



MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD



agencia española de
medicamentos y
productos sanitarios

DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

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

AQUACEN FORMALDEHYDE 380 MG/ML

CORREO ELECTRÓNICO

mresvet@aemps.es

temporalIP001059.doc

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443



MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0184/001/MR
Name, strength and pharmaceutical form	AQUACEN FORMALDEHYDE 380 MG/ML Concentrate for dip solution
Applicant	CENAVISA, S.L.
Active substance(s)	Formaldehyde
ATC Vet code	QP53AX19
Target species	Turbot (<i>Psetta maxima</i>), Gilthead (<i>Sparus aurata</i>)
Indication for use	Fish: Turbot. Control of external parasitosis by <i>Philasterides dicentrarchi</i> . At the recommended dose and posology, the mortality of infested animals is reduced, but the infestation is not completely eliminated. The treatment is not effective once the parasite has penetrated inside the fish. <u>Gilthead</u> . Treatment and control of external parasitosis by <i>Sparicotyle chrysophrii</i> .



MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (<http://www.hma.eu>).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	Day 90: 24 October 2012
Date product first authorised in the Reference Member State (MRP only)	22 February 2010
Concerned Member States for original procedure	EL and PT

I. SCIENTIFIC OVERVIEW

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 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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 380 mg/ml of formaldehyde, purified water and methanol.

The container/closure system are white 25 l barrels, made of high-density polyethylene, closed with high-density polyethylene screw caps and complex aluminum/high-density polyethylene disc for thermo induction, blue 200 and 1,000 l barrels, made of high-density polyethylene, closed with high-density polyethylene screw caps and clear 1,000 l barrels, made of high-density polyethylene, closed with high-density polyethylene screw caps.

The particulars of the containers and controls performed are provided and conform to the regulation.

The presence of the antioxidant methanol 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 using conventional manufacturing techniques. Process validation data on the product have been presented for pilot batches and process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is formaldehyde an established substance described in the European Pharmacopoeia as «Formaldehyde solution (35 per cent)». Pure formaldehyde is a gas at room temperature and is mostly produced and commercialised as aqueous solutions containing methanol as antioxidant. The raw material used as active substance is such a solution and 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 active substance manufacturer has used the ASMF procedure.

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.

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.

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.

The claim of 6 months stability after first opening the immediate packaging and of 60 minutes after dilution according to the directions is based on satisfactory in-use stability data.

H. Genetically Modified Organisms

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant reviewed the scientific literature related to the pharmacodynamics of formaldehyde. The general pharmacokinetics properties of formaldehyde were reviewed in several laboratory animals through several routes; some data obtained in fish is also available.

Toxicological Studies

The applicant has provided bibliographical data on acute toxicity, chronic toxicity, reproductive toxicity, mutagenicity and carcinogenicity.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.

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

Ecotoxicity

The applicant provided a Phase I and II Environmental Risk Assessment (ERA) in compliance with the relevant guidelines and based on a complete data package for formaldehyde. The assessment concluded that AQUACEN FORMALDEHYDE 380 MG/ML in turbot will not pose a risk to the environment. The environmental risk assessment provided in the original dossier for the target specie turbot is considered valid for the target specie gilthead because the change to the authorisation will not result in an increase in exposure of the environment.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

The applicant has provided bibliographical data to support the withdrawal period of the medicinal product AQUACEN FORMALDEHYDE 380 MG/ML.

MRLs

Formaldehyde does not require MRLs, as shown in EU Regulation 37/2010 for all food species.

<i>Pharmacological active</i>	<i>Marker residue</i>	<i>Animal Species</i>	<i>MRL</i>	<i>Target Tissues</i>	<i>Other Provisions</i>
-----------------------------------	---------------------------	---------------------------	------------	---------------------------	-----------------------------



Substance					(according to Article 14 (7) of Regulation (EC) No 470/2009)
Formaldehyde	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days-degrees for meat is justified.

.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant reviewed the scientific literature related to the Pharmacodynamics of Formaldehyde. The general Pharmacokinetic properties of Formaldehyde were reviewed in several animal species and, although sparse, some data obtained in fish is also available.

Tolerance in the Target Species

The applicant sent the Freedom of Information Summary (application: addition of fish target species for FORMALIN-F; NADA, New Animal Drug Application nº 137-687) in which a tolerance test was described. The conclusion reported in NADA was that data from these studies show that using Formalin at the recommended concentration is safe both at temperature of hot water (25°C) and cold water (18°C) in striped bass, considered as one of the species most susceptible to Formalin, so that safety would be extrapolated to all species of fishes.

On the other hand, a clinical trial was conducted with AQUACEN FORMALDEHYDE 380 MG/ML in the target species (turbot). This was an efficacy study, but one of the aims was to assess the safety of the product at various dosages. The mortality rate in the control group was significantly higher than in treated groups. No adverse effects nor mortality rate associated to the treatment were reported during the test plus the observation period.

In gilthead, one study was designed to assess the safety of the product at various doses and the data collected showed that no adverse effects or mortality rate associated to the treatment were reported during the test plus the observation period. Furthermore, in one clinical study no adverse effects were observed.

Resistance

The general **mechanisms of resistance** by bacteria to Formaldehyde were reviewed. Although most of the information dealing with resistance refers to bacteria, some little information is available in the case of protozoa and was given by the applicant.

IV.B Clinical Studies

The applicant reviewed and summarized several scientific papers that support the efficacy of Formalin, when used as dips. These studies were performed *in vitro* and *in vivo*, in various fish species, assaying different species of parasites, and using different dosage schedules.

Moreover, in turbot, one field study was performed by the applicant. Well designed and conducted, this trial meets the recommendations of the *Guideline on minor*



species/minor uses and also of the Guideline on veterinary medicinal products intended for use in farmed finfish. The results support the indication (section 4.2. of the SPC): Control of external parasitosis by Philasterides dicentrarchi. At the recommended dose and posology, the mortality of infested animals is reduced, but the infestation is not completely eliminated. The treatment is not effective once the parasite has penetrated inside the fish.

In gilthead, two studies were conducted: one carried out with the aim to determine the most suitable dose and a clinical field trial that assessed the efficacy and safety of AQUACEN-FORMALDEHYDE in this fish species. Both studies are, in general, well designed and conducted and comply with the recommendations of both the *Guidelines on minor species/minor uses and that on veterinary medicinal products intended for use in farmed finfish*. In conclusion, the documentation is suitable and the benefit-risk balance could be considered as favorable for the intended indication in gilthead (*Sparus aurata*): *Treatment and control of external parasitosis by Sparicotyle chrysophrii*.



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 risk benefit 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

Summary of change (Type; application number)	Section updated in Module 3	Approval date
ES/V/0184/001/IB/001 Addition of a new pack size (200 l)	II	13/10/2013
ES/V/0184/0014/IB/002/G Addition of 1000 liter clear package, extension of the shelf-life after first opening to 6 months, increase of the batch size and minor change in the manufacturing process	II	28/04/2015
ES/V/0184/001/DX/003 Addition of target species - Gilthead	IIIA IIIB IV	21/09/2015