IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Fatromectin 5 mg/ml pour-on solution for cattle.

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fatromectin 5 mg/ml Pour-on Solution for Cattle
Active substance(s)	Ivermectin
Marketing authorisation holder	ECO Animal Health Europe Limited
Marketing authorisation number	VPA22693/006/001
EU procedure number	IE/V/0177/001

PUBLIC ASSESSMENT REPORT

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Active substance(s)	Ivermectin
Marketing authorisation holder	ECO Animal Health Europe Limited 6th Floor South Bank House Barrow Street Dublin 4 D04 TR29 Ireland
Marketing authorisation number	VPA22693/006/001
Legal basis of application	Bibliographical, according to Article 13a of Directive 2001/82/EC as amended.
Date of authorisation	Fatromectin Cattle Pour-On was authorised in the RMS in April 2004. Subsequently, the product was authorised, through Mutual Recognition in FR and IT (Day 90: 21st December 2005) and the UK (Day 90: 27/02/2008)
Indication and target species	For the treatment and control of gastro-intestinal nematodes, lungworms, warbles, chorioptic and sarcoptic mange and sucking and biting lice of beef and non-lactating dairy cattle.
Method of sale and supply	Licensed Merchant
Additional supply restrictions	None

I. SCIENTIFIC OVERVIEW

This section reflects the initial scientific discussion on the approval of Fatromectin Cattle Pour-On. Please refer to section V for significant post-approval changes which are important for the quality, safety and efficacy of the product.

II. QUALITY ASPECTS

A. Composition

A.1 Composition of the Veterinary Medicinal Product
Active substance
Ivermectin 5 mg/ml
Excipients
Benzyl alcohol
Isopropyl alcohol
Polypropoxylate-2-myristyl ether propionate
N-methyl-2-pyrrolidone
Benzyl Alcohol
Water

A.2 Container/Closure System
The product is supplied in the following presentations :
250 ml white fluorinated high-density polyethylene bottle with a drawing tube and measuring device.
1.0 L white fluorinated high-density polyethylene bottle with a drawing tube and measuring device.
2.5 L white fluorinated high-density polyethylene back-pack with polypropylene strap and vented cap
5.0 L white fluorinated high-density polyethylene back-pack with polypropylene strap and vented cap.
250 ml natural fluorinated high-density polyethylene pour-on bottle with internal graduated calibration chamber
Closure: White polypropylene screw-cap.

A.3 Clinical Trial Formula(e)
The formulation of the batches used in key clinical studies are identical to that proposed for marketing.
A.4 Development Pharmaceutics
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

B.1 Manufacturing Formula
This information is commercially confidential.

B.2 Method of Preparation
The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

B.3 Validation of the Manufacturing Process
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C Control of Starting Materials

C.1 Active Substance
The active substance is Ivermectin, an established substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. The applicant has provided a certificate of suitability from one of the suppliers of active substance which certifies that the substance is suitably controlled by the monograph for Ivermectin. Batch analytical data demonstrating compliance with the specification have been provided.
A drug master file is provided from the second supplier and the active substance specification provided is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

C.2 Other Substances
Other substances in the product comply with relevant pharmacopoeia monographs and in-house specifications.

C.3 Packaging Materials
The product is packaged in containers of flourinated high density polyethylene (HDPE). The packaging materials comply with relevant EU standards.

D Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
There are no substances of ruminant animal origin present or used in the manufacture of this product.

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
F.1 Stability Studies on the Active Substance
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.
A retest period for the active substance is specified.

F.2 Stability Tests on the Finished Product
Stability data on the 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.

G Other Information
None

Conclusion on Quality
The manufacture of the product is adequately described and controlled. Testing methods and specifications for the raw materials and packaging components are acceptable. The control tests and specifications for the finished product are appropriate. The shelf life and storage conditions are supported by appropriate stability data.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.2.A Safety Testing

A.1 Precise Identification of the Product concerned by the Application
The product is a topical solution containing 0.5% w/v Ivermectin.

A.2 Pharmacological Studies

A.2.1 Pharmacodynamics:
Ivermectin is a mixture of two compounds belonging to the avermectin family, which are a macrocyclic lactone class of endectocides. Avermectin is a microbial metabolite of the soil organism Streptomyces avermitilis.
The evidence indicates ivermectin increases the release of γ amino butyric acid (GABA) to its post synaptic receptors which leads to consequent opening of chloride ion channels and decreased cell function. There is also evidence that ivermectin affects chloride ion channels directly and independently of GABA. The opening of the pre-synaptic chloride ion channel results in an efflux of chloride ions and depolarisation of the nerve terminal. These effects interfere with normal neurotransmission between nerves and muscles resulting in parasite paralysis and eventual death.

