek medical advice and show this warning to the physician.
- This product may cause irritation to the skin, eyes and mucous membranes. Avoid direct contact with the product. Wear gloves and protective glasses during the use of the product.

Wash hands and any exposed skin after use. If accidental contact occurs, rinse the affected area with large amounts of clean water.

- Do not eat, drink or smoke while handling this 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 as all calculated PECsoil are below the trigger threshold of 100 µg/kg.

III.B Residues documentation

Residue Studies

No depletion study was performed with the tested product.

MRLs

a. active substances

The active substance, bromhexine, is included in table 1 of the MRL regulation 37/2010, as follows,

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Not applicable	Bovine, porcine, poultry	No MRL required	Not applicable	Nor for use in animals from which milk or eggs are produced for human consumption	No entry	37/2010 of 22.12.2009

An acceptable toxicological daily intake (ADI) of 300 µg/kg bw (i.e. 18 mg/person) was defined for bromhexine.

b. excipients

The MRL status of excipients of the product TUDOMAX,10 mg/g, powder for use in drinking water/milk is indicated in the following table.

Excipient	MRL status
Citric acid anhydrous E330	Table 1, no MRL required
Lactose monohydrate	Out of scope
Silica, colloidal anhydrous	Food additives (substance with a valid E number approved as additives in foodstuffs for human consumption)

Withdrawal Periods

Given the legal basis of the application, Article 13(3) of Directive 2001/82/EC, as amended (a hybrid application) and the fact that the test and the reference product are bioequivalent and administered orally at the same dosage regimen, it is accepted that no depletion data is provided.

After discussion between the reference and the concerned member states on the data available for the reference product, the following withdrawal periods have been decided:

Cattle (calves)
Meat and offal: 2 days
Not permitted for use in cows producing milk for human consumption.

Pigs
Meat and offal: Zero days.

Chickens, turkeys and ducks
Meat and offal: Zero days

Do not use in birds producing eggs for consumption, during and 4 weeks before the laying phase.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

No tolerance studies have been conducted with the product. The product does not contain the same concentration of the active substance as the reference product. However, the safety profile of the test product for calves, pigs and poultry is expected to be similar to that of the reference product because posology and indications as listed on the product literature are identical to the reference product. Furthermore, the excipients are well known and commonly used in many medicinal products and show a very low toxicity potential, excepted in the case of lactose intolerance**.**

The product is indicated for the same claims, at the same dosages and via the same route of administration as the reference product.

The text of sections 4.6 and 4.10 of the SPC are in line with the text in the authorised SPC of the reference product.

IV.B Clinical Studies

As this is a hybrid application according to Article 13, bioequivalence with a reference product has been demonstrated, and because posology and indications as listed on the product literature are identical to the ones of the reference product, efficacy studies are not required. The efficacy claims of the tested product are based on the reference product documentation.

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.