FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
La Haute Marche
Javené BP 90203
35302 FOUGERES cedex
FRANCE

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CYDECTIN TRICLAMOX 5 mg/ml + 200 mg/ml POUR ON SOLUTION FOR CATTLE

Date: 29/02/2012

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/0201/002/DC
Name, strength and pharmaceutical form	CYDECTIN TRICLAMOX 5 mg/ml + 200 mg/ml POUR ON SOLUTION FOR CATTLE
Applicant	PFIZER 23-25 Avenue du Docteur Lannelongue 75668 PARIS CEDEX 14 - FRANCE
Active substance(s)	Moxidectin Triclabendazole
ATC Vetcode	QP54AB52, moxidectin combination
Target species	Cattle
Indication for use	Treatment of mixed trematode (fluke) and nematode infections caused by moxidectin and triclabendazole sensitive strains of: Trematodes: *Fasciola hepatica* (adult and 6-8 week immatures) Gastrointestinal roundworms (adults and fourth stage larvae): *Ostertagia ostertagi (including inhibited stages)*, *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia* oncophora, *Nematodirus helvetianus* Gastrointestinal roundworms (adults): *Cooperia punctata, Oesophagostomum radiatum, Bunostomum phlebotomum* Lungworms (adult): *Dictyocaulus viviparus*

MODULE 2

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	"Fixed Combination" Application submitted in accordance with Article 12 (b) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	15/12/2011
Concerned Member States for original procedure	AT – BE – DE – DK – EL – ES – FI – IE – IT – LU – NL – PT – SI - 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 5 mg/ml moxidectin and 200 mg/ml triclabendazole and the following excipients: butylhydroxytoluene, gamma-hexalactone, cineole, caprylocaproyl macroglycerides.

The container/closure system is HDPE bottle (500 mL, 1L, 2.5L or 5 l) closed with polypropylene caps. 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 substances are moxidectin and triclabendazole, established active substances. Moxidectin is

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described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substances specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with these specifications 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 (pharmaceuticals)

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 substances 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.
An in-use shelf-life as detailed on the SPC has 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 applicant has briefly described the mode of action of the two active ingredients. This documentation is sufficient as the product is a novel formulation of

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moxidectin and triclabendazole, which are known substances.

A pharmacokinetic study of moxidectin and triclabendazole was realised in cattle to compare the plasma profiles of moxidectin and triclabendazole when administered alone or in combination with the same vehicle as for the final formulation. The two products were also administered intravenously in order to determine the bioavailability. The results showed no pharmacokinetic interaction between the two active ingredients and gave a justification for the dosage of moxidectin (which is the same as in the monovalent product).

The main pharmacokinetic parameters of moxidectin when administered as pour-on in the final combined formulation of this product were the followings: AUClast: 50.9 ng.d.mL-1, Cmax: 4.69 ng.mL-1, Tmax: 8.7 d, MRT: 10.74 d.

The main pharmacokinetic parameters of triclabendazole sulfoxide when administered in the final combined formulation of this product were: AUClast: 26.9 µg.h.mL-1, Cmax: 2.92 µg.mL-1, Tmax: 3.3 d, MRT: 9.72 d. The main pharmacokinetic parameters of triclabendazole sulfone when administered in the final combined formulation were: AUClast: 110.2 µg.h.mL-1, Cmax: 7.78 µg. mL-1, Tmax: 12.9 d, MRT: 12.98 d.

Toxicological Studies

Moxidectin and triclabendazole are already authorised for several species in several European countries and these actives have been examined under MRL regulation (Table 1). Toxicity studies were reviewed and summary reports for the substances were adopted.
In addition to the MRL data, the applicant provided further studies with the final formulation.

The formulation contains the following excipients: butylated hydroxytoluen, eucalyptol, γ-Hexalactone and caprylocaproyl macrogolglycerides. The two first excipients of this formulation are included in table 1 (no MRL required) of MRL Regulation. The two last have no MRL status, however, available toxicological data enable to conclude that no toxicity is awaited neither for the users of the product nor for the consumers.

Observations in Humans

Moxidectin is not used in human therapeutic. However a study evaluating the safety, tolerability and pharmacokinetic of a single oral dose of moxidectin in healthy male volunteers was presented. Moxidectin was administered at 3, 9, 18 and 36 mg in cohorts of 6 subjects each. Safety assessment from all the cohorts showed that moxidectin was safe and well tolerated, although a slightly higher incidence of transient, mild and moderate central nervous system adverse reactions compared to the placebo was observed as the increased doses (18 and 36 mg).

Triclabendazole has been used in clinical trials for the treatment of parasitic infections in humans. Single and double oral doses of 10 mg/kg were well tolerated. Transient epigastric pain was attributed to the death of the parasites (see MRL report).

