EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for a type II variation for Clynav (EMEA/V/C/002390/II/0010)

Vaccine common name: Salmon pancreas disease vaccine (recombinant DNA plasmid)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Elanco GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 29 May 2019 an application for a type II variation for Clynav.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To extend the duration of immunity (DOI) from 3 months after vaccination to 12 months after vaccination.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

This variation application is submitted in order to extend the DOI of Clynav from 3 months to 12 months. In support of the proposed change, the applicant has provided a laboratory efficacy study (Study No NAH-16-055), in which two main groups of Atlantic salmon were included: one vaccinated with Clynav in accordance with recommendations (n=270) and one group that received saline (mock-vaccinated negative control group, n=270). Fish were vaccinated with a batch of Clynav that contained 6.8 µg plasmid DNA/0.05 ml dose, which is above the established minimum effective dose of 5.1 µg plasmid DNA/dose. Fish were vaccinated under freshwater conditions (mean temperature of 10.5 ºC) on study day 0 and were transferred to saltwater (mean temperature of 13.8 ºC) at 9 weeks post-vaccination, following saltwater readiness testing and successful smoltification in a corresponding non-vaccinated control group. Approximately 90 fish from the vaccinated group and 90 fish from the negative control group were challenged at each of three challenge time points; 6, 9.5 and 12 months post-vaccination. Challenge was conducted by a cohabitation challenge model in saltwater, whereby Trojan fish were added to the tanks at 20% of the fish population, having been experimentally infected with a salmonid alphavirus subtype 3 (SAV3) isolate (the same challenge model as that used in the study which supported the DOI of 3 months). In the follow-up period after each challenge, at days 19,

54 and 84 (±5 days), relative weight gain, macroscopic internal observations and mortality were evaluated. In addition, after the challenge conducted at 12 months, histopathological analysis of cardiac, pancreatic and red and white skeletal muscle was conducted at the three sampling time points post-challenge.

The results demonstrated that at all challenge time points, 6, 9.5 and 12 months, a statistically significant higher mean body weight gain was observed in the vaccinated group compared to the negative control group, at all three sampling time points (for the 9.5 month challenge) or at the second and third sampling time points (for the 6 month challenge and the 12 month challenge). At the 12th month challenge, at day 89, the mean weight was 1595.9 g and 843.6 g in the vaccinated and negative control group, respectively ($p<0.0001$).

For the 12th month challenge (the only challenge with histological analysis), statistically significantly lower microscopic pathology scores for heart, pancreas and red skeletal muscle in the vaccinated group compared to the negative control group at 19, 54 and 89 days post-challenge were reported and statistically significantly lower microscopic pathology scores for white skeletal muscle in the vaccinated group compared to negative control group at 54 and 89 days post-challenge were reported.

A reduction of mortality at 12 months post-vaccination could not be established, due to a very low incidence of mortalities in both the vaccinated group and the negative control group following challenge. While the experimental infection of the smaller Trojan fish resulted in a cumulative mortality of 93.3% (with most mortalities between 8 and 19 days post-challenge), the mortality rate due to challenge by cohabitation with the Trojan fish reached only 1.2% and 3.4% in the vaccinated group and the negative control group, respectively. However, a statistically significant difference in mortality was demonstrated at the 9.5-month challenge, with 16/82 mortalities (19.5%) in the negative control group and 1/84 (1.2%) mortalities in the vaccinated group. Therefore, while the lack of mortality in the challenge model used at 12 months post-vaccination may be reflective of a trend for decreasing mortality related to the size of the fish, and although there are no indications of a decrease of immunity at 12 months post-vaccination in respect of the improved weight gain and protection against PD-related histopathological lesions, section 4.2 of the SPC was amended to indicate a 9.5 month DOI for a reduction of mortality.

