FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Exflow 10 mg/g powder for use in drinking water for cattle (calves), pigs, chickens, turkeys and ducks

N° FR/V/0285/001/DC

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

Date: 20/08/2015

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/0285/001/DC
Name, strength and pharmaceutical form	Exflow 10 mg/g powder for use in drinking water for cattle (calves), pigs, chickens, turkeys and ducks
Applicant	CEVA SANTE ANIMALE 10 AVENUE DE LA BALLASTIERE 33500 LIBOURNE
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.

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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	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	22/07/2015
Concerned Member States for original procedure	AT - BE - BG - CZ - DE - DK - ES - HU - IT - NL - PL - PT - RO - SK – 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 9.11 mg/g bromhexine (as bromhexine hydrochloride) and excipients citric acid anhydrous and lactose monohydrate.

The

containers are bags or jars. 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(1) of Directive 2001/82/EC, as amended (a generic application). The reference product is QUENTAN POUDRE, oral powder, marketed by BOEHRINGER INGELHEIM.
No *in vivo* bioequivalence studies in calves, pig and poultry are provided.

According to Guideline EMA/CVMP/016/00-Rev-2, section 7.1.c), if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved reference veterinary medicinal product presented as an aqueous oral solution at the time of administration, bioequivalence studies may be waived if the excipient contained in it do not affect gastro-intestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), solubility (e.g. co-solvents) or in-vivo stability of the active substance. Any differences in the amount of excipients should be justified by reference to other data.
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. The product can therefore be considered as an aqueous oral solution at the time of administration.
The excipients contained in the formulation, citric acid and lactose monohydrate, are not expected to affect neither the gastro-intestinal transit at their concentrations in the solution, nor the absorption of the active ingredient.
The tested product can be considered as bioequivalent to the reference product.

As this is a generic 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.

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.

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 daily intake (ADI) was defined for bromhexine. It is 300 µg/kg bw (i.e. 18 mg/person)

b. excipients

The MRL

status of excipients of the product EXFLOW 10 MG/G ORAL POWDER FOR CALVES, PIGS AND POULTRY is indicated in the following table.

Excipient	MRL status
Citric acid anhydrous E330	Table 1, no MRL required
Lactose monohydrate	Out of scope

Withdrawal Periods

Given the legal basis of the application, Article 13(1) of Directive 2001/82/EC, as amended (a generic 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 safety profile of the test product for calves, pigs and poultry is expected to be similar to that of the reference product because the concentration of the active substance bromhexine hydrochloride is identical, all 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 text of

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

IV.B Clinical Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, 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.