A.2.2 Pharmacokinetics
Bibliographical data documenting the pharmacokinetic characteristics of the substance were provided. Post dosing, the highest tissue concentrations were found in liver and fat tissue. Depletion from fat was slower than from liver tissue. Of the tissues investigated, muscle contained the lowest residues. The parent compound makes up at least 50% of the total residues at day 14. The excretion is in the faeces, following biliary excretion. Over 60% of the dose is excreted in the first 3 days after dosing.
In addition to the bibliography, the applicant carried out a study to compare the plasma levels of ivermectin after administration of Fatromectin Pour-On compared with the pioneer product Ivomec Pour-On. The study indicated that the pharmacokinetic profiles of ivermectin following the administration of Fatromectin or Ivomec are broadly similar. After

administration of Fatromectin Pour-On, the ivermectin is absorbed through the skin into the circulation of the treated animal. The maximum concentration in plasma occurs around 70 hours after application. Peak concentrations of about 7 ng/ml are obtained. For both products there was a large variability in plasma pharmacokinetic parameters between animals. This is a common feature of this molecule and may be associated with variable absorption due to factors such as metabolism, thickness of the skin, amount of fat, etc.

A.3 Toxicological Studies

The toxicological profile of ivermectin in laboratory and domestic animal species is well characterised. The bibliographic data provided concur with the conclusions on toxicity of ivermectin documented in the CVMP MRL Summary Reports for that molecule.

A.4 Studies of other effects

A.4.1 Special Studies

The results of laboratory animals studies and clinical use in humans give no indications of any effect on the immune system.

A.4.2 Observations in Humans

In patients with onchocerciasis, the side effects observed following ivermectin treatment are generally due to the exacerbated immune response to the liberation of larvae antigens in the host.

The use of ivermectin in pregnant women did not reveal any increased incidence of birth defects compared to the reference population.

In cases of inadvertent self-injection with ivermectin for animal use, the reactions included irritation at the injection site, nausea, pain and numbness at the injection site.

On the basis of the available data, it is evident that ivermectin, when administered to humans at the recommended treatment dose of 200 µg/kg, is generally well tolerated.

A.4.3 Microbiological Studies (studies on human gut flora and organisms used in food processing)

Ivermectin residues are unlikely to have any effect on the human gut flora or on micro organisms used in the industrial processing of foodstuffs.

A.5 User Safety

Based on the user safety assessment provided, it is accepted that:

When administering Fatromectin Pour-On, the most likely routes of exposure would be thorough the skin and the eye.

Ivermectin is used as a therapeutic agent in human medicine. Published data have been presented to indicate that ivermectin at 200 µg/kg (the recommended treatment dose for onchocerciasis) is well tolerated.

Extensive experience with ivermectin based products, including pour-on formulations, indicates that the potential for sensitisation and irritancy is low.

The excipients are widely used in topical and/or injectable veterinary medicines and human medicines and cosmetics.

Based on the assessment conducted, the user safety warnings and precautions as listed on the product literature are justified and are adequate to ensure safety to users when the product is used as directed.

A.6 Ecotoxicity

Warnings and precautions as listed on the product literature are in keeping with those agreed for similar products and are considered adequate to ensure safety to the environment when the product is used as directed.

III.2.B Residues documentation

B.1 Precise Identification of the Product concerned by the Application

The product is a topical solution containing 0.5% w/v Ivermectin.

B.2 Residue Studies

A confirmatory residue study was conducted in cattle.

Animals were treated with Fatromectin Pour-On at the dosage of 500 µg/kg of ivermectin on the back mid-line. All treated animals had residue levels below the LOQ in both liver (7.5 µg/kg) and fat (10.0 µg/kg), at all the slaughter times: 28, 35, and 42 days post administration.

This study confirmed that residue levels in liver and fat are below the respective MRLs by 28 days post dosing and supports a withdrawal period of 28 days in meat.

B.3. MRLs

Ivermectin is listed in Annex I of Council Regulation 2377/90.
MRLs are listed below:

Tissue	Bovine
Liver	100 µg/kg
Fat	100 µg/kg
Kidney	30 µg/kg

B.4. Withdrawal Periods

Based on the data provided above, a withdrawal period of 28 days for meat is justified. In accordance with Regulation 2377/90, ivermectin is contraindicated for use in cattle producing milk intended for human consumption and in accordance with current recommendations a withdrawal time of 60 days for dry dairy cows and pregnant heifers applies.

B.5. Analytical Methods Used

The levels of ivermectin were measured by reverse-phase HPLC followed by fluorescence detection. The method was satisfactorily validated.

IV. CLINICAL ASSESSMENT

III.3.A Pre-Clinical Studies

A.1 Pharmacology

Refer to A.2.2 above.

