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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a type II variation for Gumbohatch (EMEA/V/C/004967/II/0005/G)

Vaccine common name: Avian infectious bursal disease vaccine (live)

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 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Laboratorios Hipra, S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 8 November 2021 an application for a grouped type II variation for Gumbohatch.

1.2. Scope of the variation

Variation(s) requested		**Type**
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	IB
B.II.d.2.a	Change in test procedure for the finished product - Minor changes to an approved test procedure	IB
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II
B.II.b.3.c	Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	II
B.II.e.5.a.1	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	IA_{IN}
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	IB

To reduce the minimum protective dose, add two new presentations of 8,000 and 10,000 doses, add a new volume of the solvent (500 ml), extend the working range of the potency test of the finished product and reduce the volume of virus added during the blending of the vaccine.
The applicant also took the opportunity to update the list of local representatives in the package leaflet and correct the name used to express the amount of unbound IBD-specific IgYs.

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, Part 2 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

Part 2 – Quality

The proposed grouped variation consists of five individual changes regarding the finished product presentations, minimum protective dose and maximum LOD of the potency test.

The variation **B.II.d.2.a** is proposed by the applicant to extend the validated range of the potency/titration test of Gumbohatch to enable release of the batches containing the maximum titre demonstrated to be safe during the initial authorisation procedure ($10^{2.8}$ PU/dose). To date, due to validation of the titration working range, the maximum titre for release was capped at $10^{2.63}$ PU/dose.

The applicant provided a validation study, including data from a previous validation study, in order to extend the working potency/titration range. This change is reflected in the increase of the upper limit of the active substance from $10^{2.63}$ to $10^{2.8}$ PU/dose in the SPC.

The study assessed the accuracy, repeatability (precision), linearity and range of the method. The accuracy was demonstrated as percent recovery of the sample's expected value in line with VICH GL2. The results were sufficiently within the acceptable range between 70 and 130% (±30%) for all six samples. The accuracy of the method has been sufficiently validated.

Due to the decrease in the titre of the minimum protective dose from $10^{1.48}$ PU/dose to $10^{1.18}$ PU/dose (variation C.I.4 discussed in Part 4) the applicant proposed two **variations B.II.e.5.a.2** to add 8,000 and 10,000 doses presentations, respectively. The addition of these new presentations for the product has become possible since the reduction of the minimum protective dose allows for higher dose number per vial filled with the amount of virus at maximum titre per vial. This change does not require stability studies, as there are no changes to composition, manufacture, fill volume or container/closure. The proposed change is considered acceptable, as the applicant sufficiently demonstrated the efficacy of vaccination in accordance with the reduction of the minimum protective dose to $10^{1.18}$ PU/dose.

Consequently, the addition of 8,000 and 10,000 doses presentations requires the addition of the solvent bags containing 500 ml of solvent **(Variation B.II.e.5.a.1).** This presentation is within the currently approved range of volume solvent bags (200 ml, 400, ml, 800 ml and 1,000 ml). No new containers will be added, as 500 ml will be contained in the 500 ml bag currently used for the 400 ml presentation of solvent. The validation report of the terminal sterilisation of the 500 ml bags containing 500 ml of solvent demonstrated the suitability of the authorised sterilisation method for this presentation; therefore, the proposed change is considered acceptable.

Type II variation B.II.b.3.c to introduce a change in the manufacturing process of the finished product concerns the introduction of an additional blending with reduced volume of the viral component per vial. This change is proposed to guarantee the availability of low dose pack sizes, which the applicant claims are in demand on the market. The volume of viral component of the blend is maintained by adding the adequate volume of water for injection. Therefore, the overall volume of vaccine per vial before lyophilisation remains the same as the currently approved. No changes in the IPC or finished product specifications, nor in the virus (active substance) or the immunoglobulins (excipient) manufacture process are introduced as consequence of this variation.

Batches manufactured with the reduced volume of the virus fraction were presented during the initial authorisation in sections 2F and 2G. Batch data analysis comparing the results of one batch manufactured according to the currently authorised volume of virus per vial to those of two batches produced according to the virus volume proposed were provided. The results obtained confirm that batches formulated

according to the change proposed in this variation have the required quality profile and satisfactory stability up to 24 months. This variation is acceptable.

