IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

SLICE 2 mg/g premix for medicated feeding stuff

PRODUCT SUMMARY

EU Procedure number	IE/V/0534/001
Name, strength and pharmaceutical form	SLICE 2 mg/g premix for medicated feeding stuff
Active substances(s)	Emamectin benzoate
Applicant	Intervet Ireland Limited Magna Drive Magna Business Park, Citywest Road Dublin 24 Ireland
Legal basis of application	Full application (Article 12(3) of Directive No 2001/82/EC)
Target species	Atlantic salmon
Indication for use	For the treatment and prevention at group level of infestations of all parasitic stages of sea lice (*Lepeophtheirus* sp. and *Caligus* sp.) on Atlantic salmon (*Salmo salar*) ranging in size from smolts in freshwater, (just prior to transfer to seawater), to market weight fish in seawater
ATCvet code	QP54AA06
Date of conclusion of the mutual recognition repeat use procedure	27 September 2018
Date product first authorised in the Reference Member State	10 April 2001 (UK) 27 October 2000 (IE)
Concerned Member States	First Use: Finland, Iceland, Ireland (now RMS) and Spain. Repeat Use: Denmark, Germany, Greece, France, Italy and Portugal UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive

2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

The application is for a premix for medicated feed containing emamectin benzoate, an avermectin, for the treatment and prevention at group level of all parasitic stages of sea lice (*Lepeophtheirus sp.* and *Caligus sp.*), on Atlantic salmon (*Salmo salar*), ranging in size from smolts in freshwater (just prior to transfer to seawater) to market weight fish in seawater.

The medicated feed is fed to fish at the recommended feeding rate of 0.5% biomass/day for 7 days which will yield a dose rate of 50 micrograms/kg biomass/day. If the feeding rate differs from 0.5% biomass/day, then the concentration of SLICE in feed must be adjusted proportionately. Refer to the Summary of Product Characteristics (SPC) for further information.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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. 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition

The product contains emamectin benzoate 2.00 mg (equivalent to 1.76 mg of Emamectin), and the excipients propylene glycol, butylated hydroxyanisole, maize starch and maltodextrin M-100.

The container/closure system consists of a heat sealed laminate foil pouch, composed of polypropylene/low density polyethylene/aluminium foil. Fill weight 2.5 kg/pouch. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the 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.

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 100kg scale batches using high-shear mixing. emamectin benzoate is adsorbed onto maize starch wetted with a solution of the antioxidant, butylated hydroxyanisole, in propylene glycol. This mixture is diluted with maltodextrin M-100. The product is filled into pre-formed pouches, 2.5 kg per pouch, and heat-sealed.

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

II.C. Control of Starting Materials

The active substance is emamectin benzoate, an established active substance which 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.

The excipients consist of propylene glycol, butylated hydroxyanisole, maize starch and maltodextrin M-100, which comply with the US Pharmacopoeia or United States National Formulary specifications.

The container is a laminate foil pouch (12 x 15) composed of polypropylene/low density polyethylene/aluminium foil. Fill weight 2.5 kg/pouch, which is heat sealed on three sides. Pack sizes are a single 2.5kg pouch or a fibre drum containing 8 x 2.5 kg pouches.

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, identity (emamectin, hydroxyanisole and benzoate), moisture, assay (emamectin & hydroxyanisole) and related compounds. The absence of a test for microbiological purity is justified by controls applied to input, and by findings of low vulnerability to spoilage organisms.

II.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.

G. Other Information

This veterinary medicinal product does not require any special storage conditions.
Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after incorporation into meal or pelleted feed: 6 months.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

No specific pharmacodynamic studies with emamectin were provided, however, reference was made to published literature. The applicant made reference to the pharmacokinetics and biotransformation of the active ingredient in rats Two pharmacokinetic studies were also carried out in Atlantic salmon. See section IV, Clinical Documentation.

Toxicological Studies

The applicant has provided bibliographical data which were reviewed by the CVMP during consideration of an application for MRLs for Emamectin.

User Safety

A Safety Expert Report was provided; which addressed the safety of the product to users.
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:

- Wear gloves, protective work clothing, dust mask and safety glasses with side shields when handling SLICE in the preparation of medicated fish feed.
- Wash hands thoroughly with soap and water after handling the product or medicated feed and before eating or smoking.
- Do not smoke or eat while handling the medicated feed.