A.2 Tolerance in the Target Species of Animals

The Applicant has provided a published document that is a review of the safety of ivermectin in the target species. It is evident that ivermectin containing products may induce adverse effects when given in overdose. However, based on a review of 53 field trials (comprising 2367 cattle) it was concluded that the subcutaneous administration of ivermectin at twice the RTD to cattle was well tolerated and did not result in an increased incidence of adverse effects compared with animals given vehicle only. In addition, repeated treatments of ivermectin to pregnant females at doses of 400 µg/kg had no effects on the number of calves born and there were no treatment related abnormalities in the progeny. Also, administration of 400 µg/kg to 10 bulls on a single occasion had no observable effect on the capacity to produce sperm, libido or reproductive performance.
In addition to the bibliographic data, two tolerance studies were conducted to demonstrate the safety of the product in cattle. Based on the findings of these studies, it can be concluded that the candidate formulation is well tolerated in the target species when administered at up to three times the RTD. In addition to the tolerance studies, no reports of adverse effects following treatment were reported in any of the three field studies conducted in support of the present application

A.3 Resistance

The Applicant has provided a number of published papers relating to the subject of anthelmintic resistance generally and resistance to ivermectin. On the basis of these documents, the following can be concluded:

Gastrointestinal nematode parasites of cattle and sheep sooner or later develop resistance to commonly used anthelmintics. The rate of resistance development is influenced by a variety of diverse factors including husbandry practices, climate and genetic nature of resistance development.

Resistance of cattle nematodes to ivermectin has been reported, but it is evident that such reports are uncommon and it can be concluded that ivermectin resistance is not a significant practical problem in European cattle husbandry at the present time.

Adequate warnings and precautions appear on the product literature.

III.3.B Clinical Studies

B.1 Laboratory Trials
The applicant has provided a number of publications in support of the efficacy of ivermectin against a wide spectrum of endo- and ecto-parasites, when administered orally, subcutaneously or topically
On the basis of the published data provided, ivermectin, when applied topically at a dose of 500 µg/kg has been shown to be effective against the following parasites of cattle:
Gastro-intestinal worms (adult and fourth stage larvae):
Haemonchus placei
Ostertagia ostertagi (including inhibited larvae)
Trichostrongylus axei
Trichostrongylus colubriformis
Cooperiapunctata (adult only).
Strongyloides papillosus (adult only)
Oesophagostomum radiatum
Lungworm (adult and fourth stage larvae):
Dictyocaulus viviparous
Warbles (parasitic stages)
Hypoderma bovis
Hypoderma lineatum
Mange mites:
Sarcoptes scabiei var. bovis. This product may also be used to reduce infection of the mange mite *Chorioptes bovis*, but complete elimination may not occur.
Sucking and biting lice:
Linognathus vituli, Haematopinus eurysternus and Damalinia bovis.
Fatromectin pour-on has persistent activity against infections of Trichostrongylus axei and Cooperia spp. up to 14 days after treatment, but only in the case of group treatment, Ostertagia ostertagi and Oesophagostomum radiatum up to 21 days after treatment and Dictyocaulus viviparus up to 28 days after treatment. In addition it also has persistent activity against horn flies (Haematobia irritans) for up to 28 days after treatment. Partial efficacy against Haematobia irritans may last for up to 35 days post treatment.
B.2 Field Trials
The efficacy of ivermectin, when administered orally, parenterally or topically, against both endo- and ecto-parasites is well described in the literature. Having reviewed the available data, it is clear that ivermectin when administered topically at a dose of 500 µg/kg bodyweight is an effective substance to treat parasite infections associated with the species detailed in the indications for use for Fatromectin Pour-On. In addition, the persistent activity of ivermectin against certain nematode species is well documented.
In support of the bibliographic data, the applicant conducted field studies to confirm the efficacy of Fatromectin Pour-On against a limited number of parasite species. Although conducted with a limited number of parasite species, these studies indicate that Fatromectin Cattle Pour-On is therapeutically equivalent to Ivomec Pour-On for the parasite species studied and that both products demonstrated an acceptable level of efficacy.
In the absence of specific studies relating to the effect of rainfall at or around the time of treatment on the efficacy of the product, the product literature includes a recommendation that animals should not be let out in the rain for at least 2 hours after application, and should not be treated when the coat is wet.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

This is a bibliographic application according to Article 13a.
In support of this application, the applicant has provided the necessary published studies and where appropriate has augmented that information with a variety of studies conducted using the final formulation.
Based on the data presented, it is accepted that, when used as recommended, this product poses minimal risk to the end user or the environment. Appropriate warning statements are included on the product literature.
The proposed withdrawal period of 28 days is justified. In accordance with Regulation 2377/90, ivermectin is contraindicated for use in cattle producing milk intended for human consumption and in accordance with current recommendations a withdrawal time of 60 days for dry dairy cows and pregnant heifers applies.
The candidate formulation is well tolerated in the target species when administered at up to three times the RTD. Use of Fatromectin Pour-On in accordance with the recommended conditions of use should not increase the risk of resistance emergence.

Based on the available efficacy data, it is clear that Fatromectin Pour-On when administered topically at a dose of 500 µg/kg bodyweight is an effective substance to treat parasite infections associated with the parasite species detailed in the indications for use. In addition, the persistent activity of ivermectin against certain nematode species is well documented.
The overall benefit-risk is positive.

VI. 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 HPRA website. 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.

Changes:
Safety/Efficacy Changes

Summary of change (Application number)	**Approval date**
Introduction of changes to the SPC arising from the outcome of the Article 83 Referral for all veterinary medicinal products containing N-methyl pyrrolidone as an excipient, EMEA/V/A/146, (2023)2311 of 28 Mar 2023.	14/09/2023