Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A PROPOSED VETERINARY MEDICINAL PRODUCT

Maximec Plus 10mg/ml + 100 mg/ml Solution for Injection for Cattle

Date Created: June 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Maximec Plus 10mg/ml + 100 mg/ml Solution for Injection for Cattle
Applicant	Bimeda Animal Health Limited Unit 2/3/4 Airton Close Tallaght Dublin 24 Ireland
Active substance	Clorsulon, Ivermectin
ATC Vetcode	QP54AA51
Target species	Cattle
Indication	For the treatment of mixed infestation with liver fluke, (*Fasciola hepatica*), and nematodes and arthropods as detailed in the Scientific Overview section below.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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 conclusion of the procedure	8th May 2019

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, Maximec Plus 10 mg/ml + 100 mg/ml, Solution for Injection for Cattle, submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Ivomec Super Injection for Cattle, authorised in the UK since August 1987. The dossier for this product was previously assessed for Bimectin Plus, 10/100 mg/ml Solution for Injection for Cattle.

The product is indicated for the treatment of mixed infestations of adult liver fluke, and for a variety of nematodes and arthropods:

Nematodes:
Gastrointestinal roundworms (adult and fourth-stage larvae):
Ostertagia ostertagi (including inhibited larval stages), *O. lyrate, Haemonchus placei, Trichostrongylus axei, T. colubriformis, Cooperia oncophora, C. punctate, C. pectinate, Bunostomum phlebotomum, Oesophagostomum radiatum, Strongyloides papillosus* (adult), *Nematodirus helvetianus* (adult), *N. spathiger* (adult) and *Trichuris* spp. (adult).

Lungworms (adult and fourth-stage larvae):
Dictyocaulus viviparus
Eye worms (adult):
Thelazia spp.

Arthropods:
Warbles (parasitic stages):
Hypoderma bovis
H. lineatum

Mange mites:
Psoroptes bovis
Sarcoptes scabiei var. *bovis*
Sucking lice:
Linognathus vituli
Haematopinus eurysternus, Solenopotes capillatus.

This product may also be used as an aid in the control of biting lice *(Damalinia bovis)* and the mange mite *Chorioptes bovis,* but complete elimination may not occur.

Persistent Activity

This product given at the recommended dosage of 0.2 mg per kg bodyweight controls re-infection with *Haemonchus placei, Cooperia* spp. and *Trichostrongylus axei* acquired up to 14 days after treatment; *Ostertagia ostertagi* and *Oesophagostomum radiatum* acquired up to 21 days after treatment and *Dictyocaulus viviparus* acquired up to 28 days after treatment.

The timing of treatment should be based on epidemiological factors and should be customised for each individual farm. The recommended dosage is 200 µg ivermectin and 2 mg clorsulon per kg bodyweight corresponding to a single dose of 1 ml per 50 kg bodyweight. Divide doses greater than 10 ml between two injection sites. The timing of treatment should be based on epidemiological factors and should be customised for each individual farm. A dosing programme should be established by a qualified professional person.

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, any reactions observed are indicated in the SPC.[1] 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 [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 100 mg/ml clorsulon and 10 mg/ml ivermectin. The container/closure system consists of a box of 1 bottle of 50ml, 250ml, 500ml or 3 x 500ml natural serum bottles composed of HDPE resin. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the mixing of the excipients, followed by the addition of the active ingredients. The batch is made up to volume and pH checked. The bulk is then sterilised and filled into containers.

II.C. Control of Starting Materials

The active substances are clorsulon and ivermectin, established active substances. Ivermectin is described in the European Pharmacopoeia, (Ph. Eur) and clorsulon in the United States Pharmacopoeia. The active substances are 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. Acceptable specifications and Certificates of Analysis were provided.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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 have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, pH, container inspection, moisture, identity of the active substances and relevant, related impurities, fill quantity and sterility.

II.F. 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.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
- Shelf life after first opening the immediate packaging: 28 days.
- Protect from light.
- Keep the container in the outer carton in order to protect from light.
- Discard unused material.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the application, no additional toxicological or pharmacological data were required. The applicant submitted a bioequivalence study and tolerance study, discussed in part IV. A user safety risk assessment (URA) and an environmental risk assessment were also submitted.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the final formulation has the potential to cause skin and eye irritation. The applicant considered exposure to the user and correctly identified accidental self-injection as the primary risk. The applicant proposed the same user safety warnings as those for the reference product. This approach was acceptable, however, in order to bring the user warnings in accordance with current user safety guideline, additional amendments to the user safety warnings were required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- This product may cause eye and skin irritation.
- Avoid contact with skin or eyes.
- In case of skin or eye contact, wash exposed area with plenty of clean water. If symptoms persist, seek medical advice.
- Do not eat or smoke while handling the product.
- Take care to avoid accidental self-injection: the product may cause local irritation and/or pain at the site of injection.
- In case of accidental self-injection, seek immediate medical advice and show the information leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

The product is a parasiticide used in pasture animals and a Phase II ERA was required. (Question 16 VICH decision tree).

