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

Asperix Vet, 49.5 % w/w Hydrogen Peroxide Concentrate for Solution for Fish Treatment

Date Created: 20th March 2018

PuAR correct as of 27/02/2019 when RMS was transferred to NO.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0625/001/DC
Name, strength and pharmaceutical form	Asperix Vet, 49.5 % w/w Hydrogen Peroxide Concentrate for Solution for Fish Treatment
Applicant	Evonik Resource Efficiency GmbH Rellinghauser Straße. 1-11 D-45128 Essen Germany
Active substance(s)	Hydrogen peroxide
ATC Vetcode	QD08AX01
Target species	Atlantic salmon (*Salmo salar)*
Indication for use	For the treatment of salmon suffering from infestation with motile (pre-adult to adult) sea lice, *Lepeophtheirus salmonis* or *Caligus spp,* prior to the stage where serious tissue damage occurs.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

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 conclusion of the decentralised procedure	18th October 2017
Date product first authorised in the Reference Member State (MRP only) For Repeat Use or Extension, add date of original procedure	Not applicable
Concerned Member States for original procedure	Iceland, Norway

I. SCIENTIFIC OVERVIEW

This was a generic application in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The reference product is Paramove 50, 50% hydrogen peroxide solution, concentrate for bath treatment which was authorised in the UK between 1995 and 2006.The product is indicated for the treatment of salmon suffering from infestation with motile (pre-adult to adult) sea lice, *Lepeophtheirus salmonis* or *Caligus spp,* prior to the stage where serious tissue damage occurs. The product is a concentrate for solution for fish treatment which is administered by the total enclosure method.

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.[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 [2] 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.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 49.5% w/w hydrogen peroxide and the excipients disodium dihydrogen diphosphate, nitric acid and deionised water.

The container/closure system consists of a reusable stainless steel ISO-container with the capacity of 25 000 litres. 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 a simple mixing of the active substance and ingredients. 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 hydrogen peroxide which is manufactured to manufacturers specifications. 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 excipient nitric acid is described in the European pharmacopoeia (Ph. Eur) with a content of 68.0 to 70.0% w/w. However, for safety reasons nitric acid is purchased from the supplier as a 20% solution. Therefore, specifications are based on the requirements of the Ph.Eur with appropriate modifications for the assay. The identification tests comply with United States National Formulary. Disodium dihydrogen diphosphate is manufactured to the manufacturers own specifications.

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 include those for: assay, appearance, identity, colour, apparent pH, phosphates, nitrate, and total carbon.

II.F. Stability

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.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 12 months

Store in the original container.
Do not return product to original container.
Store in a secure place and out of reach of children
Do not store above 25 °C.
Protect from direct sunlight. Store away from heat sources.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

This application was a generic application based on Article 13(1) of Directive 2001/82/EC, as amended. The product is for topical treatment and therefore it is not possible to demonstrate bioequivalence with the reference product. However, the product has the same pharmaceutical form, contains the same active substance in the same quantity, and the same excipients in similar quantities, as the reference product; and the minor differences in formulation are not considered to impact on availability or local tolerance of the active substance. Therefore, the absence of pharmacological and toxicological data is acceptable.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. The posology and indications are the same as those of the reference product and the same user warnings that feature on the SPC of the reference product are proposed. 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:

Harmful

Corrosive

Oxidising Agent

Do not attempt to administer the product unless you have been fully trained to handle and use the product, and are fully aware of operational and safety procedures. Hydrogen peroxide is corrosive.

This product is harmful if swallowed or if inhaled and may cause respiratory irritation. Avoid breathing dust/ fume/ gas/ mist/ vapours/ spray.

Avoid contact with skin and eyes. This product may cause skin irritation and serious eye damage.

Wear personal protective equipment whilst handling this product, consisting of chemically resistant headgear, face shield or safety goggles, chemically resistant PVC acid suit/ oilskins, chemically resistant PVC gloves (with cuff under suit) and safety rubber boots (with suit over boots).

Before commencing handling of this product ensure a supply of fresh water and preferably eye wash solutions are available.

IN CASE OF INHALATION: Remove person to fresh air and keep comfortable for breathing. If you feel unwell SEEK IMMEDIATE MEDICAL ATTENTION by calling a physician or National Poisons Information Centre.

IN CASE OF ACCIDENTAL EYE CONTACT: Rinse immediately with plenty of clean water for several minutes. SEEK IMMEDIATE MEDICAL ATTENTION by calling a physician or National Poisons Information Centre. Remove any contact lenses, if easy to do so and continue rinsing eyes.

IN CASE OF ACCIDENTAL SKIN CONTACT: Immediately remove any contaminated clothing. Wash the exposed skin immediately with water and seek medical advice if irritation persists. Thoroughly clean the contaminated clothing by soaking with plenty of water before re-using.

IN CASE OF ACCIDENTAL INGESTION: Seek medical attention immediately and show the package leaflet or the label to the physician.

Always wash hands with soap and water directly after use.

Environmental Safety

The environmental risk assessment (ERA) was carried out in accordance with VICH[3] and CVMP[4] guidelines.

Phase I:
The Phase I VICH exposure decision tree was completed. Since it was confirmed that the aquatic species to be treated is not reared in a confined facility (Question 9 of the VICH decision tree), a Phase II risk assessment was required.

Phase II Tier A:
A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physicochemical properties, environmental fate and effects.

Exposure of the environment will be via the water containing hydrogen peroxide, used to treat farmed Atlantic salmon, being discharged directly into the marine environment. Results from proprietary studies and from studies available in published literature were provided. The active substance, hydrogen peroxide, was used in the assays.

