Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Gerichtstraße 49
13347 Berlin
(Germany)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Taurador 10 mg/ml Solution for Injection for cattle, sheep and pigs (Doramectin)

Date: 30 October 2024

PRODUCT SUMMARY

EU procedure number	DE/V/0345/001/DC
Name, strength and pharmaceutical form	Taurador 10 mg/ml Solution for Injection
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate H18 W620 MONAGHAN, CO MONAGHAN Ireland
Active substance(s)	Doramectin
ATC vetcode	QP54AA03
Target species	cattle, sheep and pigs
Indication for use	Cattle: For the treatment of gastrointestinal roundworms, lungworms, warbles, lice, mange mites and eyeworms (not specified in detail here). Sheep: For the treatment of gastrointestinal roundworms, lungworms, mange mites and nasal bots (not specified in detail here). Pigs: For the treatment of gastrointestinal roundworms, lungworms, kidney worms, sucking lice and mange mites in pigs (not specified in detail here).

Taurador 10 mg/ml Solution for Injection for cattle, sheep and pigs	DE/V/0345/001/DC
Norbrook Laboratories (Ireland) Limited	DCP
Publicly available assessment report	

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	generic application in accordance with Article 18 of Regulation (EC) 2019/6 as amended.
Reference product (RP)	Dectomax S Injektionslösung 10 mg / ml Lösung für Schweine
Marketing authorisation holder	Elanco
MS where the RP is or has been authorised	Germany
Marketing authorisation number EU procedure number	400207.00.01; DE/V/0199/001/MR
Date of authorisation	17.07.1998
Reference to proprietary data of an additional VMP linked to the reference product	Dectomax, 10 mg/ml, Injektionslösung für Rinder und Schafe
Marketing authorisation holder	Elanco
MS where the RP is or has been authorised	Germany
Marketing authorisation number EU procedure number	400202.00.00
Part of the dossier referred to	Target species
Date of completion of the original decentralised procedure	30 October 2024
Concerned Member States for original procedure	BE; CZ; ES; FR; HU; IE; NL; PT; RO; SK
Concerned Member States for subsequent recognition procedure	n.a.
Withdrawn CMS during original decentralised procedure	n.a.

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; cattle, sheep and pigs the reactions observed are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

A. Product description

The VMP contains 10.0 mg/ml of doramectin as active substance and the excipients ethyl oleate and sesame oil as well as two antioxidants, butylhydroxyanisole and butylhydroxytoluene.

The container/closure system is composed of an amber coloured type II glass vial, closed with a nitryl rubber stopper and sealed with an aluminium cap, packed into a protective plastic container.

The choice of the formulation is justified.

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

B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

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

C. Production and control of starting materials

The active substance is doramectin, an established active substance. 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.

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

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 VMP.

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 tests

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 VMP throughout its shelf life and in-use shelf life when stored under the approved conditions.

3. SAFETY DOCUMENTATION (safety and residues tests)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been accepted, results of safety tests are not required. Safety aspects of this VMP are identical to the reference VMP.

A. Safety tests

No data on safety are required.

User safety assessment

The applicant has provided a user safety assessment in compliance with the relevant guideline. Although the safety aspects of this VMP are identical to the reference VMP, additional warning phrases regarding a mild eye-irritating potential of doramectin and risks for pregnant/nursing users were included in the SPC under 3.5 “Special precautions to be taken by the person administering the veterinary medicinal product to animals” to further minimize health risks to the user administering this veterinary medicinal product.

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

Environmental Risk Assessment

According to the Reflection paper on the interpretation of Article 18(7) of Regulation (EU) 2019/6 (EMA/CVMP/ERA/622045/2020), an ERA for the product under application was not required as comparable products were authorised after 1 October 2005. However, a Phase I and Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines and is summarised in the following.