During the variation procedure, the applicant was requested to comment if the temperature range (12 ± 2 ºC) under which the 3-month duration of immunity was established required amendment to reflect the conditions of the 12-month duration of immunity study. In their response, the applicant confirmed that the temperature range for the duration of the study was 9.4 to 16.5 ºC. Considering the wide range of temperature in the study, CVMP considered that it was no longer meaningful to specify the temperature range of the study conditions in the SPC, therefore this information was removed, and replaced with the more relevant information that the laboratory conditions under which the DOI was demonstrated was a saltwater cohabitation challenge model.

In summary, it is accepted that the data provided demonstrate a reduction of impaired daily weight gain and reduction of cardiac, pancreatic and skeletal muscle lesions caused by pancreas disease following infection with SAV3 at 12 months post-vaccination, and a reduction of mortality at 9.5 months post-vaccination, following vaccination with a vaccine dose containing 6.8 µg plasmid DNA/0.05 ml. However, given that the revised DOI has not been supported following the administration of a minimum effective dose of vaccine (5.1 µg plasmid DNA/dose), it is unknown if the extended DOI would be attained in fish vaccinated with a minimum effective dose of Clynav. According to Annex II of Directive 2001/82/EC, as amended, Part 4 Efficacy Tests, Chapter II B. Laboratory Trials, it is stated that *'For live vaccines, batches containing the minimum titre or*

potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified.' Furthermore, Ph. Eur. 5.2.7. 'Evaluation of efficacy of veterinary vaccines and immunosera', states: *'During development of the product, tests are carried out to demonstrate that the product is efficacious when administered by each of the recommended routes and methods of administration…. As part of tests carried out during development to establish efficacy, the tests described in the Production section of a monograph may be carried out; the following must be taken into account. The dose to be used is that quantity of the product to be recommended for use and containing the minimum titre or potency expected at the end of the period of validity.'* As no acceptable justification for deviating from this requirement was provided, the specifications for the minimum content of active substance for Clynav should be increased to 6.8 µg plasmid DNA/dose to permit acceptance of the revised DOI. Furthermore, the applicant has presented data from 20 Clynav batches, indicating that representative batches are unlikely to have plasmid DNA levels below 6.8 µg per dose, thereby calling into question the need to specify the minimum dose as 5.1 µg plasmid DNA.

The applicant was requested to address the issue regarding that the acceptance of the revised DOI is subject to the updating of the minimum specification of plasmid DNA per dose to reflect the dose administered in the new pivotal efficacy study provided in support of this change. In the applicant's response it was argued that no changes to the minimum specification were required, because the dose used in the pivotal study contained a 'dose that is recommended for use' in accordance with the manufacturing method for routine production batches, and that the increase in minimum specification would necessitate significant changes to the manufacturing process. Furthermore, it was argued that the mechanism of action of DNA vaccines is different to that of conventional IVMPs, and it was claimed that very few copies of plasmid DNA are required to establish long-lasting immunity. Given that the vast majority of injected plasmid DNA is cleared from the site of injection within the first three months post-vaccination, it was claimed that any differences in the plasmid DNA remaining in fish that would be vaccinated with a dose of 5.1 µg compared to a dose of 6.8 µg DNA would be negligible at 12 months post-vaccination.

Whilst this argument was noted, it remains unknown whether the levels of plasmid DNA remaining at 9 – 12 months post-vaccination, or the initial dose, and the subsequent 'strength' of the immune response generated at that time point, are primarily responsible for the longevity of the immune response. Consequently, it was considered that inadequate information was available to permit concluding that plasmid DNA acts as a suitable/surrogate marker for immunity and therefore, whether the administration of a dose of 5.1 µg plasmid DNA at time of vaccination would provide adequate immunity at 9 – 12 months post-vaccination.

In order to accept the revised DOI, the CVMP requested the applicant to increase the minimum specification at time of release to 6.8 µg plasmid DNA, and at end of shelf life to 6.0 µg plasmid DNA, to allow for an expected decline of 0.8 µg over the course of the shelf life. This approach will ensure that doses containing below 6.0 µg plasmid DNA will not be marketed.