As part of this variation, the applicant proposes to harmonise the units used for immunoglobulin in the vaccine. The use of serum neutralisation units (SNU) is considered misleading for the end user as it implies that the immunoglobulins are derived from serum. The two editorial changes proposed by the applicant are to introduce the word "egg" when referring to the IgYs in the new version of Product Information and to change the name of the units that define the presence of unbound IgYs, from serum neutralisation units (SNUs) to IgY neutralising units (IgYNU). Introduction of the word "egg" clearly identifies the origin of the immunoglobulins for the end-user, however the proposed expression of units as IgYNU suggests that the units neutralise the immunoglobulins. The term "NUs" (neutralising units) in combination with the description of the excipient as "unbound IBDV-specific egg antibodies" is considered to be unambiguous and avoid any misinterpretation. The applicant amended the units for expression of unbound IgY to "NU" across the dossier.

Part 4 - Efficacy

Type II variation C.I.4 to introduce a change in the Summary of Product Characteristics, Labelling or package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

The proposed variation is submitted to establish a lower minimum protective dose $10^{1.18}$ PU/dose, compared to the currently authorised minimum protective dose of $10^{1.48}$ PU/dose.

The vaccine is indicated for the reduction of clinical signs and lesions of the bursa of Fabricius caused by very virulent avian infectious bursal disease virus, when administered to chickens, by the *in ovo* route to 18-day-old embryonated eggs, or by the subcutaneous route to 1-day-old chicks. The onset of immunity depends on the initial MDA level of the broiler chickens/chicken eggs and in practice occurs from approximately 24 days of age. The duration of immunity is up to 43 days of age. The vaccine contains live attenuated IBDV, strain 1052, forming an immune complex (Icx) with IBD-specific immunoglobulins IgY. The vaccine virus is an 'intermediate-plus' virulence vaccine strain.

A GLP-compliant laboratory challenge study was conducted to evaluate the efficacy of a lower dose ($10^{1.18}$ PU/dose) than the currently authorised minimum titre of the live, attenuated IBD virus strain included in Gumbohatch. The study was conducted on a randomised basis, and it was confirmed by the applicant that the study personnel responsible for evaluating clinical signs were blinded to treatment allocation.

Two challenges were included in the study, one to investigate the onset of immunity at day 24 and one to investigate the duration of immunity up to day 45. The study was conducted in seropositive commercial broiler eggs/chicks with mean MDA levels within the same range of MDA levels for which the efficacy of vaccination has been demonstrated in the original dossier. The conduct of this study in seropositive eggs/chicks is acceptable as this is the intended target species; the vaccine is not intended for use in flocks seronegative against IBDV.

Two hundred and four eggs were randomly divided into three groups: A, B and C (68 eggs/group). Group A were administered Gumbohatch *in-ovo* at day -3; Group B were administered Gumbohatch subcutaneously after hatching on day 0; Group C were administered PBS *in-ovo* at day -3 and then subcutaneously after hatching on day 0 (mock). All groups were divided in two subgroups, 1 and 2. Groups A1, B1 and C1 were challenged at day 24 (30 birds/group), and groups A2, B2 and C2 were challenged at day 45 (30 birds/group) with a vvIBDV strain. Chicks were observed daily for 6 days after challenge. On the 6th day after challenge, the birds were weighed, euthanised and necropsied: bursa of Fabricius (BF) and spleens were weighed and examined macroscopically, and a histopathological analysis of BF was performed.

The vaccine was administered *in-ovo* to 18-day old embryonated eggs and subcutaneously to 1-day old chicks, in accordance with the currently authorised recommendations for use.

The challenge strain used in the presented study is a very virulent (vv) IBDV strain, VG-248, heterologous to the vaccine strain. The strain of the challenge virus and the route of administration were the same as those used to define the currently authorised onset and duration of immunity of Gumbohatch. The birds were challenged oculo-nasally with 10^5 EID_{50}/animal by oculo-nasal inoculation of 0.2 ml/bird. The challenge dose in the study provided was higher than the dose used in the original study, and given that the study is intended to demonstrate the protection conferred by a lower dose compared to the currently authorised minimum titre of the live, attenuated IBD virus strain included in Gumbohatch, this would be expected to result in a more severe challenge. The primary variables of this study were the histopathological scores for bursal damage and clinical signs after challenge. Secondary variables were macroscopic lesions on the bursa of Fabricius, presence of external oedema in the bursae, the relative weight of the bursae of Fabricius, spleen and growth rate of birds.

Onset of immunity:

The results demonstrated that no clinical signs were observed in birds in the vaccinated groups, whereas 30% of birds in the mock-vaccinated group displayed clinical signs. The clinical signs induced were consistent with those reported (albeit at a milder level) in the laboratory efficacy studies in the original marketing authorisation application for Gumbohatch. The difference in clinical signs was reported to be statistically significantly different between the vaccinated and mock-vaccinated groups.