Phase I:

The initial predicted environmental concentration in soil (PECsoil, initial = 7.82 µg/kg max. for intensively reared animals and 1.67 µg/kg max. for pasture reared animals) is less than 100 µg/kg

A Phase II ERA is required as the VMP is an ectoparasiticide and endoparasiticide for cattle, sheep and pigs and the target animals (cattle and sheep) are reared on pasture.

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).

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	OECD 105	2.22 mg/L (20°C)	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 123	logK_{ow} = 6.74	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Koc = 29,078 (geomean) 46,170 (OECD 3, Silt Loam, clay = 20.2%, pH = 5.8, C_{org} = 2.5%) 13,398 (OECD 2, Clay Loam, clay = 30.4%, pH = 7.1, C_{org} = 3.9%) 36,142 (Calcareous 1, Sandy Loam, clay = 12.9%, pH = 7.1, C_{org} = 1.5%) 31,339 (Calcareous 2, Loam, clay = 19.6%, pH = 7.1, C_{org} = 1.8%) 29,671 (OECD 5, Sandy Loam, clay = 13.5%, pH = 4.8, C_{org} = 1.3%) K_d = 589 (geomean) 1,154 (OECD 3, Silt Loam, clay = 20.2%, pH = 5.8, C_{org} = 2.5%) 523 (OECD 2, Clay Loam, clay = 30.4%, pH = 7.1, C_{org} = 3.9%) 542 (Calcareous 1, Sandy Loam, clay = 12.9%, pH = 7.1, C_{org} = 1.5%) 561 (Calcareous 2, Loam, clay = 19.6%, pH = 7.1, C_{org} = 1.8%) 386 (OECD 5, Sandy Loam, clay = 13.5%, pH = 4.8, C_{org} = 1.3%)	List all values with pH, Corg, soil texture including clay content
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50, 20°C}$ = 96/87/65/174 d $DT_{50, 12°C\ worst\ case}$ = 371 d Transformation products >10%: 2 Component D: max. 10.26% (90d), S748 Component E: 24.33% (90d), S748 % non-extractable residues (NER): 8.05-13.55% (d129)	Soils: sandy loam, sandy clay loam, clay loam, sand Transformation products not identified

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks
Algae and or cyanobacteria, growth inhibition test/*P. subcapitata*	OECD 201	EC_{50}	200	µg/l	
Daphnia sp. immobilisation	OECD 202	EC_{50}	0.049	µg/l	
Daphnia magna, reproduction	OECD 211	NOEC	0.038	µg/l	Tier B
Fish, acute toxicity/*C. carpio*	OECD 203	EC_{50}	2.3	µg/l	
Sediment dwelling organism/species	OECD 218	NOEC	32	µg/kg	Tier B
Bioaccumulation in fish/*D. rerio*	OECD 305 Type: Aquatic exposure	BCF_k BCF_{KgL}	131 71	l/kg l/kg	5% lipids

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	0.0038 µg/l	0.0017 µg/l	0.45
groundwater	0.0038 µg/l	0.00088 µg/l	0.23
sediment	10 $\mu g/kg_{dwt}$	4.97 $\mu g/kg_{dwt}$	0.50

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water, sediment and groundwater compartments indicating that the product will not pose a risk to those compartments when used as recommended. A risk to soil dwelling organisms can be excluded based on respective data for comparable products.

A risk characterisation for dung fauna has not been made as no regulatory acceptable endpoints (NOEC, EC_{50}) has been derived. However, the data provided clearly indicate a risk for dung fauna and in accordance with an Article 35 referral for injectable and pour-on doramectin containing products (EMEA/V/A/081), risk mitigation measures are required for this product.

Hence, the following information on environmental properties and precautions are included in the product literature, as agreed on in the Art. 35 referral on doramectin:

SPC

3.5:

Special precautions for the protection of the environment

Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of doramectin (and products of the same anthelmintic class).

The risk to aquatic ecosystems will be reduced by keeping treated animals away from water bodies for two to five weeks after treatment.

4.3:

Environmental properties

Like other macrocyclic lactones, doramectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of doramectin may take place over a period of several weeks. Faeces containing doramectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

Doramectin is very toxic to aquatic organisms and may accumulate in sediments.
Doramectin is very persistent in soils.

