15 February 2023
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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Gumbohatch (EMEA/V/C/004967/VRA/0008/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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Laboratorios Hipra, S.A. (the applicant), submitted to the European Medicines Agency (the Agency) on 26 September 2022 an application for a group of variations requiring assessment for Gumbohatch.

1.2. Scope of the variation

Variation(s) requested	
G.I.18	G.I.18 - One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004
G.I.4	G.I.4 - Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

to add a mixed, associated use of two vaccines Gumbohatch and Evanovo; to align the product information with version 9.0 of the QRD templates; to process the editorial changes - add the wording "for poultry vaccines" to the solvent name and reword the name "vaccine" instead of "lyophilisate" in the solvent's labelling.

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, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

At present, Gumbohatch does not have an approved compatible use claim for use with any other vaccine, and consequently, the following wording is currently included within the product information concerning interactions with other veterinary medicinal products:

"*No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis*."

The applicant, with this variation, proposes to update the SPC, section 3.8 to include the following additional information at the start of this section:

"*Safety and efficacy data are available which demonstrate that this vaccine can be mixed with EVANOVO prior to use and administered simultaneously in ovo. The product information of EVANOVO should be consulted before administration of the mixed products.*

The mixed administration of GUMBOHATCH and EVANOVO should only be used when vaccinating 18-day-old embryonated eggs.

For mixed use, the onset and duration of immunity of the IBD virus included in the GUMBOHATCH vaccine have been demonstrated to be equivalent to those determined for GUMBOHATCH when used alone."

In addition, section 3.9 of the SPC is updated with instructions for vaccine preparation for mixed use of both vaccines.

Laboratory studies have been performed to demonstrate both the safety and efficacy of the associated use, according to the *Guideline on the requirements for combined vaccines and associations of IVMPs* (EMA/CVMP/IWP/594618/2010), which indicates that the basis of association should be a demonstration of acceptable safety and absence of serious interference between the IVMPs involved. In support of the proposed change to add a mixed use claim of Gumbohatch with Evanovo, the applicant has presented one GLP-compliant laboratory safety study and two laboratory efficacy studies, one of which investigated the efficacy of associated use of both vaccines for the coccidiosis-related claims and one which investigated the efficacy of associated use of both vaccines for the IBDV-related claims following *in ovo* administration of the mixed vaccines. In addition, an in-use stability study for the associated use of Gumbohatch and Evanovo, assessing the stability of Gumbohatch after being reconstituted with Evanovo and stored at 20 ± 5 °C, is provided.

It is noted that the safety and efficacy of mixed use of Gumbohatch and Evanovo has already been considered to have been adequately demonstrated by CVMP within the assessment of the marketing authorisation application procedure for Evanovo. Therefore, this variation is a so-called "reverse variation" to add the approved mixed use claim to the product information of Gumbohatch.

In addition, with this variation, the applicant proposes to align the product information with version 9.0 of the QRD template.

Part 2 Quality

An in-use stability study was performed to support the associated use of Gumbohatch and Evanovo, assessing the stability of Gumbohatch after being reconstituted with Evanovo and stored at 20 ± 5 °C. In accordance with EMA/CVMP/IWP/250147/2008 'Guideline on data requirements to support in-use stability claims for veterinary vaccines', data is provided for potency and stability at T0 and T0+X hours. Appearance and pH were also determined. The demonstrated in-use stability for Gumbohatch when reconstituted in PBS is 2 hours, therefore 2 hours is also proposed as the in-use stability for Gumbohatch when reconstituted with Evanovo diluted in Hiprahatch solvent. Due to the nature of the Evanovo vaccine, which contains coccidia oocysts that are extremely resistant to degradation, there is no potential impact of the components of Gumbohatch on the stability of Evanovo, which has a 10 hour in-use shelf life, and therefore the proposed 2 hour in-use shelf life could be considered suitable for Evanovo when combined with Gumbohatch.

To confirm the suitability of an in-use stability of 2 hours, two batches of Gumbohatch were reconstituted

with two batches of Evanovo which had been previously diluted in Hiprahatch solvent. Once reconstituted, all mixed vaccines were stored at room temperature until the end of the study. The data provided demonstrates that all parameters assessed are within the acceptance criteria 2 hours after mixing. The data satisfactorily demonstrates the absence of virucidal effects and physico-chemical interactions for the 2 hours after mixing the two vaccines, in accordance with EMA/CVMP/IWP/594618/2010 'Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)'. The data provided supports an in-use shelf-life of 2 hours for the mixed vaccines.

