



**College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board**

**Graadt van Roggenweg 500  
3531 AH Utrecht  
The Netherlands**

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY  
MEDICINAL PRODUCT**

**Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs**

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

## PRODUCT SUMMARY

EU procedure number	NL/V/0431/001
Name, strength and pharmaceutical form	Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs
Applicant	Interchemie werken "De Adelaar" B.V. Metaalweg 8 5804 CG Venray The Netherlands
Active substance(s)	Ivermectin
ATC vetcode	QP54AA01
Target species	Cattle, sheep and pig
Indication for use	<p>For cattle, sheep and pigs with, or at risk from mixed infections by species of nematodes, warbles, mites and lice. The veterinary medicinal product is only indicated when treatment against the following parasites is indicated at the same time:</p> <p><b><u>Cattle:</u></b></p> <p><b>Gastrointestinal nematodes:</b> <i>Ostertagia ostertagi</i> (adult, L3, L4, inhibited larvae), <i>Ostertagia lyrata</i> (adult, L4), <i>Haemonchus placei</i> (adult, L3, L4), <i>Trichostrongylus axei</i> (adult, L4), <i>T. colubriformis</i> (adult, L4), <i>Cooperia oncophora</i> (adult, L4), <i>C. punctata</i> (adult, L4), <i>C. pectinata</i> (adult, L4), <i>Cooperia</i> spp. (L3), <i>Oesophagostomum radiatum</i> (adult, L3, L4), <i>Nematodirus helvetianus</i> (adult), <i>N. spathiger</i> (adult), <i>Strongyloides papillosus</i> (adult), <i>Bunostomum phlebotomum</i> (adult, L3, L4), <i>Toxocara vitulorum</i> (adult).</p> <p><b>Lungworms:</b> <i>Dictyocaulus viviparus</i> (adult, L4, inhibited larvae).</p> <p><b>Roundworms:</b> <i>Parafilaria bovicola</i>, <i>Thelazia</i> spp. (adult).</p> <p><b>Warbles:</b> <i>Hypoderma bovis</i>, <i>H. lineatum</i>, <i>Dermatobia hominis</i>.</p> <p><b>Lice:</b> <i>Linognathus vituli</i>, <i>Haematopinus eurysternus</i>, <i>Solenopotes capillatus</i>.</p> <p><b>Mites:</b> <i>Psoroptes ovis</i>, <i>Sarcoptes scabiei</i> var. <i>bovis</i>, <i>Chorioptes bovis</i></p> <p><b><u>Persistent Activity:</u></b> Given at the recommended dosage of 0.2 mg ivermectin per kg bodyweight, the veterinary medicinal product controls re-infection with the following nematodes up to the duration shown:</p> <p><i>Cooperia</i> spp. 7 days</p>

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

	<p><i>Ostertagia</i> spp. 7 days  <i>Dictyocaulus viviparus</i> 14 days</p> <p><b><u>Sheep:</u></b></p> <p><b>Gastrointestinal nematodes:</b> <i>Teladorsagia (Ostertagia) circumcincta</i> (adult, L3, L4, inhibited larvae), <i>Teladorsagia (Ostertagia) trifurcata</i> (adult, L4), <i>Haemonchus contortus</i> (adult, L3, L4), <i>Trichostrongylus axei</i> (adult), <i>T. colubriformis</i> (adult, L3, L4), <i>T. vitrinus</i> (adult), <i>Cooperia curticei</i> (adult, L4), <i>Oesophagostomum columbianum</i> (adult, L3, L4), <i>O. venulosum</i> (adult), <i>Chabertia ovina</i> (adult, L3, L4), <i>Trichuris ovis</i> (adult), <i>Nematodirus filicollis</i> (adult, L4), <i>N. spathiger</i> (L3, L4), <i>Strongyloides papillosus</i> (L3, L4).</p> <p><b>Lungworms:</b> <i>Dictyocaulus filaria</i> (adult, L3, L4), <i>Protostrongylus rufescens</i> (adult).</p> <p><b>Warbles:</b> <i>Oestrus ovis</i> (all larval stage).</p> <p><b>Mites:</b> <i>Psoroptes communis</i> var. <i>ovis</i>, <i>Sarcoptes scabiei</i>, <i>Psorergates ovis</i>.</p> <p><b><u>Pig:</u></b></p> <p><b>Gastrointestinal nematodes:</b> <i>Ascaris suum</i> (adult, L4), <i>Hyostromylus rubidus</i> (adult, L4), <i>Oesophagostomum</i> spp. (adult, L4), <i>Strongyloides ransomi</i> (adult).</p> <p><b>Lungworms:</b> <i>Metastrongylus</i> spp. (adult).</p> <p><b>Kidneyworms:</b> <i>Stephanurus dentatus</i> (adult, L4).</p> <p><b>Lice:</b> <i>Haematopinus suis</i>.</p> <p><b>Mites:</b> <i>Sarcoptes scabiei</i> var. <i>suis</i></p>
--	--

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
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).