Although it was noted that there would still be a difference between the dose shown to be efficacious for the revised DOI (6.8 µg) compared to that which could potentially be marketed (if vaccine batches close to their expiry date were administered to fish [6.0 µg]), the CVMP was of the opinion that this difference could be considered within the context of the total information available, and that the overall risk arising from this discrepancy could be accepted, on the basis that:

- at the time of submission of the marketing authorisation, the MUMS classification was valid and Clynav was therefore authorised as MUMS product (and it will be referred to as such in the future even if the MUMS classification has now expired). Additionally, it may be worth noting during discussions at CVMP that, in fact, products for Atlantic salmon will be considered 'limited

market' as they are VMPs for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats, according to the new veterinary Regulation (EU) 2019/6,
- the OOI and DOI of 3 months have been established with the minimum effective dose,
- that the mechanism of action is different for this DNA vaccine compared to a conventional IVMP,
- of the 20 batches manufactured from 2015 – 2018, none were below 6.8 µg plasmid DNA/dose at time of release (in fact, many were higher [up to 8.3 µg plasmid DNA/dose]).

3. Benefit-risk assessment of the proposed change

Clynav is authorised for the active immunisation of Atlantic salmon to reduce impaired daily weight gain, and reduce mortality, and cardiac, pancreatic and skeletal muscle lesions caused by pancreas disease following infection with salmonid alphavirus subtype 3 (SAV3). Onset of immunity occurs within 399-degree days (mean water temperature in °C multiplied by number of holding days) following vaccination. The DOI is approximately 3 months after vaccination (demonstrated under laboratory conditions at a water temperature of 12 ± 2 °C).

The proposed variation is to extend the DOI from 3 months after vaccination to 12 months after vaccination.

3.1. Benefit assessment

Direct therapeutic benefit

The currently authorised DOI is approximately 3 months after vaccination (demonstrated under laboratory conditions at a water temperature of 12 ±2 °C, using a sea water challenge model). At the time of authorisation of Clynav, it was noted that the DOI is not sufficient to demonstrate that the vaccine would be efficacious throughout the period that salmon are at risk but that it is clinically relevant, especially for young fish immediately after sea transfer.

With this variation, the direct therapeutic benefit is further strengthened, on the basis that the DOI for the claims for a reduction of impaired daily weight gain and for a reduction of cardiac, pancreatic and skeletal muscle lesions are demonstrated at 12 months post-vaccination in a sea water challenge model, and a reduction of mortality at 9.5 months post vaccination. However, these data were obtained following vaccination of fish with above the established minimum effective concentration of plasmid DNA per dose. Therefore, final acceptance of the change to the benefits of the product has been subject to a revision of the minimum specification of active substance (from 5.1 to 6.8 µg plasmid DNA/dose at time of release) to reflect the dose administered in the new pivotal efficacy study provided in support of the change.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety remains unaffected by this variation.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, environment and consumer and to provide advice on how to prevent or reduce these risks. Risk management or mitigation measures remain unaffected by this variation.

3.4. Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk is deemed positive.

The product has been shown to be efficacious for 1-year reduction in impaired daily weight gain, and cardiac, pancreatic and skeletal muscle lesions and for 9.5-months reduction of mortality (demonstrated in a laboratory efficacy study in saltwater conditions using a cohabitation challenge model).

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Clynav can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

Duration of immunity: 1 year for reduction in impaired daily weight gain, and cardiac, pancreatic and skeletal muscle lesions and 9.5 months for reduction of mortality (demonstrated in a laboratory efficacy study in saltwater conditions using a cohabitation challenge model).

As a consequence of this variation, sections 2 and 4.2 of the SPC are updated. In addition, minor editorial changes have been implemented in sections 4.4, 4.5, 4.6, 4.10 and 6.2. The corresponding sections of the Package Leaflet are updated accordingly.