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline. Ways of exposure for the user are likely to be via the oral, dermal and ocular routes. Potential hazards from the two active ingredients in this product have been cited

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by the applicant. Furthermore, specific studies with the final formulation have been provided. The risk assessment concluded that precautions for use are necessary. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Wear gloves, protective work clothing and safety glasses when using the product Do not smoke, drink or eat while handling the product.
- Avoid direct contact with skin and eyes
- Wash hands after use
- If splashed in the eye or on the skin, wash with plenty of clean, running water immediately.
- People with known hypersensitivity to the active substance should not handle the product. If irritation persists, seek medical advice and show the label to the doctor.

Ecotoxicity

The applicant provided Phase II risk assessments for both moxidectin and triclabendazole.
The assessment concluded that a potential risk of moxidectin to aquatic organisms cannot be excluded. Warnings regarding the toxicity of the product to aquatic organisms 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: “the product should not enter water courses as this may be dangerous for fish and other aquatic organisms”.

III.B Residues documentation

Residue Studies

Results of two tissue residue studies in cattle at various timepoints after administration were provided. These GLP-compliant studies analysed the use of a single administration of the product at the recommended dose. A suitable number of animals were treated and then necropsied at several timepoints post-treatment. Samples of liver, kidney, muscle, fat, and muscle underlying the injection point were analysed. The analytical methods used were HPLC-based.

MRLs

Moxidectin and Triclabendazole are listed in Table I of Regulation (EU) No 37/2010 of 22 December 2009.

MRLs are listed below:

Pharmaco-logically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Moxidectin	Moxidectin	Bovine, ovine, *Equidae*	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	No entry	Antiparasitic agents/ Agents against endo- and ectoparasites	37/2010 of 22.12 2009
		Bovine, ovine	40 µg/kg	Milk			

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Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Triclabendazole	Sum of extractable residues which may be oxidised to ketotriclabendazole	All ruminants	225 µg/kg 100 µg/kg 250 µg/kg 150 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.	Antiparasitic agents/ Agents against endoparasites	37/2010 of 22.12 2009

Withdrawal Periods

Based on the data provided above, a withdrawal period of 143 days for meat and offal in cattle was established. The product is not permitted for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using multiples of the recommended dose in the target species.

No study has been performed to evaluate safety in breeding cows. However the two actives are currently approved for use in pregnant and lactating cattle. As there was no interaction between moxidectin and triclabendazole in the pharmacocinetic study, it is reasonable to assume that the combination product can be safe for use in pregnant and lactating animals.

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

Resistance

The applicant has provided sufficient documentation to address the resistance of parasites to moxidectin and triclabendazole in cattle.

The SPC warnings about resistance address appropriately this matter:

- Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:
  - Too frequent and repeated use of anthelmintics from the same class, over an extended period of time.

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- Underdosing, which may be due to underestimation of body weight, misadministration of the product, or lack of calibration of the dosing device (if any).

• Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. Faecal Egg Count Reduction Test). Where the results of the test(s) strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to another pharmacological class and having a different mode of action should be used.

• In 2010, no confirmed resistance to moxidectin in cattle parasites has been reported in Europe, however, resistance to other macrocyclic lactones (MLs) has been reported mainly in *Cooperia oncophora* in some European countries, and resistance to moxidectin has been reported in the Southern Hemisphere. Resistance to other MLs in some strains of *Cooperia* spp. can imply concurrent resistance to Moxidectin. Resistance to triclabendazole has been reported in *Fasciola hepatica* in cattle in some European countries. Triclabendazole resistant *F. hepatica* hosted in sheep can be transferred to cattle grazing the same pasture. Therefore the use of this product should be based on local (regional, farm) epidemiological information about susceptibility of parasites, local history of treatments and recommendations on how to limit further selection for resistance to anthelmintics. This product should not be used for the treatment of single infections.

IV.B Clinical Studies

Laboratory Trials

In order to justify the dosage of triclabendazole and moxidectin in the formulation and to support the claimed efficacy of the product in the treatment of nematode and fluke infections in cattle, two dose determination studies and four confirmation dose studies have been submitted.

Field Trials

The applicant has provided six field trials carried out in UK, France and Australia and scientific literature which confirmed that a single topical application of the product administered directly to the hair and skin along the midline of the back of the animal from the withers to the tail head is efficient against mixed trematode (fluke) and nematode infections caused by moxidectin and triclabendazole sensitive strains of:
 Trematodes: *Fasciola hepatica* (adult and 6-8 weeks immatures)

- Gastrointestinal roundworms (adults and fourth stage larvae): *Ostertagia ostertagi* (including inhibited stages), *Haemonchus placei*, *Trichostrongylus axei*, *Cooperia oncophora*, *Nematodirus helvetianus*
- Gastrointestinal roundworms (adults): *Cooperia punctata*, *Oesophagostomum radiatum*, *Bunostomum phlebotomum*
- Lungworms (adult): *Dictyocaulus viviparous*

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.

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