Part 3 Safety

One GLP laboratory study was conducted to investigate the safety of administration of a single dose of Evanovo mixed with a single dose of Gumbohatch.

Eighteen-day-old SPF eggs were administered either the two vaccines mixed (maximum dose of each vaccine), or PBS by *in ovo* vaccination. Following hatching, 75 birds per group were maintained in the study. Follow-up was carried out for 35 days after hatch, with daily monitoring for clinical signs, mortality, faecal appearance and body weight. Fresh faeces and litter with faeces were collected for oocyst counts/elimination profiles. Necropsies were performed on birds from both groups at appropriate timepoints during the study and all remaining animals were euthanised on study day 35. Intestinal lesion scoring according to Ph. Eur. 2326 Coccidiosis vaccine (live) for chickens was conducted in addition to evaluation of macroscopic lesions of the bursae, weight of bursa and spleen, and scoring of the degree of microscopic bursal damage according to Ph. Eur. 0587.

No clinical signs or changes in faecal appearance were reported in either group. No mortalities were reported related to vaccine administration. No differences between groups in bodyweights were reported at different time points. This study has previously been presented to CVMP in the MAA procedure for Evanovo, during which it was raised as a concern that vaccinated animals gained significantly less weight compared to control animals. In the absence of a control group vaccinated with either vaccine alone, it was not possible to exclude that this parameter was negatively impacted by the mixed use of both vaccines. In response to this concern, the applicant justified that differences in weights between groups were attributed to housing factors (groups were housed in separate rooms), rather than as a result of associated vaccine use.

To fully address the concern, the applicant conducted an additional study to demonstrate the lack of adverse effect of mixed use on weight gain, with a similar design to the one discussed above. In this study, all birds were housed in the same room and thus were exposed to identical conditions (in contrast to the previous laboratory safety study, in which treatment groups were housed separately). The results of this additional study demonstrated that no statistically significant differences in body weight or growth rates were observed between treatment groups during the study.

Safety parameters related to Gumbohatch: Vaccinated animals showed evidence of significant histological damage to the bursa of Fabricius (BF), as expected, with statistically significant differences in lesion score in the BF in the vaccinated group compared to the control group. The mean lesion scores were higher at the first time points, but lower values were reported at the last time points, considered to represent evidence of recovery of the BF by repopulation with lymphocytes after peak bursal damage at days 7 – 14. Significant bursal lesions were expected to occur in vaccinated SPF birds (with no MDA against IBDV). The vaccine strain of Gumbohatch is an intermediate plus strain, thus, it falls out of scope of the specific monograph no. 0587 of the Ph. Eur. which only applies to vaccines containing virus strains of low virulence. It is also noted that birds in the control group had mild bursal lesions at day 7 and 14. Statistically significant differences in mean histopathological score between groups were detected at all timepoints, as expected. Section 4.6 (now 3.6) of the SPC of Gumbohatch currently states that lymphocyte depletion followed by repopulation and regeneration of the bursa of Fabricius is very common and is not associated with immunosuppression. Thus, although the

results for the histopathological damage are not in compliance with the requirements of Ph. Eur. 0587, this has previously been accepted in the original dossier for use of Gumbohatch alone, and the presence of vaccine-related bursal damage is accepted as being distinct from bursal damage induced by IBDV (and is not associated with any clinical signs).

Safety parameters related to Evanovo: Evaluation of intestinal lesions was performed at multiple time points throughout the study. Apart from mild macroscopic lesions which were reported in 2 vaccinated birds and 1 control bird at a later day during the study (accepted as non-specific/non-vaccine related), no other macroscopic lesions were observed, at any of the timepoints evaluated in the vaccinated group. None of the data presented (including oocyst elimination profiles) were indicative of a change in the safety profile of Evanovo due to associated use with Gumbohatch and were consistent with the findings presented in the laboratory safety study for use of Evanovo alone.

No clinical signs or mortalities attributable to vaccination were observed in the three groups during the study.

It was therefore accepted that the data presented supported the safety of mixed use of Evanovo and Gumbohatch. No adverse impact on weight gain or growth rates up to 35 days of age, when compared to separate use of either Evanovo or Gumbohatch, was observed following mixed use.

The combined results of both laboratory safety studies are considered to adequately support the conclusion that the associated use of Evanovo and Gumbohatch mixed together before administration to 18-day-old embryonated chicken eggs can be considered as safe as when either Gumbohatch or Evanovo are administered separately.

In conclusion, the safety of the proposed compatible use claim for mixed administration of Evanovo and Gumbohatch is considered to have been sufficiently supported.