Environmental Safety

An Expert Report was provided concluded that the use of emamectin benzoate to treat lice infestation in salmon should create no risk of adverse impacts on sensitive pelagic life, vertebrate on invertebrate.

III.B.2 Residues documentation

Residue Studies

Pharmacokinetic studies were carried out in rats and the target species. The studies in rats were reviewed by the CVMP during consideration of the application for maximum residue limits (MRLs), for emamectin, the applicant also provided bibliographical data.

Conclusion:

- Concentrations of the marker residue in all samples of muscle plus skin in natural proportions were below the limit of quantification of the analytical method.
- In a study at 5˚C, using 10 fish per time point, concentrations of total radiolabelled residues in all samples of muscle and skin were below the MRL of 100 *µg/kg*.
- *A zero withdrawal period is appropriate.*

MRLs

Emamectin is currently included in Annex I of Council Regulation (EEC) No. 2377/90 as follows:

Pharmacologically active substance(s)	Marker residue	Animal Species	MRLs	Target tissues	Other provisions
Emamectin	Emamectin B 1 a	Salmonidae	100 *µg/kg*	Muscle and skin	

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days is justified.

To ensure that tissue residues do not exceed the MRL, fish must not be treated more than once in the 60 days prior to their first being harvested for human consumption.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics:

Emamectin benzoate is a member of the avermectin family, which as an antiparasitical group, are active against a range of nematodes (roundworms) and arthropods (insects, ticks, lice, mites).

No specific pharmacodynamic studies with emamectin have been provided and it is acknowledged that the precise mechanism by which emamectin benzoate kills sea lice has not been elucidated. However, pharmacodynamic aspects have been addressed by reference to published literature, and extensive research on the mode of action of avermectin compounds against invertebrate species has shown that the avermectins competitively bind to glutamate-gated chloride channels on invertebrate nerves. The distribution of glutamate-gated chloride channels in the invertebrate may be localised to specific muscles such as those of the pharyngeal pump.

Pharmacokinetics:

Emamectin benzoate is relatively slowly absorbed but it is also widely distributed to the tissues. Excretion is also relatively slow. Two studies were carried out in Atlantic salmon, these comprised of a whole-body autoradiography study (single dose), and a metabolism and residue depletion study (multiple dose). The studies supported the indication cited in the SPC.

Tolerance in the Target Species

The applicant has conducted a target animal tolerance study using multiples of the recommended dose in the target species for 7 days.

At the recommended dose emamectin benzoate produced no undesirable effects in the clinical trials, apart from a slight reduction in appetite during the medication period in two trials. A change in the source and pellet size of the medicated diet may have contributed to this effect. The SPC carries suitable warnings.

Resistance

The bibliography / additional information provided suggests that drug resistance has developed to some of the avermectins in terrestrial parasites and so it could be expected that sole reliance of a sea lice avermectin would increase the selection pressure to develop a tolerant strain.

To reduce the possibility of resistance development in sea lice, it is recommended that SLICE be used in integrated control programmes.

Adequate warnings and precautions are included in the SPC and appear on the product literature.

IV.II. Clinical Documentation

An extensive clinical programme was undertaken observing use of the proposed product in Atlantic salmon, which included:

- Probe efficacy study.
- Dose titration study.
- Two laboratory based dose confirmation studies.
- Three higher water temperature UK field trials with natural disease outbreaks.
- Two lower temperature UK field trails with natural disease outbreaks.
- A Canadian field trial.
- A laboratory based duration of efficacy study.
- Four Norwegian field trails.

Dose Confirmation Study (1)

This study was initiated in order to confirm the optimum dose of emamectin benzoate in the treatment of sea lice (*L. salmonis*) infection in Atlantic salmon. Sixteen fish were placed into each of 9 tanks at ambient conditions, and infected with *L. salmonis*. All fish were fed either an unmedicated feed or the proposed product for 7 days, after which, all fish were fed unmedicated feed. Lice were counted on days 7, 14 and 21. No adverse effects were attributable to application of the product. A dose of 50 µg/ml of emamectin benzoate was considered efficacious, and used in further studies.

Dose Confirmation Study (2)

A second study conducted under the same conditions as study 1 above was undertaken. The selected dose for emamectin benzoate was 50 µg/ml. Efficacy of the product was confirmed at this dose.

Field trials

For all field trials, the percentage efficacy was calculated by Abbott's formula, based on the geometric mean number of sea lice/fish. The average weight of the fish was noted.