Phase II Tier A:
A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physicochemical properties, environmental fate and effects. Studies were carried out using the active substances, ivermectin and clorsulon, unless indicated otherwise.

Physicochemical properties (Ivermectin)

Study type	Guideline	Result
Water solubility	OECD 105	4 mg/l
Vapour Pressure	OECD 104	<1.5 x 10^{-9} mm Hg (2 x 10^{-7} Pa)
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 123	977 000 (log K_{ow} = 5.99) Determined at pH 3 5.22 - 5.41at 25.0 ± 0.2°C.

As the log K_{ow} is >4, which suggests that ivermectin could partition to lipid, the potential for bioaccumulation, secondary poisoning and for ivermectin to be a persistent, bioaccumulative and toxic (PBT) substance has been considered in Tier B of the ERA.

Physicochemical properties (Clorsulon)

Study type	Guideline	Result
Water solubility	OECD 105	1 mg/ml (0.042 - 2.06 mg/ml). Clorsulon is soluble in organic solvents such as ethyl acetate, methanol, ethanol and acetone, and is slightly soluble in diethyl ether.
Vapour Pressure	OECD 104	6.13 x 10^{-11} Pa (9.68 x 10^{-5} Pa)
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	1.18 (1.09)

As the Log Pow is <4, bioaccumulation does not need to be considered.

Environmental fate (Ivermectin)

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	**Soil** / **K_{oc} (l/kg)** Artificial, ECT: 4 000 York: 25 800 Madrid, INIA: 12 800 Clay Loam: 12 600 Silty Clay Loam: 15 700 Sand: 17 640 Clay: 54 810
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT_{50} values range from 16.1 to 37.1 days at 20°C

Environmental fate (Clorsulon)

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	**Soil** / **K_{oc} (l/kg)** LUFA 2.2: 135 LUFA 5M: 140 LUFA 6S: 119
Aerobic and Anaerobic Transformation in Soil	OECD 307	**Soil** / **DT_{50} (days)** LUFA 2.2: 80 LUFA 5M: 81 LUFA 6S: 78

Clorsulon is classified as having high mobility.

Environmental effects (Ivermectin)

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/*Species*	OECD 201	EC50	72 hour (growth inhibition): >4 mg/l
Daphnia sp. immobilisation	OECD 202	EC50	48 hour. Range of 1.2 and 10.7 ng/l
Fish, acute toxicity/*Species*	OECD 203	LC50	96 hour. 73.3 µg/l (*Danio rerio*)
Earthworm/*Species* subacute/reproduction	OECD 220/222	NOEC	2.5 mg/kg
Dung fly larvae	OECD 228	EC50	*Scathophaga stercoraria*. 19.6 µg/kg

Environmental effects (clorsulon)

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/*Species*	OECD 201	EC50	72 hour (growth inhibition): 84 µg/l
Daphnia sp. immobilisation	OECD 202	EC50	48 hour. >100 mg/l
Fish, acute toxicity/*Species*	OECD 203	LC50	96 hour. >100 mg/l (Rainbow trout)
Earthworm/*Species* subacute/reproduction	OECD 220/222	NOEC	229 mg/kg
Dung beetle/fly larvae	OECD 228	EC50	*Scathophaga stercoraria*. >230 mg/kg *Aphodius constans* 185 mg/kg

Exposure assessment (Predicted exposure concentration)

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product.

Ivermectin

Target animal	PEC			
	Soil (µg/kg)	Dung (µg/kg)	Ground water (µg/l)	Surfacewater (µg/l)
Beef cattle	0.84	Day after treatment PEC 5 185 10 96 25 16	0.0005	0.000171 run-off Refined using FOCUS. 0.00 µg/l (drainage scenarios) 0.000001 to 0.000010 µg/l for the 4 run-off scenarios. 0.209 direct excr. Refined (sediment partition): Day 5: 0.000058 Day 10: 0.000029 Day 25: 0.000005

Clorsulon

Target animal	PEC			
	Soil (µg/kg)	Dung (mg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Beef cattle	8.36	Day after treatment PEC (fresh) 3 5.3 4 to 7 4 Excretion was judged to be complete 7 days after dose.	0.83 Refined using FOCUS PEARL to be 0.079	0.28 run-off

Risk Characterisation (Risk Quotient)
Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal.

