IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

ALPHA JECT 3000 Emulsion for injection for Atlantic salmon

PRODUCT SUMMARY

EU Procedure number	IE/V/0219/001/MR
Name, strength and pharmaceutical form	ALPHA JECT 3000 Emulsion for injection
Active substance(s)	*Aeromonas salmonicida* subsp. *salmonicida;* AL 2017 RPS[1]≥ 70 (Ph.Eur) *Listonella anguillarum* serotype O1; AL 112 RPS[2]≥ 75 (Ph.Eur) *Listonella anguillarum* serotype O2a; AL 104 RPS[2]≥ 75 (Ph.Eur) RPS: Relative Percentage Survival is based on results from challenge studies on Atlantic salmon at end[1] or 60%[2] mortality in the control group. **Adjuvant:** Paraffin, light liquid (mineral oil): 46 mg
Marketing Authorisation Holder `	PHARMAQ AS Skogmo Industriområde N-7863 Overhalla Norway
Legal basis of application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of Authorisation	1 October 2002
Target species	Atlantic salmon (*Salmo salar*) of a minimum weight of 15 g.
Indication for use	Reduction of mortality by the diseases caused by *Aeromonas salmonicida* (furunculosis) and *Vibrioanguillarum s*erotype O1 and O2 (vibriosis) in Atlantic salmon.
ATCvet code	QI10AB02
Concerned Member States	FI, IS, NO

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 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.
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

A.Qualitative and Quantitative Particulars

The vaccine is an inactivated, adjuvanted water-in-oil bacterial vaccine containing formaldehyde-inactivated antigens of *Aeromonas salmonicida* and *Vibrio anguillarum*.

Active substances:

Formaldehyde inactivated bacteria cultures of:
Aeromonas salmonicida
subsp. *salmonicida;* AL 2017 RPS[1] ≥ 70 (Ph.Eur)
Listonella anguillarum serotype O1; AL 112 RPS[2] ≥ 75 (Ph.Eur)
Listonella anguillarum serotype O2a; AL 104 RPS[2] ≥ 75 (Ph.Eur)

RPS: Relative Percentage Survival is based on results from challenge studies on Atlantic salmon at end[1] or 60%[2] mortality in the control group.

Adjuvant:

Paraffin, light liquid (mineral oil): 46 mg.

Excipient(s):

Polysorbate 80
Sorbitan oleate
Formaldehyde
Water for injection

The container/closure system for the vaccine consists of a 0.5 litre injection bag made of a multilayer plastic foil with ethylene vinyl acetate as the product contact layer. The giving port is closed with a bromobutyl based rubber stopper and an aluminium cap with plastic lid. The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the vaccine strains, the adjuvant, the inactivating agent, and the absence of a preservative are justified.
The inactivation process and the detection limit of the control of inactivation are correctly validated.
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 at a licensed manufacturing site.
The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C.Control of Starting Materials

Starting materials of non-biological origin used in production comply with the relevant Ph. Eur. monographs or in-house specifications.
Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the relevant Ph. Eur monographs and guidelines; any deviation was adequately justified.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

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

Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D.Control on Intermediate Products

The tests performed during production are described and the results of three consecutive production runs, conforming to the specifications, are provided.

E.Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular tests for sterility, safety and potency of the vaccine.

The demonstration of the batch to batch consistency is based on the results of three consecutive production batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F.Stability
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 in-use shelf-life of the broached vaccine is supported by the data provided.

G.Other Information
None

Conclusion on Quality
The manufacture of the product is adequately described and controlled. The quality of the product has been demonstrated in accordance with Directive 2001/82/EC and the relevant Ph. Eur. monographs. The quality of ALPHA JECT 3000 has been sufficiently demonstrated and there is no public health concerns related to the use of this product.

III. SAFETY ASSESSMENT

The vaccine batches used in the safety studies were representative of the production process. The safety of ALPHA JECT 3000 has been adequately demonstrated using a batch of vaccine containing the maximum antigen content of the finished product. Some of the safety studies have been conducted using ALPHA JECT 4000. This is an acceptable approach for the demonstration of safety of ALPHA JECT 3000 because ALPHA JECT 4000 contains the same active substances and excipients as ALPHA JECT 3000, but also contains an additional antigen *V. salmonicidia*. Conclusions with the larger combination vaccine are applicable to ALPHA JECT 3000.