First high temperature field trial

The study was designed to observe the efficacy of emamectin benzoate against *L. salmonis* and *C. elongates* in Atlantic salmon, at a dose rate of 50 µg/kg biomass/day. Fish were kept at a temperature range of between 12 – 15.5^{o}C.

Each of two cages contained 180 Atlantic salmon. Medicated feed was prepared by dissolving emamectin in propylene glycol, combining the mixture with herring oil and coating the feed with the medicated fish oil. Fish were fed at a rate of 0.75%

biomass/day; 0.25% unmedicated for both groups followed by 0.5% either as unmedicated feed or medicated feed for 7 consecutive days. The initial unmedicated feed was used to reduce the appetite of the more aggressive fish to produce a more even feed response when the medicated feed was given. After the first 7 days, all fish were fed unmedicated feed.

No adverse effects attributable to emamectin were noted. Fish treated with emamectin had fewer lesions than untreated fish.

Efficacy was observed to be more striking against *L. salmonis* than against *C. elongatus*.

Second high temperature field trial

A second study was performed to evaluate emamectin benzoate in a field trial against *L. salmonis* and *C. elongatus*. Four cages, two cages treated with the proposed product and two untreated cages, each contained 149 salmon.

Medicated feed was prepared by dissolving emamectin benzoate in propylene glycol, combining the mixture with herring oil and coating the feed with the medicated fish oil. Fish were fed at a rate of 0.75% biomass/day; 0.25% unmedicated for both groups followed by 0.5% either as unmedicated feed or medicated feed for 7 consecutive days. After the first 7 days, all fish were fed unmedicated feed. Sea lice were counted on 20 fish selected at random from each cage on study days -2, 7, 14 and 21.

Fish treated with emamectin showed reduced numbers of parasites compared with the control group. Efficacy was observed to be more striking against *L. salmonis* than against *C. elongatus*.

First low water temperature field trial

The purpose of this study was to evaluate the efficacy of emamectin benzoate in a field trial against natural sea lice (*L. salmonis*) infestations in Atlantic salmon under winter conditions, using a dose of 50 µg/ml. Four sea cages were used consisting of two treated cages (fed medicated feed), and two untreated cages (fed unmedicated feed). The sea temperature ranged from 5.8 - 8.5°.

Each cage contained 360 Atlantic salmon. Medicated feed was prepared by dissolving emamectin in propylene glycol, combining the mixture with herring oil and coating the feed with the medicated fish oil. Fish were fed at a rate of 0.5% biomass/day; 0.1% unmedicated for both groups followed by 0.4% either as unmedicated feed or medicated feed for 7 consecutive days. After the first 7 days, all fish were fed unmedicated feed. Sea lice were counted on 20 fish selected at random from each cage on study days -1, 7, 14 and 21.

Fish treated with emamectin benzoate showed reduced numbers of parasites compared with the control group.Second low temperature water trial

The objective of this study was to evaluate the efficacy of emamectin benzoate in the treatment of natural sea lice (*L. salmonis*) infestations in Atlantic salmon. The proposed dose of 50 µg/kg/day was used.
Four sea cages were divided into 4 replicate blocks, each consisting of a treated cage (fed medicated feed, and an untreated cage (fed unmedicated feed). The sea temperature ranged from 5.5 - 7.5°C.
Each cage contained 16,000-18,000 Atlantic salmon. Medicated feed was prepared by dispersing emamectin benzoate .2% aquaculture premix in sunflower oil, then coating the feed with the medicated oil. Fish were fed at a rate of 0.4 % biomass/day either an unmedicated feed or medicated feed for 7 consecutive days. After the first 7 days, all fish were fed unmedicated feed. Sea lice were counted on 15 fish selected at random from each cage on study days -1, 7, 14, 21 and 5 fish per cage on study days 28 and 35.
Fish treated with emamectin showed reduced numbers of parasites compared with the control group.
Third high temperature water trial
This study evaluated the efficacy of emamectin in the treatment of natural sea lice (*L. salmonis*) infestations in Atlantic salmon. The proposed dose of 50 µg/kg/day was used.
Sixteen pens were used, consisting of 12 treated pens (total = 184,908 fish) and four untreated pens (total = 62,435 fish). The sea temperature ranged from 9.8 - 14.0°C.
Medicated feed was prepared at a commercial feed mill by coating emamectin benzoate 0.2% aquaculture premix onto the feed and finally coating the feed with fish oil. Fish were fed at a rate of 1.0 % biomass/day. After the first 7 days, all fish were fed unmedicated feed. Sea lice were counted on 10 fish selected at random from four treated and four untreated pens on study days -1, 13, 27 and 77. In addition, sea lice were counted on 5 fish from one treated and one untreated pen on study days 34, 42, 49, 54, 64 and 72.
The results indicate that 90-96% efficacy against *L. salmonis* was obtained from day 27 through to day 64.