Part 4 Efficacy

Two studies are presented in support of the proposed change.

The efficacy of mixed use of one dose of Evanovo and Gumbohatch in 18-day-old embryonated chicken eggs was investigated in a GLP-compliant laboratory study (efficacy of Evanovo following mixed use). The response to challenge at 21 days of age (the approved onset of immunity for Evanovo) for each of the four *Eimeria* strains against which Evanovo is claimed to protect was investigated in 18-day-old embryonated SPF chicken eggs vaccinated with Evanovo mixed with Gumbohatch and compared with a mock-vaccinated control group. The claims at onset of immunity for Evanovo for the group vaccinated with Evanovo and Gumbohatch were considered to have been adequately supported (similar to that which had been demonstrated in laboratory challenge studies supporting the efficacy of Evanovo when used alone) and it was accepted that mixed use of Gumbohatch with Evanovo did not adversely impact the efficacy profile of Evanovo. This study has been evaluated in the MAA for Evanovo and was accepted by CVMP to support the efficacy of associated use of Evanovo with Gumbohatch. These data will not be discussed further in this variation assessment report to register the approved mixed use compatibility claim to the product information of Gumbohatch.

The efficacy of mixed use of one dose of Evanovo and Gumbohatch in 18-day-old embryonated chicken eggs was investigated in a GLP-compliant, randomised, blinded laboratory challenge study (efficacy of Gumbohatch following mixed use). It should be noted that in the first study referred to above, the applicant evaluated antibody titres to IBDV as a surrogate marker of response to vaccination, however this was considered as insufficient support for the demonstration of absence of impact of efficacy of mixed use on the efficacy profile of Gumbohatch. As a consequence, this additional study was provided. The onset of immunity at 24 days of age (i.e., the currently authorised onset of immunity for Gumbohatch) following *in ovo* vaccination was investigated in 18-day-old embryonated seropositive chicken eggs. Two groups of 12 animals were used, one vaccinated

with Evanovo + Gumbohatch *in ovo* (with each vaccine at minimum titre) and one control mock-vaccinated group.

At 24 days of age, 10 animals from the vaccinated and control groups were challenged with a very virulent IBDV strain by the oculonasal route (the same challenge strain and route of administration as originally used to support the efficacy of Gumbohatch). Chicks were observed daily for 6 days after challenge, with monitoring of clinical signs (with a scoring system used for clinical signs relevant to IBDV infection, as per the original efficacy studies conducted for Gumbohatch), mortality, serological response and weight of animals. At 6 days post-challenge, when the acute phase of the infection was expected, animals were necropsied. Bursae were examined macroscopically for presence of external oedema, followed by histopathological analysis. Growth rate of animals and the oocysts eliminated were also monitored.

Results demonstrated that no clinical signs were observed in either group in the pre-challenge period from hatching to challenge. After challenge, no clinical signs or mortality were observed in the vaccinated group. No mortality occurred in the control group, however 40% of birds displayed mild clinical signs compatible with Gumboro disease. The differences between the study groups for the proportion of clinical signs were statistically significantly different. The relevance of the mild clinical signs in the control group was demonstrated by a corresponding statistically significant difference in growth rate between the day prior to challenge and the end of the study with a higher growth rate in the vaccinated group compared to the control group.

External oedema of the bursa was observed in 90% of animals in the control group and in no bursae of the vaccinated group.

There was a statistically significant difference observed between groups for the sum of macroscopic lesions of the bursa of Fabricius at day 30. Histopathological examination of bursal lesions demonstrated that the summary score for 'acute histological functional lesions score' was statistically significant different between the vaccinated group compared to the control group. Bursae from animals in the control group presented a moderate to severe mixed, diffuse, inflammatory infiltrate in the plica (including lymphoid necrosis) accompanied by severe oedema that affected the full thickness of the bursae. In contrast, bursae from the vaccinated group presented a significantly lower inflammatory infiltrate and a total absence of oedema. Whilst there was no difference in the mean score for lymphoid depletion between groups, early lymphoid follicles indicative of a repopulating process were observed only in the vaccinated group. It is accepted that the histopathological scoring system used in this study is appropriate and allows the differentiation between vaccine-induced bursal damage and bursal damage induced by very virulent IBDV, and that the study findings are supportive of a reduction of bursal damage caused by very virulent IBDV.

Other secondary variables also supported a positive effect of vaccination compared to the control group (BF: body weight ratio, spleen: body weight ratio).

As stated, MDAs were present in chicks, decreasing on the day before challenge. Six days after challenge, a serological response in the vaccinated group was evident, whereas titres remained low in the control group.