Acceptable risk to groundwater.
Combined (clorsulon plus ivermectin) RQs are <1 for earthworms.
Combined (clorsulon plus ivermectin) RQs are >1 for dung organisms.
Combined (clorsulon plus ivermectin) RQs are <1 for aquatic organisms and sediment dwellers, providing appropriate risk mitigation are followed (see below).
Neither clorsulon nor ivermectin are classified as PBT or vPvB substances.

Due to the risk characterisation, the following risk mitigation and environmental properties information were included on the product literature:

Other precautions
Ivermectin is highly toxic to aquatic organisms, dung beetles and sediment dwelling insects. Long-term effects on dung insects caused by continuous or repeated use cannot be excluded.
The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of ivermectin and products of the same anthelmintic class in cattle, sheep and pigs.
Therefore, the repetition of treatment in a pasture during a season should be performed only in the absence of alternative treatment and on veterinary advice.
Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment.

Environmental Properties
Like other macrocyclic lactones, ivermectin has the potential to adversely affect non- target organisms. Faeces containing ivermectin excreted onto pasture by treated animals may reduce the abundance feeding organisms which may impact on the dung degradation. Ivermectin is very toxic to aquatic organisms and may accumulate in sediments.

Disposal Advice
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements. EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container.

III.B.2 Residues documentation

No residue depletion studies were conducted because the proposed product was considered to be essentially similar to the reference product in this respect.

Withdrawal Periods

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 28 days.

- Protect from light.
- Keep the container in the outer carton in order to protect from light.
- Discard unused material.

IV. CLINICAL DOCUMENTATION

This MA was granted in 2010 via the mutual recognition procedure (MRP) (EU ref: FR/V/0337/001) involving nine CMS, with UK as the RMS. Part IV of the dossier for Maximec Plus reflected the assessment report from this previous MRP procedure, where appropriate. It was been updated to include assessment of new data concerning post-marketing experience with Bimectin Plus and a short review of relevant resistance data.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

No specific studies were required for this product. The pharmacodynamic properties are the same as those of the reference product, and have been widely review in product literature:

Ivermectin
Ivermectin is a member of the macrocyclic lactone class of endectocides which have a unique mode of action, leading to an increase in the permeability of the cell membrane to chloride ions and resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The margin of safety for compounds of this class is attributable to the fact that mammals do not have glutamate-gated chloride channels, the macrocyclic lactones have a low affinity for other mammalian ligand gated chloride channels and they do not readily cross the blood-brain barrier.

Clorsulon
Clorsulon is rapidly absorbed into the blood. Erythrocytes with bound drug as well as plasma are ingested by *Fasciola* spp. Adult *Fasciola spp.* are killed by clorsulon due to the inhibition of enzymes in the glycolytic pathway.

Pharmacokinetics

The pharmacokinetic properties of the test product and the reference product were compared during a bioequivalence study in cattle and were shown to be bioequivalent.

After subcutaneous administration of 2 mg clorsulon and 0.2 mg ivermectin per kg bodyweight, the plasma profile demonstrated a slow, steady absorption of ivermectin with mean peak plasma concentrations (C_{max}) of 65.8 ng/ml at a mean T_{max} (time of peak plasma concentration), of 1.63 days post dose. Average plasma half-life (t ½) was 4.13 days. In contrast, clorsulon is more rapidly absorbed with mean peak plasma concentrations (C_{max}) of 2.58µg/ml, a mean T_{max} of 0.36 days but shows similar steady elimination to ivermectin with an average plasma half-life of 5.8 days.

Tolerance in the Target Species

The applicant conducted a controlled target animal tolerance study using elevated doses for an extended use pattern in the target species.

An authorised reference product containing the same active substance was used as a control in addition to a saline negative control. All doses were administered by subcutaneous injection on various occasions. Clinical and blood parameters were evaluated statistically by One-way ANOVA unless not normally distributed in which case Kruskal-Wallis ANOVA was used. The significance level was 5% ($p<0.05$).

Minimal adverse effects were seen following treatment. Submitted product literature accurately reflects the type and incidence of adverse effects which might be expected. The SPC carries suitable warnings.

Resistance

Bibliographic data were provided. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Due to the nature of the application, no data were required for this section.

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 of the product is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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