In support of the claim for a reduction of lesions of the bursa of Fabricius caused by vvIBDV, the primary variable is the detailed histopathological analyses at 6 days post-challenge, in addition to secondary variables (BF:BW ratios and macroscopic lesions of BF). In comparing the histopathological findings between the vaccinated and control groups, a summary score obtained with a sum of individual scores of histological observations indicative of acute lesion in the bursae was calculated (heterophil and mononuclear infiltration, haemorrhage, luminal exudate, plical oedema, oedema of the muscular wall, serosal oedema and lymphoid necrosis, which are the features indicating acute lesions). The summary score ('acute histological functional lesions score') was compared between groups, and results showed statistically significant differences between group A1 vs C1 (mean score of 1.80 vs 7.20 in the vaccinated and control group, respectively, $p<0.001$, Mann-Whitney test), and between group B1 vs C1 (mean score of 2.20 and 7.20, respectively, $p<0.001$, Mann-Whitney test).

Regarding the secondary variables, given that it is known that the vaccine itself is capable of inducing damage to the BF, and statistically significantly lower BF:BW ratios were reported in both of the vaccinated groups compared to the mock-vaccinated group, the BF:BW ratio is considered as a less informative parameter for this vaccine. It has been previously accepted that the vaccine-induced lymphoid depletion is not associated with other characteristic macro- and microscopic changes associated with severe acute stages of vvIBDV infection, such as clear signs of oedema and lymphoid necrosis. A severe depletion of the follicles in the bursae and a clear mixed, diffuse, inflammatory infiltrate in the plica, including lymphoid necrosis accompanied by clear oedema affecting the full thickness of the bursae were observed in the mock-vaccinated group (as discussed above). In the vaccinated groups, a complete absence of oedema, a statistically significantly lower lymphoid depletion and a statistically significantly lower inflammatory infiltrate were reported.

A statistically significant reduction of macroscopic lesions of the BF and the absence of external oedema were demonstrated in the vaccinated birds compared to 29/30 unvaccinated birds with external oedema of BF reported.

Overall, the reduction of lesions of the bursa of Fabricius caused by very virulent avian infectious bursal disease virus infection, at the onset of immunity, is considered to have been adequately demonstrated with the proposed lower titre of $10^{1.18}$ PU/dose.

There was a statistically significant difference in the growth rate observed between *in-ovo* vaccinated and unvaccinated groups (in favour of the vaccinated group). However, this effect on growth rate was not reported in the subcutaneously vaccinated group. Since there is no claim in the SPC for a positive effect of vaccination on growth rate, this parameter was not considered further. On the day of necropsy, blood samples were evaluated for the presence of IBDV antibodies by ELISA using the same method that was used in the OOI/DOI studies submitted with the original application for marketing authorisation. The serological data demonstrated that chicks were MDA-positive at Day 0 of the study as shown by evaluation of titres in the hatchability control group. On the day before challenge the vaccinated groups were seropositive, although a lower percentage of the subcutaneously vaccinated group were seropositive, while none of the mock-vaccinated group were seropositive. The difference in seropositivity in the in-ovo vaccinated versus subcutaneously vaccinated groups is likely related to the approximate 3-day difference in timing of vaccine administration, and the dynamics of the decline in MDAs versus the take of the vaccine virus. Notwithstanding the difference in serological status in vaccinated groups prior to challenge, there do not appear to be any notable differences in vaccine efficacy following challenge. Furthermore, 100% of birds in both groups A1 and B1 were seropositive at 6 days post-challenge.

Overall, a reduction of clinical signs and reduction of lesions of the bursa of Fabricius caused by vvIBDV is considered to have been adequately supported by this study at the onset of immunity at 24 days of age.

Duration of immunity:

The results of the challenge conducted on day 45 demonstrated that no clinical signs were observed in the vaccinated groups compared to clinical signs being observed in 33% of the birds in the mock-vaccinated group. As discussed for the challenge conducted at 24 days of age, these data are accepted as adequately demonstrating a reduction of clinical signs.

The claim for the reduction of lesions of the bursa of Fabricius is also considered to have been adequately demonstrated by the data presented at the longer proposed duration of immunity of 45 days of age. Similar to the data following the challenge at day 24, a comparison of the summary score for acute histological functional lesions demonstrated that this score was statistically significantly lower in the vaccinated groups compared to the mock-vaccinated group.

