MINISTERIO
DE SANIDAD, CONSUMO
Y BIENESTAR SOCIAL

agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

IVERTOTAL 10 mg/ml Solution for injection

CORREO ELECTRÓNICO

mresvet@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0311/001/MR
Name, strength and pharmaceutical form	IVERTOTAL 10 mg/ml Solution for injection
Applicant	S.P. VETERINARIA, S.A. Ctra. Reus – Vinyols Km 4,1 43330 Riudoms (Tarragona) Spain
Active substance(s)	Ivermectin
ATC Vet code	QP54AA01
Target species	Cattle, sheep and pigs.
Indication for use	**Cattle:** For the treatment of gastrointestinal nematodes, lungworms, eyeworms, warble flies, mites and lice (as shown below) of beef and non-lactating dairy cattle: Gastrointestinal worms (adults and 4th stage larvae): *Ostertagia ostertagi* *Ostertagia lyrata* *Haemonchus placei* *Trichostrongylus colubriformis* *Cooperia oncophora* (adults) *Cooperia punctata* (adults) *Cooperia pectinata* (adults) *Bunostomum phlebotomum* *Oesophagostomum radiatum* Lungworms (adult and 4th stage larvae): *Dictyocaulus viviparus* Eyeworms (adult): *Thelazia spp*. Warble flies (parasitic stages): *Hypoderma bovis* *H. lineatum* Mites: *Psoroptes ovis* *Sarcoptes scabiei var. bovis* Sucking lice: *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* May also be used as an aid in the control of the mange mite *Chorioptes bovis* but complete elimination may not occur.

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	Treatment with the product at the recommended dose rate prevents re-infection with *Haemonchus placei*, *Cooperia oncophora*, *Cooperia pectinata* and *Trichostrongylus axei* for 7 days after treatment, *Ostertagia ostertagi* and *Oesophagostomum radiatum* for 14 days after treatment and *Dictyocaulus viviparus* for 21 days after treatment. **Sheep** For the treatment of psoroptic mange (sheep scab), gastrointestinal nematodes, lungworms and nasal bots of sheep: <u>Gastrointestinal roundworms (adults):</u> *Ostertagia circumcincta* *Haemonchus contortus* *Trichostrongylus axei* *T. colubriformis and T. vitrinus* *Cooperia curticei* *Nematodirus filicollis* Variable activity may be observed against *Cooperia curticei* and *Nematodirus filicollis*. <u>Lungworms:</u> *Dictyocaulus filaria* (adults) <u>Mange mites:</u> *Psoroptes ovis* <u>Nasal bot:</u> *Oestrus ovis* (all larval stages) **Pigs** For the treatment of gastro-intestinal nematodes, lungworms, lice and mange mites of pigs. <u>Gastro-intestinal worms (adult and fourth stage larvae):</u> Ascaris suum Hyostrongylus rubidus *Oesophagostomum spp.* *Strongyloides ransomi* (adults). <u>Lungworms:</u> *Metastrongylus spp.* (adults) <u>Lice:</u> *Haematopinus suis* <u>Mange Mites:</u> Sarcoptes scabiei var. suis

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Art/icle 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 01/08/2018
Date product first authorised in the Reference Member State (MRP only)	12/12/2013
Concerned Member States for original procedure	PT

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. Qualitative and quantitative particulars

The product contains 10 mg/ml of ivermectin, as the active substance, benzyl alcohol as preservative, and the excipients, ethanol 96% propylene glycol and water for injection.

The container/closure system comprise 250 ml and 500 ml sterile polyethylene terephthalate (PET) vials and polypropylene (PP) vials suitable for parenteral solutions, with type I bromobutyl stopper and *flip-off* aluminium cap

The choice of the presence/absence 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.

C. Control of Starting Materials

The active substance is ivermectin, an established active 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.

Scientific data and/or certificates of suitability issued by the EDQM have been provided (R1-CEP 2008-104-Rev 01) and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

Not applicable.

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.

F. 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.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC, and bioequivalence with a reference product has been demonstrated, results of safety tests 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 the same as those of the reference product and are adequate to ensure safety of the product to users, environment and consumers.

III.A Safety Testing

Pharmacological, toxicological and other safety studies

Since this is an application under Article 13(1) of Directive 2001/82/EC, as amended, the applicant is not required to provide data regarding the pharmacology, toxicology or other safety studies.

User Safety

Despite not having provided a user risk assessment, it can be accepted that the proposed formulation will not present any greater risk to the user than that posed by the reference product.

The risk management measures proposed by the applicant are the same as those authorised for the reference product and are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The product is an endectocide for pigs, cattle and sheep. Cattle and sheept can be reared in pasture, therefore a phase II assessment was necessary.

Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1), The data were considered to be complete and acceptable.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	Bibliographic	2 ug/l	None
Dissociation constants in water pKa	Bibliographic	Neutral at all pH values	None
n-Octanol/Water Partition Coefficient logP_{ow}	Bibliographic	Log Kow = 3.22	None

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Artificial: Koc =4000 l/kg, Kd = 109 l/kg York: Koc = 25800 l/kg, Kd 396 l/kg Madrid: Koc = 12800 l/kg, Kd = 57 l/kg	Artificial soil: Sandy loam, 8% clay, 4.7% O.M., pH 6.09 York: Sandy loamy, 11.9% clay, 2.65% OM, pH 6.3 Madrid: Sandy loam, 9.4% clay, 0.77% OM, pH 8.7
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50 (days) / SFO / BFO / AAFO Madrid 20º: 16.1 / 10.3 / 12.6	Artificial: Sandy loam, 16.6% clay Madrid: Sandy loam 29.6% silt Tarstrup: Sandy loam, 85% silt York: Sandy loam, 11.9% silt

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Environmental fate						
		Tarstrup 20º	37.1	35.4	36.1	
		Tarstrup 6ºC	88.8	87.8	87.4	
		York 20ºC	67	33.7	32.6	
		York 6ºC	105	831	n.r	
		Artificial	458	986	n.r	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Cyanobacteria, growth inhibition test/ *P. subcapitata*	OECD 201	EC50	> 4000 (yield & growth)	µg/l	
Daphnia sp. immobilisation	OECD 202	LC50	0.0057	µg/l	
Daphnia magna, reproduction	OECD 211	NOEC	3E-7	µg/l	*Tier B*
Fish, acute toxicity/ *D. rerio*	OECD 203	NOEC	220	µg/l	
Earthworm (*Eisenia foetida*) reproduction	OECD 222	NOEC	NOEC (56 d reproduction) = 2.5 mg/kg NOEC (28d, biomass) = 5 mg/kg EC50 (56 d, reproduction) = 5.3 mg/kg	mg/kg	

Sediment dwelling organism/ *C. riparius*	OECD 218	NOEC	3.1	µg/kg	*Tier B*
Dung fly larvae *S. stercoraria*	OECD 228	EC50	97.58 ug/kg dw	µg/kg	None
Dung beetle larvae	OECD GD 122	LC50	590 ug/kg dw	µg/kg	None

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1)

Using the assessment factors (AF) in these VICH guidelines, predicted no effect concentrations (PNEC) were calculated and compared with the PEC values. This results in a risk quotient (RQ) for each compartment as follows:

Compartment	**PNEC**	**PEC**	**RQ**
surface water	0.3E-7	0.0211	73333.3
sediment	0.31	5.77	14.96
soil	250	2.867	0.01
dung	2536.8	0.312	8130

The risk characterisation resulted in risk quotient (RQ) below 1 for the soil compartment indicating that the product will not pose a risk to those compartments when used as recommended.

The results of the assessment for the surface water, sediment and dung compartments indicate that a risk for the environment is indicated and that the following risk mitigation measures and environmental properties are required for this product:

4.5 Special precautions for use

Other precautions:

Ivermectin is very toxic to aquatic organisms and to coprophilous insects. Treated animals should not have direct access to ponds, streams or ditches for 14 days after treatment. Long-term effects on coprophilous insects caused by continuous or repeated use cannot be excluded. Therefore, repeated treatments on a pasture in the same season should only be administered on the advice of a veterinarian.

5.3 Environmental properties

Ivermectin has adverse effects on the environment. After treatment, toxic levels of ivermectin are excreted for weeks. Faeces excreted on the grass by treated animals reduces the abundance of coprophagous organisms which could affect the degradation of feces.
Ivermectin is very toxic to aquatic organisms and the coprophagous fauna and can accumulate in soil and sediment.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Treated animals should not have access to surface waters for 7 days after treatment to avoid effects on aquatic organisms. Do not contaminate surface waters or ditches with product or used container. Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

III.B Residues documentation

Residue Studies

As this application is in accordance with Article 13(1) of Directive 2001/82/EC, the applicant shall not be required to provide the results of residues tests because all these data are in the documentation that supports the marketing authorisation of the reference product.

MRLs

Ivermectin is listed in table 1 of the annex to the Commission Regulation (EU) No 37/2010. The marker substance is 22,23-Dihydro-avermectin B1a.

MRLs are listed below:

	All mammalian food producing species
Muscle	30 µg/kg
Liver	100 µg/kg
Kidney	30 µg/kg
Fat	100 µg/kg

Not for use in animals from which milk is produced for human consumption.

Withdrawal Periods

The applicant proposes the same withdrawal period as approved for the reference product. As this is a generic application according to Article 13 (1), and bioequivalence with the reference product has been demonstrated, the following withdrawal periods are justified and there are adequate to ensure consumer safety:

Cattle: Meat and offal: 49 days

Do not use in lactating cows producing milk for human consumption. Do not use in non-lactating dairy cows, including pregnant dairy heifers, within 60 days of calving.

Sheep: Meat and offal: 42 days

Do not use in lactating ewes producing milk for human consumption. Do not use in sheep which are intended to produce milk for human consumption within 60 days of lambing.

Pigs: Meat and offal: 28 days.

IV. CLINICAL ASSESSMENT (EFFICACY)

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 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 veterinary Heads of 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