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

## 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)	Ivomec 10 mg/ml, solution for injection
Marketing authorisation holder	Boehringer Ingelheim Animal Health Netherlands B.V.
MS where the RP is or has been authorised	NL
Marketing authorisation number	REG NL 1438
EU procedure number	
Date of authorisation	9 March 1999
Date of completion of the original mutual recognition procedure	27 November 2024
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	17 April 2023
Concerned Member States for original procedure	AT, CY, CZ, DE, EL, ES, FR, HR, HU, IT, LT, LV, MT, PT, SI, SK
Concerned Member States for subsequent recognition procedure	
Withdrawn CMS during original mutual recognition procedure	NA

\*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; the reactions observed are indicated in the SPC.

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

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, a solution for injection, contains 10 mg/mL ivermectin and the excipients propylene glycol and glycerol formal.

The VMP is packed in clear type II glass vials of 50 mL sealed with bromobutyl rubber stoppers and aluminium caps or an aluminium flip-off cap with polypropylene cover packed into an outer cardboard box.

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.

The VMP is manufactured using conventional manufacturing techniques. Process validation data for the manufacturing process has been presented with three commercial batches spanning the production size range in accordance with the relevant European guidelines. The tests performed during manufacture are described.

### **C. Production and control of starting materials**

The active substance is ivermectin, an established active substance described in the European Pharmacopoeia (Ph. Eur.) monograph 1336. The active substance is manufactured in accordance with the principles of good manufacturing practice. A CEP is used.

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.

The excipients, glass vials and rubber stoppers are in conformity with Ph. Eur. requirements.

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

### **D. Control tests carried out on isolated intermediates during the manufacturing process**

Not applicable.

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

## **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**

The re-test period of 2 years when stored in double polyethylene bags placed in a fibre drum for the active substance is evidenced by the CEP.

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 (3 years) when stored under the approved conditions.

The claim of 28 days stability after broaching has been justified.

## **G. Other information**

None.

## **3. SAFETY DOCUMENTATION (safety and residues tests)**

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, results of safety and residue tests are not required.

The safety and residue aspects of this VMP is/are identical to the reference VMP.

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

## **A. Safety tests**

### ***User safety***

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that this veterinary medicinal product may cause neurologic effects and may be irritating to the eye. Accidental injection may cause local irritation and/or pain at the injection site. This veterinary medicinal product may cause harm to the unborn foetus.

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

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

### **Environmental Risk Assessment**

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

#### **Phase I:**

A Phase II ERA is required as the VMP is an ectoparasiticide and endoparasiticide for cattle sheep and pigs and the target animals 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 (EMA/CVMP/ERA/418282/2005-Rev.1), The data were considered to be complete and acceptable.

<b>Substance: ivermectin</b>			
<b>CAS-number: 70288-86-7</b>			
<i>Phase II, Tier A Physical-chemical properties and fate</i>			
<b>Study type</b>	<b>Test protocol</b>	<b>Result</b>	<b>Remarks</b>
Water solubility	OECD 105	1.19 mg/L	pH 5.7-6.4; 20 °C
pK <sub>a</sub>			
Dissociation constants in water	OECD 112	neutral at all pH values	
UV-Visible Absorption Spectrum	OECD 101	maxima: 237, 245 and 253 nm	
Melting Point	OECD 102	approx. 150°C	
Vapour Pressure	OECD 104	2.0 x 10 <sup>-7</sup> Pa	20 °C
n-Octanol/Water Partition Coefficient	OECD 123	818465 (log K <sub>ow</sub> = 5.91)	pH 5.8-6.4; 25 °C
Soil Adsorption/Desorption	OECD 106	K <sub>oc</sub> (L/kg) = 12800 (loamy sand) 14526 (loamy sand) 25800 (loamy sand) 879 (sandy) 934 (sandy clay loam) 451 (sandy) 817 (clay)	all soils from different origin, geometric mean of 2829 L/kg is used in risk assessment
Soil Biodegradation	OECD 307		no reliable data provided on biodegradation in soil.

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

Manure Degradation			no reliable data provided on biodegradation in manure.
Degradation in aquatic sediment-water systems	OECD 308	DT <sub>50, water</sub> = 0.25 d (dissipation) DT <sub>50, whole system</sub> = 337 d Transformation products > 10 %: 11.2%, not identified Mineralisation not reported % NER: 30.6%	reliable with limitations, as test temperature was not reported
Photolysis		-	data not provided
Hydrolysis	OECD 111	-	data not provided