Concerning the secondary efficacy parameters, the mean BF:BW ratios were evaluated, and no statistically significant differences were observed between the control group compared to both vaccinated groups at day 51 of the study. The macroscopic evaluation of BF showed statistically significant differences between the control group and vaccinated groups in the presence of macroscopic lesions and external oedema. No statistically significant differences were observed in growth rate between the vaccinated and unvaccinated groups between day 45 and 51 of the study. As for the earlier challenge, statistically significant differences ($p<0.001$) between the vaccinated groups and control group for spleen:BW ratio (higher in the unvaccinated group), indicative of splenomegaly but unrelated to the currently authorised indications for use, were reported.

The serological data showed that at day 44 (prior to challenge), 100% of the birds from both vaccinated groups were seropositive with high titres of IBDV-specific antibodies, while unvaccinated birds remained seronegative. At day 51, the titres in the vaccinated groups remained at the same or at a higher level, while the unvaccinated group also seroconverted with noticeably lower titres.

Overall, the data presented following challenge at 45 days of age are considered to support the currently approved claims for a reduction of clinical signs and a reduction of lesions of the bursa of Fabricius,

following in-ovo or subcutaneous vaccination with the proposed lower dose of Gumbohatch. Consequently, the extension of the DOI from 43 days of age to 45 days of age is considered acceptable.

The results presented in this study are considered to adequately support the currently authorised OOI ("from 24 days of age") and the proposed DOI of up to 45 days of age, following the administration of the revised lower titre of Gumbohatch ($10^{1.18}$ PU/dose).

As result of variations C.I.4 and B.II.d.2.a, the specification range for the IBDV is proposed to be widened from $10^{1.18}$ to $10^{2.8}$ PU/dose in the product literature. The safety of administration of $10^{2.8}$ PU/dose has been demonstrated during the initial application for marketing authorisation, therefore this increase in the upper limit of the active substance is considered acceptable and no additional safety data are required (that is, the upper limit of the active substance will not exceed that which has been demonstrated as safe in the original laboratory safety study conducted to investigate the safety of a 1x maximum dose).

3. Benefit-risk assessment of the proposed change

This product is a vaccine containing live attenuated IBDV, strain 1052, authorised for the active immunisation of 1-day-old broiler chicks and embryonated broiler chicken eggs to reduce clinical signs and lesions of the bursa of Fabricius caused by very virulent avian infectious bursal disease virus infection. A single dose of vaccine is proposed to be administered by either the *in-ovo* route for chicken embryos on the 18th day of incubation or by the subcutaneous route for 1-day-old broiler chickens.

In the vaccine formulation an attenuated virus is present as an immune complex with an IBDV-specific antibody.

Gumbohatch is presented as a lyophilisate and solvent for suspension for chickens. The withdrawal period is zero days.

The proposed variation is to establish a minimum protective dose lower than the current one (due to new preclinical data), add two new presentations of 8,000- and 10,000-dose vials of lyophilisate, add a new volume of the solvent (500 ml), extend the working range of the potency test in the finished product and add a new, lower, volume of virus in the blending of the vaccine. The DOI is extended from 43 days of age to 45 days of age.

The applicant also took the opportunity to update the list of local representatives in the package leaflet and correct the name of unit used to express the amount of unbound IBDV-specific IgYs.

3.1. Benefit assessment

Direct therapeutic benefit

Gumbohatch has previously been demonstrated to be efficacious for the reduction of clinical signs and reduction of lesions of the bursa of Fabricius caused by very virulent avian infectious bursal disease virus infection. With this variation, proposed to lower the minimum protective dose, there are no changes to the direct therapeutic benefit as the currently approved indications for use are considered to be supported following vaccination with the lower dose. However, the DOI has been extended from 43 days of age to 45 days of age, which is considered to represent a positive attribute regarding the direct therapeutic benefit.

Additional benefits

Not applicable for the current variation.

3.2. Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety:

No safety risk identified as result of the current grouped variation.

3.3. Risk management or mitigation measures

Not applicable for the current variation. Appropriate information is already 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 to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

The benefit-risk balance remains unchanged.

4. Conclusion

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

Variation B.II.d.2.a, Type IB: to extend the working range of the potency test of the finished product;

Variations B.II.e.5.a.2, Type IB: to add two new presentations of 8,000 and 10,000 doses;

Variation B.II.e.5.a.1, Type IAIN: to add a new volume of the solvent (500 ml);

Variation B.II.b.3.c, Type II: to add a new, lower than the one currently authorised, volume of virus added during the blending of the vaccine

Variation C.I.4, Type II: to reduce the minimum protective dose.

Additionally, to update the list of local representatives in the package leaflet and correct the name of unit used to express the amount of unbound IBD-specific IgYs.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above-mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I, IIIA, IIIB and A

Please refer to the separate product information showing the tracked changes.

As a consequence of these variations, sections 2, 4.2, 4.9, 6.5 and 8 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.