The oocyst elimination profile demonstrated oocyst elimination and recycling in the vaccinated group, confirming the response to Evanovo vaccination. No oocysts were detected in faeces in the control group.

It is accepted that this study is supportive of the currently authorised indications for use of Gumbohatch, when this vaccine is administered mixed with Evanovo. Although a study group vaccinated with Gumbohatch alone was not included, the results following challenge of the vaccinated group (Gumbohatch plus Evanovo) support the currently authorised indications for use at the onset of immunity timepoint, that is, a reduction in clinical signs and lesions of the bursa of Fabricius caused by very virulent IBDV. The study was conducted in commercial broiler eggs with MDA against IBDV, consistent with the fact that Gumbohatch should only be used in chickens with MDAs against IBDV and it is noted that the average ELISA units of the hatchability control

group was within the range stated in the product information for the level of MDAs at hatching for which efficacy of the vaccine has been demonstrated.

Overall, it is accepted that the efficacy of Gumbohatch is not negatively affected by the simultaneous administration (mixed use) of Evanovo when administered *in ovo* at the 18th day of embryonation, at the onset of immunity timepoint of 24 days of age. Although this study only investigated efficacy by way of challenge at the approved onset of immunity (24 days) and no data has been provided in respect of challenge at the approved duration of immunity (up to 45 days), given the findings of this study and the absence of any negative impact on efficacy at the onset of immunity and therefore lack of demonstrated interference of combined use of Evanovo and Gumbohatch, there is no reason to believe that similar findings would not also be expected 21 days later at the approved duration of immunity for this product.

In addition, it should be noted that CVMP have previously concluded, based on these data, that the efficacy of Gumbohatch is not adversely affected when used mixed with Evanovo.

In conclusion, the proposed variation for Gumbohatch to register a compatible use claim (mixed use) with Evanovo is considered to have been adequately supported. The additional text which the applicant wishes to include in section 3.8 of the SPC is acceptable. In addition, section 3.9 is updated with instructions for mixed use of both vaccines, this is also considered acceptable.

During this variation, the applicant additionally proposed to align the product information with version 9.0 of the QRD template. The information has been largely transcribed directly from the relevant sections of the previously approved product literature for the product, to the relevant sections of the newly proposed product literature presented with this application. A few amendments were additionally proposed and they are all considered acceptable. The revised PI therefore reflects both the associated use claim with Evanovo, and the updated PI in line with version 9.0 of the QRD template.

3. Benefit-risk assessment of the proposed change

Gumbohatch is a vaccine intended for chickens consisting of a lyophilisate to be reconstituted in the Hiprahatch solvent. The vaccine can then be administered either i*n ovo* (18 days embryonated eggs) or subcutaneously (1 day of age).

Gumbohatch contains a live attenuated infectious bursal disease virus (IBDV) and it is intended for the active immunisation of chickens to reduce clinical signs and lesions of the bursa of Fabricius caused by very virulent avian infectious bursal disease virus infection.

The proposed variation is to add a mixed, associated use of Gumbohatch with the recently authorised vaccine of the same company Evanovo. Evanovo already contains the claim for the associated use. Evanovo is authorised for administration *in ovo* only.

Moreover, with this variation, the applicant wishes to align the product information with version 9.0 of the QRD template and to process a few editorial changes to the labelling.

3.1. Benefit assessment

Direct therapeutic benefit

The benefits of the product remain unaffected by this variation.

Additional benefits

This variation request proposes the mixed use of Gumbohatch with another vaccine, Evanovo, which is indicated for protection against coccidiosis in chickens, which is also administered via the *in ovo* route. The additional benefit of this change is a reduction in the number of separate vaccinations necessary for *in ovo* vaccination for common diseases affecting chickens.

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:

Safety (user, consumer, environmental, target animal) remains unaffected by this variation.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, consumer safety, target animal safety, efficacy.

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

4. Conclusion

Based on the original and complementary data presented on quality, safety 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 (Regulation (EU) 2019/6), as follows:

to add a mixed, associated use of two vaccines Gumbohatch and Evanovo;

to align the product information with version 9.0 of the QRD template;

to process the editorial changes - add the wording "for poultry vaccines" to the solvent name and reword the name "vaccine" instead of "lyophilisate" in the solvent's labelling.

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 and IIIB

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

As a consequence of these variations, sections 3.8 and 3.9 of the SPC are updated due to the G.I.4 variation, in addition to many sections throughout the product information due to the G.I.18 variation. The corresponding sections of the Package Leaflet are updated accordingly.