<b>Phase II, Tier A Effect studies</b>					
<b>Study type</b>	<b>Test protocol</b>	<b>Endpoint</b>	<b>Result</b>	<b>Unit</b>	<b>Remarks</b>
Algae, Growth Inhibition Test	OECD 201	EC50	>1.3	mg/L	growth rate
<i>Daphnia</i> sp. immobilization	OECD 202	EC50		µg/L	no reliable data provided, because of the availability of a chronic endpoint the submission of a study on acute toxicity is not required
Fish, acute toxicity	OECD 203	LC50	73.3	µg/L	<i>Danio rerio</i>
Nitrogen Transformation	OECD 216	% effect		µg/kg	not required
Terrestrial plants	OECD 208	EC50		µg/kg	not required
Earthworm subacute/reproduction	OECD 222	NOEC	1.6	mg/kg	<i>Eisenia andrei</i>
Enchytraeid reproduction	similar to OECD 220	EC10	14	mg/kg	<i>Enchytraeus crypticus</i>
Collembolan	ISO 11267	EC10	0.19	mg/kg	<i>Folsomia fimetaria</i>
	ISO 11267	EC10	0.0084	mg/kg	<i>Folsomia candida</i>

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

Dung fly larvae	OECD 228	EC50	19.6	µg/kg	<i>Scatophaga stercoraria</i>
Dung beetle larvae		LC50	3.76	mg/kg	<i>Aphodius constans</i>
<b>Phase II, Tier B studies</b>					
Bioaccumulation	OECD 305	BCF	113	L/kg	
Algae, Growth Inhibition Test	OECD 201	NOEC	≥1.3	mg/L	growth rate
Daphnia magna, Reproduction	OECD 211	NOEC	0.0003	ng/L	<i>Daphnia magna</i>
Fish, early-life stage	OECD 210	NOEC	-	µg/L	not required
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	% effect	-	µg/kg	not required
Terrestrial Plants, Growth Test	OECD 208	NOEC	-	µg/kg	not required
Sediment dwelling organism	OECD 218	NOEC	6.7	µg/kg	<i>Chironomus riparius</i>

### **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 (EMA/CVMP/ERA/418282/2005-Rev.1).

In the Phase II assessment, it is concluded that the product is very toxic to invertebrates and risks to surface water, soil, sediment and dung are identified. No risks for human consumption of groundwater, groundwater ecosystems and secondary poisoning are anticipated on the basis of the preliminary calculations.

The following risk mitigation measures are required for this VMP:

*The veterinary medicinal product is very toxic to aquatic organisms, soil organisms and dung insects.*

*The veterinary medicinal product should not be allowed to enter surface waters as it has harmful effects on aquatic and sediment organisms.*

*Treated cattle should not have direct access to surface water for 31 days and sheep for 16 days after treatment to avoid adverse effects on aquatic organisms.*

*Long-term effects of ivermectin on the population dynamics of dung organisms have not been investigated. Therefore, it is advisable not to treat animals on the same pasture every season.*

*In order to avoid accumulation of ivermectin in soil, it is advised not to spread manure containing the active substance on the same area of land in successive years.*

*Repeated treatments on a pasture within a season should only be given on the advice of a veterinarian*

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

The following information on environmental properties needs to be included in the product literature:

*Ivermectin is very toxic to aquatic organisms and dung fauna and can accumulate in soil and sediment. Like other macrocyclic lactones, ivermectin has the potential to adversely affect non-target organisms. Following treatment, excretion of potentially toxic levels of ivermectin may take place over a period of several weeks. Faeces containing ivermectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.*

### **PBT assessment**

The compound is not considered as PBT nor vPvB

## **B. Residues documentation**

### **Residue tests**

No residue depletion studies were conducted because it was demonstrated by comparative analysis of the candidate product with reference product 'Ivomec' that the candidate product contains the active substance as well as the excipients in very similar quantities as the reference product. No further residue depletion studies are therefore required as similar residue depletion is expected for the candidate product when compared to the reference product.

### **Maximum Residue Limits**

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

<b>Pharmacologically active substance</b>	<b>Marker residue</b>	<b>Animal Species</b>	<b>MRL</b>	<b>Target tissues</b>	<b>Other provision</b>	<b>Therapeutic Classification</b>
Ivermectin	22, 23-dihydro-avermectin B1a	All mammalian food producing species	30 µg/kg 100 µg/kg 100 µg/kg 30 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	Antiparasitic agents/ Agents acting against endo and ectoparasites

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

					consumption	
--	--	--	--	--	-------------	--

### **Withdrawal Periods**

Based on the data provided above, the following withdrawal periods are justified:

#### Cattle

*Meat and offal: 49 days.*

*Not authorised for use in animals producing milk for human consumption.*

*Do not use in pregnant animals which are intended to produce milk for human consumption within 60 days of expected parturition.*

#### Sheep

*Meat and offal: 63 days.*

*Not authorised for use in animals producing milk for human consumption.*

*Do not use in pregnant animals which are intended to produce milk for human consumption within 60 days of expected parturition.*

#### Pigs

*Meat and offal: 28 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.

### ***Development of resistance and related risk in animals***

Adequate warnings and precautions appear on the product literature.

### ***Tolerance in the target species of animals***

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

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

## 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.

Intermectin Injection 10 mg/ml solution for injection for cattle, sheep and pigs	NL/V/0431/001
Interchemie werken "De Adelaar" B.V.	MRP
Publicly available assessment report	

## 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.