Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Azasure 500 mg/g Powder for Suspension for Fish Treatment
(United Kingdom)

Azasure vet 500 mg/g Powder for Suspension for Fish Treatment – vet
(Norway)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0492/001/DC
Name, strength and pharmaceutical form	Azasure 500 mg/g Powder for Suspension for Fish Treatment
Applicant	Ground Animal Health Ltd Unit 8 Dock Offices Surrey Quays Road London England SE16 2XU
Active substance(s)	Azamethiphos
ATC Vetcode	QP53AF17
Target species	Farmed Atlantic salmon (*Salmo salar*)
Indication for use	For the control of mature pre-adult to adult sea-lice (*Lepeophtheirus salmonis*) or (*Caligis* species) on farmed Atlantic salmon.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23rd October 2013
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Norway.

I. SCIENTIFIC OVERVIEW

Azasure 500 mg/g Powder for Suspension has been developed as a generic of Salmosan 50% Powder for Suspension. Azasure 500 mg/g contains the active substance azamethiphos and is indicated for the control of sea-lice on farmed Atlantic salmon. The product is suspended in water and a concentration of 0.1 mg/l azamethiphos is produced in use.

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[1].

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.

[1] SPC – Summary of Product Characteristics

II. QUALITY ASPECTS

A. Composition

The product contains the active substance azamethiphos and the excipients sodium lauryl sulphate, naphthalene sulphonic acid formaldehyde concentrate, kaolin light and colloidal silicon dioxide .

The container/closure system consists of either a 20g pack size of a heat-sealed polyvinylalcohol water soluble bag containing 20g of product contained in a sealed aluminium/polyethylene sachet. Either 2 x 20g packages in an outer carton or 5 x 20g packages in an outer carton. Or, 100 g of product contained in a heat sealed polyvinylalcohol water soluble bag packaged in a sealed aluminium/ polyethylene sachet. The product is supplied in an outer carton containing 5 x 100 g sachets. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation is 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. The product is manufactured by blending and milling the azamethiphos and excipients to form a powder. The powder is then re-blended and filled into PVA bags which are then heat sealed before sealing in an outer aluminium/polyethylene sachet. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is azamethiphos an established active substance not described in a Pharmacopoeia. Data on the active substance were supplied in the form of an in-house specification. 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.

The excipients sodium lauryl sulphate, colloidal silcicon dioxide and kaolin light comply with their respective monographs. In-house specifications have been provided for naphthalene sulphonic acid formaldehyde condensate. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

Not applicable.

F. 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. The tests on the finished product include tests for appearance, assay of the active substance, pH, active suspensibility, wettability, wet sieve residue, moisture, disintegration and microbial purity.

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.

G. 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. The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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. Data were presented for batches stored at 30°C/60%RH and 40°C/75%RH. A shelf life of 6 months has been established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the product as packaged for sale: 2 years.
- Do not store above 25°C.
- Store in the original unopened packaging.
- Store in a dry place.
- Store away from food, drink and animal feedingstuff.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because if the nature of the product, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because if the nature of the product, results of toxicological studies are not required.

User Safety

A full user safety assessment was not required as this is a generic application and bioequivalence with the reference product can be assumed. The same warnings and precautions as listed on the reference product are adequate to ensure safety to users of the product:

- The prescribing veterinary surgeon must ensure that farm staff have received adequate instruction in the safe use of the product.
- MAY CAUSE SENSITISATION BY INHALATION AND SKIN CONTACT
- The Control of Substances Hazardous to Health Regulations 1988 (COSHH) applies to the use of this product at work.
- The product contains azamethiphos. Azamethiphos is an organophosphorus compound. DO NOT USE if under medical advice not to work with such compounds.
- WEAR SUITABLE PROTECTIVE CLOTHING (WATERPROOF COVERALLS), SUITABLE PROTECTIVE GLOVES (heavy duty gauntlet style nitrile at least 300mm in length and 0.5mm thick are recommended) AND FACE PROTECTION (FACE SHIELD) when handling the concentrate (i.e., mixing or transferring product from one container to another) and when applying the diluted chemical to the pen. Renew protective clothing and gloves regularly and certainly when cracking or damage has occurred. Initial dilution of the water soluble bags into a small volume of distilled water must be carried out on land, ensure that the drum container is securely closed during this process.
- RINSE APPLICATION EQUIPMENT AND CONTAINERS AFTER USE
- WASH ALL PROTECTIVE CLOTHING thoroughly after use especially the insides of gloves.
- REMOVE HEAVILY CONTAMINATED CLOTHING IMMEDIATELY, wash or destroy.
- DO NOT EAT, DRINK OR SMOKE without first withdrawing from the work area, removing protective clothing and washing hands, face and exposed

skin.

- AVOID ALL CONTACT BY MOUTH, WITH THE SKIN OR EYES.
- ACCIDENTAL SPLASHES ON EXPOSED SKIN OR EYES should be washed off immediately with plenty of water.
- WASH HANDS, FACE AND EXPOSED SKIN after leaving the work area.
- KEEP AWAY FROM FOOD, DRINK AND ANIMAL FEEDINGSTUFFS.

MEDICAL ADVICE TO USERS

- If you have previously felt unwell after using a product containing an organophosphorus compound consult your doctor before working with this product and show your doctor the product label.
- If you feel unwell after using this product consult your doctor and show your doctor the product label.
- Treat any cases of heavy contamination as an emergency. You should go straight to hospital after removing contaminated clothing, and rinse with plenty of water areas of skin which came into contact with the product.
- If the product has been swallowed go straight to hospital and take the product label with you.