<u>Canadian field trial</u>
The objective of this trial was to evaluate the efficacy of emamectin against natural infestations with sea lice (*L. salmonis*) on Atlantic salmon. Fish had been treated with ivermectin prior to the trial, but all treatment had stopped one month before the emamectin benzoate trial.
A total of 151,351 first year Atlantic salmon were treated at two sites with either SLICE in feed, (76,210 fish), at the proposed dose of 50 µg/kg/day for 7 consecutive days, or acted as untreated controls (75,141 fish). After the first 7 days, all fish were fed unmedicated feed. Fish were fed at a rate of 2.33% biomass/day (Minsters Island) or 2.77% biomass/day (Davidson Head). Medicated feed was prepared by coating Slice, with fish oil, onto prepared commercial salmon pellets.

At each site, 4 pens of fish were used consisting of 2 treated cages (fed medicated feed), and two untreated cages (fed unmedicated feed). The sea temperature ranged from 9.0 - 15°C.
Sea lice (copepodite/chalimus, pre-adult/adult and gravid female) were counted on Study Days -5/-6, 7/8, 14/16, 22, 28/29 and 43/44 at both sites. Lice were also counted at site 1 on Study Day 35, and at site 2 Study Days -12, 57, 73, 92 and 115.
Untreated control pens received bath treatments with azimethiphos on Study Days 9, 22 and Study Days 31 (site 1) and 10, 33 and 58 (site 2) in order to avoid excessive production losses.
Within 3 weeks of treatment (Study Days 28/29), the efficacy of Slice had increased to>90% against all life stages of sea lice.
Because the untreated controls received 3 baths with azimethiphos, there was a reduction in efficacy against copepodite/chalimus and the total number of lice/fish at those time points.
The efficacy against pre-adult/adult and gravid females was 93-100% from 14-67 days after treatment. Mortality rates were similar for both groups and no mortality or adverse effects attributable to emamectin benzoate were noted.
The study demonstrated that emamectin benzoate had excellent efficacy for at least 67 days after treatment.

Laboratory-based duration of efficacy trial
The duration of efficacy trial demonstrated that constantly challenged Atlantic Salmon were protected from significant infestation for up to 55 days after the end of treatment.

Norwegian field trials
This study was performed at 4 locations evaluating the efficacy of emamectin benzoate 0.2% aquaculture premix in the oral treatment of natural sea lice infestations in Atlantic salmon. Sea lice infestations were predominantly of *L.salmonis* and to a lesser degree, *C. elongatus*. Fish were under reinfestation pressure throughout these trials.

A total of 1,170,543 first year Atlantic salmon were involved in the study. 561,266 fish were treated with emamectin benzoate 0.2% aquaculture premix in feed at a target dose rate of 50 µg/kg bodyweight/day for 7 consecutive days and 609,277 fish were treated with an insect growth regulator at a target dose rate of 10 mg/kg bodyweight/day for 7 consecutive days. Fish were then held under commercial rearing conditions. At each site, 6 pens of fish were divided into 3 replicates, which each consisted of a pen treated with emamectin benzoate and a pen treated with teflubenzuron. The sea temperature ranged from 12.8 - 15.8°C.

Counts of sea lice were made on study days -3, 1, 8, 15 and 21. (Study day 0 was the first day of treatment). In addition, sea lice were counted at one site on study day 35 and at another site on day 51.

The number of sea lice fell following treatment with both emamectin benzoate and teflubenzuron and remained low during the subsequent observation period. Of the total number of fish treated, those treated with emamectin benzoate had statistically significantly lower total lice counts on days 14 and 21 than those treated with teflubenzuron.

In the locations at which sea lice were counted beyond day 21, a more persistent effect was apparent in the emamectin treatment group compared with the teflubenzuron treatment group. No fish mortality or adverse effects attributable to treatment with emamectin benzoate were noted.

Lack of a negative control lessened the power of the study, but data contributed to the establishment of the efficacy of the product and to the final information contained within the SPC.

The comprehensive programme of field trials indicated that control of sea lice was very effective as lice numbers at all stages were reduced.

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.