Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Butox Protect 7.5 mg/ml pour-on suspension

Date: 28 June 2010

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0134/001/DC
Name, strength and pharmaceutical form	Butox Protect 7.5 mg/ml pour-on suspension
Applicant	Intervet Deutschland GmbH Feldstr. 1a 85716 Unterschleißheim
Active substance(s)	Deltamethrin
ATC Vetcode	QP53AC11
Target species	Cattle, sheep
Indication for use	Cattle: For the treatment and prevention of infestations with the following ectoparasites: - sucking lice (*Linognathus vituli, Haematopinus eurysternus*) - biting lice (*Bovicola bovis*) For the control of: - stinging flies (*Stomoxys calcitrans, Haematobia spp.*) as well as nuisance flies (*Musca spp., Hippobosca spp.*) Sheep: For the treatment and prevention of infestations with the following ectoparasites: - sucking lice (*Linognathus ovillus*) - biting lice (*Bovicola ovis*) - sheep keds (*Melophagus ovinus*)

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	24.02.2010
Date product first authorised in the Reference Member State (MRP only)	N.A.
Concerned Member States for original procedure	AT, BE, BG, CY, DK, EE, EL, FI, LT, LU, LV, NL, SE, SI

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.
The safety and efficacy aspects of this product are identical to the reference product Butox 7,5 mg/ml pour on. The 10-year protection period has elapsed since the reference product has been authorised in Ireland on 1 October 1989.
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 overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The pour-on suspension contains the active substance deltamethrin in a concentration of 7.5 mg/ml. The suspension contains the following excipients: formaldehyde solution 35% (as preservative), sodium laurylsulphate, precipitated

silica, xanthan gum, citric acid monohydrate, propylene glycol, Rhodorsil 416, Rhodorsil 426R, Dispersogen SI and purified water.

The suspension is on the market in different pack sizes. The 250 ml and 1000 ml polyethylene bottles include an integrated dosing chamber and a screw-on applicator. The 2500 ml polyethylene bottle is delivered with an applicator gun and a connection kit. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and presence of preservative are 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.

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

C. Control of Starting Materials

The active substance deltamethrin is an established active substance described in the British Veterinary Pharmacopoeia. Micronised deltamethrin is used for the manufacturing of the finished product. Supporting data have been provided in the form of an Active Substance Master File (ASMF). 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

There are no intermediate products.

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.

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.

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.

The claimed 30 week shelf-life after first opening the bottle has been proved.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13 (1), and Butox Protect 7.5 mg/ml pour on suspension and the reference product are identical, results of pharmacological and toxicological tests and data on bioequivalence are not required. The safety aspects of this product are identical to the reference product.

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

Observations in Humans

The applicant has provided information on six cases of adverse drug reactions in humans after accidental topical exposure including exposure via contaminated

clothes reported as local skin reactions (burning, eczema), allergic reactions (urticaria, face swelling, pruritus and burning of face) and systemic reactions (emesis, nausea, loss of weight, lethargy). A user exposed to Butox Protect 7.5 mg/ml pour on suspension via a small skin lesion showed symptoms of photosensitivity, anorexia, emesis, headache and ataxia and had to get intensive care.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that skin contact is the predominant exposure route to the product.
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 further assessment was required. No risk has been identified for the aquatic compartment (surface water, ground water) as well as for the sediment. A risk of secondary poisoning could also be excluded. For the terrestrial compartment no risk has been identified for earthworm. However, deltamethrin is very toxic to dung insects. Based on the data provided, long term effects caused by continuous or repeated use could not be excluded. Warnings regarding toxicity of deltamethrin on dung insects are therefore required.

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

III.B Residues documentation

Residue Studies

The applicant has conducted residue depletion studies in cattle and sheep. In the bovine study, deltamethrin was not detectable in muscle and liver in any test animal at any time point. Kidney residues exceeded the maximum residue limit (MRL) in one sample after five days only. Residues in fat were below the MRL in all test animals after 15 days of withdrawal. Statistical analysis of residue data resulted in a withdrawal period of 18 days. In the ovine study, the marker residue was not detectable in muscle and liver of all animals at any time point. In fat and kidneys, residues were occasionally detected, but remained below the limit of quantification.

The elimination of deltamethrin via milk was investigated in dairy cows at doses higher than recommended (worst case scenario). Levels of deltamethrin were below the limit of quantification in all samples at all time points and the withdrawal time for bovine milk was set to zero days. Residue depletion studies using the final formulation have also been conducted in ovine milk. Samples of milk were taken

from animals at several time points prior and after treatment. No residues were detectable in any sample at any time point. The withdrawal period for ovine milk was set to 12 hours.

The analytical method based on gas chromatography coupled with mass spectrometric detection. The method was fully validated. The limits of quantification for deltamethrin were 5 µg/kg in muscle, liver, and kidney, 25 µg/kg in fat, and 10 µg/kg in milk i. e. ½ MRL in the resp. tissues and milk.

MRLs

Deltamethrin is listed in Annex I of Commission Regulation (EU) No 37/2010 of 22 December 2009. The marker substance is deltamethrin.

MRLs are listed below:

	Cattle	Sheep
Muscle	10 µg/kg	10 µg/kg
Liver	10 µg/kg	10 µg/kg
Kidney	10 µg/kg	10 µg/kg
Fat	50 µg/kg	50 µg/kg
Milk	20 µg/kg	20 µg/kg

Withdrawal Periods

Based on the data provided above, withdrawal periods of 18 days for meat in cattle, one day for meat in sheep, zero hours for bovine milk and 12 hours for ovine milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13 (1), and Butox Protect 7.5 mg/ml pour on suspension and the reference product are identical, target animal tolerance studies are not required.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The information provided suggests that resistance to deltamethrin in stinging and nuisance flies in cattle and lice in sheep may occur.

Updated warnings and adequate precautions appear on the product literature.

IV.B Clinical Studies

As this is a generic application according to Article 13 (1), and Butox Protect 7.5 mg/ml pour on suspension and the reference product are identical, efficacy 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 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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section 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.

<None>