Physicochemical properties

Study type	Result	Remarks
Water solubility	100%	In published literature
Dissociation constants in water (pKa)	11.62 at 25ºC	In published literature. Indicates a weak, inorganic acid
UV-Visible absorption spectrum	Not applicable as hydrogen peroxide has absorption maxima from 200 to 750 nm	
Melting point/ Melting range	-0.43°C at 101.3 KPa	In publish literature
Vapour pressure	299 Pa at 25°C	In publish literature

[3] VICH – Veterinary International Conference on Harmonisation.
[4] CVMP - Committee for Medicinal Products for Veterinary Use.

Study type	Result	Remarks
n-Octanol/Water partition coefficient ($logP_{ow}$)	-1.57 at 20ºC)	No significant potential. As the $logP_{OW}$ is <4, assessments for bioaccumulation, PBT status or secondary poisoning are not required.

Hydrogen peroxide is a hydrophilic compound and miscible with water in all proportions. On entry into seawater, only the water column will be exposed to the active substance.

Environmental fate

Study type	Result	Remarks
Degradation in aquatic system (DT_{50})	1.6 days at 9°C	Indicates that degradation in aquatic systems will proceed rapidly in the presence of catalytic materials such as metals and organic matter.

Environmental effects

Study type	Endpoint	Result
Fish, acute toxicity (*Pimephales promelas*)	LC_{50}	16.4 mg/l
Aquatic invertebrates (*Daphnia pulex)* acute toxicity	EC_{50}	2.4 mg/l
Aquatic invertebrates, Marine acute toxicity (*Acartia tonsa)* ISO 14669:1999	LC_{50} NOEC	1.07 mg/l 0.38 mg/l
Aquatic invertebrates (*Daphnia magna)* 21 day (chronic) toxicity	NOEC	0.63 mg/l
Algae/ Marine *Skeletonema costatum* acute toxicity PARCOM 1990	EC_{50} NOEC	1.62 mg/l 0.63 mg/l

Risk Characterisation

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNECs) were calculated from the above environmental effect concentrations. In this instance, the PNEC value acts as a surrogate for an environmental quality standard (EQS) value. The PNEC/EQS values are compared with predicted exposure concentration (PEC) values which are determined using the modelling discussed below.

$PEC_{surface\ water}$ values have been calculated according to the SEPA[5] manual for models as recommended by the CVMP guidance document, EMEA/CVMP/ERA/418282/2005-Rev.1. Both short-term and the long-term bath treatment models were employed as implemented by SEPA (SEPA, 2008). The modelling accounted for the proposed use patterns in Norway and the UK, including cage and well boat scenarios.

[5] Scottish Environment Protection Agency

For the short-term model, the volume of the plume is calculated as the product of its area and the depth of the mixing zone. The short-term bath treatment model does not account for any degradation of the active substance within the plume.

For the long-term model, the model can simulate multiple releases made during a treatment episode (e.g. treating every cage in turn), predicting the dispersion of the plumes from each release. The dispersion of the medicine is determined by parameters such as the residual current and tidal amplitude, the diffusion coefficient, and the distance between the fish farm and the shore. The long-term model also accounts for degradation of the active substance.

Two results are reported by the model: the peak concentration, and the total area wherein a specified concentration, usually an environmental quality standard (EQS) value, has been exceeded. To assess the potential risk associated with environmental exposure, the peak concentration is compared with the Maximum Allowable Concentration (MAC), and the area exceeding the EQS is compared with the Allowable Zone of Effect (AZE).

For the assessment of the risk from hydrogen peroxide, following the intended use of the product, the timeframe and the critical concentration are required inputs for the model. SEPA has not set an EQS or timeframe/area where the EQS can be exceeded (AZE) as it is considered that hydrogen peroxide will rapidly degrade both during and after the treatment due to the presence of high concentrations of organic matter (treated fish, fish food, fouling on pen nets, other organic matter near cages). In terms of the AZE, the same parameters as agreed for azamethiphos, which are the lesser value of 0.5 km^2 or 2% of the loch area. This approach is considered to be conservative and therefore acceptable.

The findings from the above modelling indicate that there may be a potential risk to some marine organisms, directly after use of the product. However, this risk can be mitigated with dilution and degradation which are increased by water movements. The product is not expected to pose a risk for the environment when used as recommended, and providing the following environmental safety information is adhered to.

SPC Section 4.5.iii ‘Other precautions’

- The most important mechanisms for removal of hydrogen peroxide in coastal waters are dilution and degradation which are increased by water movements, including the flushing effects in sea lochs. Do not use at times of slack water as poor dilution and dissociation of residuals may occur.

- After treatment, care should be taken to provide sufficient water through the net to dilute residual hydrogen peroxide. The water from a boat’s propeller may be used to increase water exchange in cases where low water exchange rates cannot be avoided. These measures will help to prevent possible adverse effects on aquatic life.

III.B.2 Residues documentation

Residue Studies

Due to the legal base of the application residues depletion study data were not provided. This was considered acceptable. The same meat withdrawal period as authorised for the reference product was proposed and accepted.

MRLs

Hydrogen peroxide is listed in Table 1 of Regulation 37/2010 with no MRL Required.

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days for meat in salmon is justified.

IV CLINICAL DOCUMENTATION

This application was a generic application based on Article 13(1) of Directive 2001/82/EC, as amended. The product is for topical treatment and therefore it is not possible to demonstrate bioequivalence with the reference product. However, the product has the same pharmaceutical form, contains the same active substance in the same quantity, and the same excipients in similar quantities, as the reference product; and the minor differences in formulation are not considered to impact on availability or local tolerance of the active substance. Therefore, the absence of pre-clinical and clinical data is acceptable.

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.

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)