Laboratory Trials

The safety of the administration of one dose and an overdose in the target animal is demonstrated in the following studies:

–**Safety of one dose, a 2x overdose, and a 4x overdose in Atlantic salmon:**
Fish in which the average weight was below the minimum weight recommended for vaccination received either one dose, a 2x overdose, a 4x overdose, or saline. Fish were observed for 12 weeks, and adhesions and pigmentation according to the Spielberg classification, weight and serology were monitored.

–**Safety of a 2x overdose and a 4x overdose in Atlantic salmon:**
Fish in which the average weight was below the minimum weight recommended for vaccination received either a 2x overdose, a 4x overdose, or saline. Fish were observed for 12 weeks, and adhesions and pigmentation according to the Spielberg classification, weight and serology were monitored.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.
Adverse reactions in the form of visceral adhesions and pigmentation occur in the vaccinated fish, with varying severity. However, all vaccinated fish are expected to develop some degree of undesirable effects compared to fish that are not vaccinated. Pigmentation on the viscera occurs frequently, whereas pigmentation in the muscle rarely occurs. The monitoring of adverse reactions was conducted on fish at 6 to 12 weeks post-vaccination, rather than at 21 days post-vaccination as recommended in the relevant Ph. Eur. monographs, and it is known that the severity of local reactions continue to increase beyond 21 days. Following an overdose, there is a higher incidence and severity of adverse reactions. Appropriate warnings have been placed in section 4.6 (Adverse reactions) of the SPC, and in section 4.10 (Overdose).

The safety of the repeated administration of one dose in the target animal was not investigated because the vaccine is recommended for single use only.

No investigation of effect on reproductive performance was conducted. Thus, the product should not be used on fish intended as future breeders.
As the product is an inactivated vaccine, there are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study to investigate this was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant and excipients used are included in Annex II of Council Regulation No. 2377/90. Based on this information, no withdrawal period is proposed.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

Field Studies
Two field studies were conducted to investigate the safety of the vaccine in the field. A total of 2359 fish were included in these studies, which support the results of laboratory investigations. In one study, mortality in fish was high due to a non-related disease outbreak in the field. However, an adequate safety profile of ALPHA JECT 3000 during use in field conditions has been fully demonstrated.
Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The product is an inactivated bacterial vaccine, therefore there is no risk of spread of live organisms. Neither the active substances nor the excipients are considered hazardous to animals, humans or the environment at the concentrations used. The assessment concluded that the level of environmental risk is low.

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

User Safety
The product contains mineral oil as an adjuvant. Accidental self-injection by the person administering the vaccine is dangerous. An appropriate warning is included on the SPC to highlight this risk and to outline action that should be taken in the event of accidental self-injection.

IV. CLINICAL ASSESSMENT

The vaccine batches used in the efficacy studies were representative of the production process. The efficacy of the vaccine has been adequately demonstrated using a batch of vaccine containing the minimum antigen content of the finished product. Some of the efficacy studies have been conducted using ALPHA JECT 4000 and ALPHA JECT 6.2. This is an acceptable approach for the demonstration of efficacy of ALPHA JECT 3000 because the two vaccines contain the same active substances and excipients as ALPHA JECT 3000, but also contain additional antigens *(V. salmonicidia* in ALPHA JECT 4000, and *V. salmonicida*, *Moritella viscosa* and Infectious Pancreatic Necrosis Virus in ALPHA JECT 6.2) Conclusions with the larger combination vaccines are applicable to ALPHA JECT 3000.

IV.BClinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show the efficacy of the vaccine with regard to the claims.

The efficacy of the vaccine was evaluated according to the requirements of the relevant Ph. Eur. monographs. Fish of the recommended weight for vaccination were vaccinated according to the recommended schedule for vaccination, and control fish received a saline injection. Fish were challenged with virulent strains of *V. anguillarum* O1, O2 or *A. salmonicida* at 5 weeks post-vaccination. The relative percent survival (RPS) at 60% control mortality exceeded the requirements of the relevant Ph. Eur. monographs for efficacy of each of the antigen components of ALPHA JECT 3000.
Other efficacy studies support the claims on the SPC.

Field Trials
A study was conducted with ALPHA JECT 3000 under field conditions. A total of 2000 fish were included in the field trial, however natural challenge did not occur during the trial. Six months post-vaccination, fish were removed from the study in order to perform experimental challenge. Field efficacy has not been demonstrated, but the fish that were experimentally challenged at six months post-vaccination fulfilled the requirements for potency as per the relevant Ph. Eur. monographs and were protected against mortality due to *A. salmonicida*, subsp *salmonicida*, *V. anguillarum* O1 and *V. anguillarum* O2.

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.

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:
None.