5.5:

Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as doramectin is extremely dangerous for fish and other aquatic organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

Package leaflet

6:

Special precautions for the protection of the environment:

Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.

The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of doramectin (and products of the same anthelmintic class).

The risk to aquatic ecosystems will be reduced by keeping treated animals away from water bodies for two to five weeks after treatment.

12:

Medicines should not be disposed of via wastewater or household waste.

This veterinary medicinal product should not enter water courses as doramectin is extremely dangerous for fish and other aquatic organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

17:

Like other macrocyclic lactones, doramectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of doramectin may take place over a period of several weeks. Faeces containing doramectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

Doramectin is very toxic to aquatic organisms and may accumulate in sediments. Doramectin is very persistent in soils.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	131 l/kg	not B
Persistence	$DT_{50,\ soil,\ 12\ °C}$	371 d	vP
Toxicity	NOEC	0.038 ng/l	T
PBT-statement:	The compound is not considered as PBT nor vPvB.		

B. Residues documentation

Residue tests

This application is for a generic product, submitted in accordance with Article 18 of Regulation (EU) No. 2019/6. No residue depletion studies were conducted because the product is essentially similar to the reference products based on its composition and pharmaceutical form.

Maximum Residue Limits

Doramectin is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Doramectin	Doramectin	All mammalian food-producing species	40 µg/kg 150 µg/kg 100 µg/kg 60 µg/kg	Muscle Fat Liver Kidney	For porcine species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which

					milk is produced for human consumption.

The excipients are ethyl oleate, sesame oil, butylhydroxyanisole and butylhydroxytoluene. Ethyl oleate is in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 with the status “no MRL required”. Sesame oil also does not require an MRL because it does not fall within the scope of Regulation (EC) No. 470/2009 when used as in this product (out-of-scope list). Butylhydroxyanisole (E 321) and butylhydroxytoluene (E 320) are approved food additives.

Withdrawal Periods

The withdrawal periods are appropriate; they match those of the reference products, which in turn were harmonized following a referral according to Article 35 of Directive 2001/82/EC (EMEA/V/A/081):

Cattle
Meat and offal: 70 days.
Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant cows or heifers which are intended to produce milk for human consumption within 2 months of expected parturition.

Sheep
Meat and offal: 70 days.
Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant ewes which are intended to produce milk for human consumption within 70 days of expected parturition.

Pigs
Meat and offal: 77 days.

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and essential similarity to a reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

A. Pre-Clinical Studies

No pre-clinical studies were performed.

Development of resistance and related risk in animals

The applicant has provided bibliographical data, which shows that resistance to macrocyclic lactones occurs in Europe, especially in small ruminants (sheep and goats) but also in horses and cattle. Genera of *Haemonchus, Trichostrongylus* and *Teladorsagia* are most frequently affected and could also be multidrug-resistant (benzimidazoles, imidazothiazoles, and macrocyclic lactones), in particular in sheep across Europe. Furthermore, in *C. elegans* it was demonstrated that both moxidectin and ivermectin can induce cross-resistance. One report of doramectin resistance in sheep farms in Austria was also provided.

Additionally, various resistance mechanisms have been described, such as modifying the gene expression level and the allele frequency of ATP-transporter, mutation in the dyf-7 gene and the induction of the detoxification system and malfunction in the integrity of chemosensory neurons.

Although the candidate product is not expected to present any greater risk for parasitic resistance development than that posed by the reference product, the resistance situation has been changed compared to the time of approval of the reference product. Consequently, the applicant has updated the information regarding resistance development in Europe, the known mechanism of resistances in the relevant sections 3.4 and 4.2 of the SPC and added the standard warnings in line with the recommendations of GL on the summary of products characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005-Rev.1).

Therefore, adequate warnings and precautions appear on the product literature.

B. Clinical trials

No clinical trials were performed.

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5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None