MEDICAL ADVICE TO DOCTORS

Poisoning from organophosphorus compounds results from blockage of acetylcholinesterase, with a resultant over-activity of acetylcholine.

Symptoms include headache, exhaustion and weakness, mental confusion together with blurred vision, excessive salivation and sweating, cramp-like abdominal pain, chest tightness, diarrhoea, constricted pupils and bronchorrhea. These may develop for up to 24 hours after exposure. Severe poisoning can include general muscle twitching, loss of coordination, extreme difficulty with breathing and convulsions which may lead to unconsciousness in the absence of medical treatment. Treat symptomatically and seek urgent hospital transfer if poisoning is suspected. Advice on clinical management is available from the National Poisons Information Service.

REPORTING INCIDENTS

In the UK

Illness suspected to be a result of working with the medicine may be reportable under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995. If in doubt contact your local Health and Safety Executive Officer.

Report human or veterinary suspected adverse reactions to the Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS or online at http:www.vmd.defra.gov.uk/adversereactionreporting/.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required as the product is an endoparasiticide to be used in a non-confined aquatic environment.

A Phase II assessment was provided. The applicant submitted summaries of field studies including a Sentinal Species Deployment Study. The study found no significant impact when investigating azamethiphos toxicity in mussel larvae and could not relate any lobster larvae mortalities to azamethiphos. A summary was also provided for a long term post-authorisation monitoring programme that was set up with the aim of determining if azamethiphos use would have long-term or wide-scale ecological consequences. No adverse effects were observed on zooplankton or phytoplankton and no treatment related effects were seen on meiobenthos, macrobenthos and barnacle settlements following use of azamethiphos at commercially operating fish farms.

The applicant also provided PEC[2] calculations for surface water (PEC_{sw}) and determined the risk quotient (PEC/PNEC[3]). The applicant has followed VICH guidelines and calculated the PEC values in accordance with SEPA (Scottish Environment Protection Agency) as recommended by the CVMP. Due to the nature of the product the risk to the environment is greatest immediately after treatment (RQ >1) but that this will reduce over time. The applicant has refined the calculations to produce the risk quotient (RQ) for aquatic organisms 3 hours post-treatment of a single cage of 0.76 and an RQ for aquatic organisms 72 hours post last treatment of 1.4 within the allowable zone of effect (AZE) and <1 outside the AZE. The $PEC_{sediment}$ was also provided and the RQ calculated to be <1. It was concluded that the risk to aquatic organisms and sediment dwellers is acceptable.

The following warnings are included on the SPC and product literature:

- This product is dangerous to fish and other aquatic organisms in the concentrated form. Do not contaminate ponds, streams, lochs or inlets with product or used packaging.

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

In addition the following warning appears under Section 5.3 of the SPC:

- Azamethiphos is highly soluble in water (>1 g/L) with a low octanol/water partition coefficient (log Kow) of 1 g/mL. These characteristics indicate that azamethiphos will remain in the aqueous phase and will not bioconcentrate or bioaccumulate in biota. Azamethiphos has a moderate

[2] PEC – Predicted Environmental Concentration
[3] PNEC – Predicted No Effect Concentration

propensity to adsorb to suspended organic matter (koc 500 l/kg), however it is unstable in saltwater, degrading with a half-life <5 days (12°C) producing non-toxic transformation products.

III.B Residues documentation

Residue Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because if the nature of the product, results of residue studies are not required.

MRLs

There are no MRLs established for azamethiphos in Salmon. The residues in salmon muscle and skin were always below the limit of detection in data submitted to the CVMP for assessment. MRLs are also not required for the excipients sodium lauryl sulphate, kaolin light and silicic acid. Napthalene sulphonic acid formaldehyde condensate is considered to be outside the scope of Regulation 470/2009 so also has no MRL.

Withdrawal Periods

A withdrawal period of 10 degree days has been established.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because if the nature of the product, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because if the nature of the product, no new target animal tolerance data has been generated. The applicant has provided reference papers to support the use of the immersion bath method of administration. The risks to the fish have been identified and the importance of adequate oxygenation highlighted. Necessary warnings have been included in the SPC:

- At water temperatures above 10°C it is advisable to limit treatment periods to 30 minutes. Vigorous oxygenation of the water must be provided during treatment.

- For external use only.
- During treatment, careful observation of fish behaviour must be maintained. If signs of distress, e.g., fish falling on their side, occur after 30 minutes of treatment, remove the tarpaulin and ensure vigorous oxygenation of the water.
- The product should be applied to salmon suffering from infestation with sea-lice before the stage at which serious skin damage is evident.

Resistance

The applicant has referenced published studies relating to the resistance of sea lice to azamethiphos. The results of the study showed variable resistance to azamethiphos in different populations of sea lice. Resistance has been identified to organophosphates and the mechanisms of resistance include delayed penetration and target site resistance with different acetylcholinestarases identified with different sensitivity to azamethiphos. Resistance is thought to have developed through repeated use of a single chemotherapeutic agent.

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

SPC Section 4.4

Repeated use of the same class of chemotherapeutic agent may result in the development of resistance.

In order to reduce the risk of resistance to the product developing, the product should be used as part of a multi-tactic pest-management program.

Oxygenation must be provided during treatment. Vigorous oxygenation is recommended in the treatment cage. Where several cages are to be treated a large reservoir of oxygen bottles should be available.

Do not use the product prophylactically. Only use when infestation with adult lice has been diagnosed.

SPC Section 5.1

Azamethiphos is an organophosphorus insecticide.

Resistance of sea lice to azamethiphos, and other organophosphates, can occur through alteration of acetylcholinesterase due to genetic mutation influenced by natural selection.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because of the nature of the product, results of laboratory trials are not required.

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 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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)