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Veterinary Medicines and Product Data Management

Withdrawal Assessment Report for

Gallimune Flu H5N9(i) (EMEA/V/C/002229)

Withdrawal at Day 120

Introduction

An application for the granting of a Community marketing authorisation of Gallimune Flu H5N9(i) was submitted to the European Medicines Agency on 1 December 2009 by Merial in accordance with Regulation (EC) No. 726/2004. The product was eligible for the centralised procedure under Article 3(2) last paragraph of Regulation (EC) No 726/2004 since avian influenza is a disease subject to Community prophylactic measures.

Gallimune Flu H5N9(i) contains 0.3 ml dose and is presented in packs/containers of 300 ml. It is indicated for active immunisation of chickens to reduce mortality, clinical signs and viral excretion caused by avian influenza virus type A, highly pathogenic subtype H5N1. The route of administration is intramuscular use. The target species is chickens.

The letter of intent was sent in 2006. At that time, outbreaks of Asian Influenza H5N1 in poultry were regarded as being of high risk in Europe. Currently, the disease situation in Europe can be regarded as quiet. There are no reported infections with HPAIV H5N1, neither in poultry or wild birds. Currently high risks are only expected from illegal trade from Asia and Africa. The introduction by wild birds, travellers, vehicles and waterfowl trade is regarded as being low. The introduction by legal trade with third countries and within Europe as well as by travellers and vehicles is regarded as negligible (Source: Friedrich-Löffler-Institut, February 2010).

The application was validated on 15 December 2009 and the assessment was carried out by the CVMP in line with its normal timetable. A List of Questions was adopted at day 120 of the procedure on 14 April 2010 and communicated to Merial. Merial then informed the European Medicines Agency on 30 September 2010 that it withdraws the application for Gallimune Flu H5N9 (i). This withdrawal report therefore reflects the CVMP assessment at that stage.

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Part 2 - Quality

The conclusion on the data presented in the quality part of the dossier can be regarded as sufficient to allow risk assessment of production and control of Gallimune Flu H5N9(i) but there are open major objections and other concerns which need to be resolved.

The starting materials comply with the requirements on purity as defined by Ph.Eur. No products of ruminant origin are used. Therefore, a risk from TSE can be excluded up to current scientific knowledge.

The manufacturing of the vaccine (production and control) complies with GMP and are certified accordingly.

Protocols for MSV and WSV and different batches concerning active ingredient and final product are provided. However, details of how the MSV has been tested for extraneous agents are lacking.

The inactivation process is as yet insufficiently validated.

The tests performed comply with the current legislation. All tests performed in process are well described and validated with the exception of one where no validation data was provided. Additionally a titration of the virus harvest needs to be introduced.

Tests on the final product are well described but the Standard Operating Procedure for the batch safety test needs to be revised because it does not correspond to the recommended use of the vaccine. Furthermore the potency test method requires further validation and the pass criteria need to be justified.

The stability of the final product cannot yet be finally assessed as no data on the quantitative composition of the vaccine have been provided. Therefore the additional data from another vaccine with the same composition cannot yet be regarded as supportive. Stability data on the vaccine itself are missing.

Part 3 – Safety

Gallimune Flu H5N9(i) is a liquid inactivated vaccine adjuvanted by a w/o emulsion against Avian Influenza (AI) infection. The vaccine is packed in 300ml bottles containing 1000 doses of 0.3ml of vaccine. The vaccine strain is an Avian Influenza H5N9 strain. The components of the excipients are of non animal origin. The antigen content of fixed formulation of commercial vaccine batches is set to a fixed quantity in order to ascertain a defined serological conversion (Haemagglutination Inhibition units) in the potency test. The vaccine intended for chickens (broilers and future laying pullets) is administered by i.m. route.

Primary vaccination in broilers: One injection from 3 weeks of age.

Primary vaccination in future layer chickens: 1st injection from 3 weeks of age and 2nd injection: 2 to 4 weeks later.

Revaccination in future layer chickens: 2 to 4 weeks before the onset of lay.

The dose volume (0.3ml) is specific of the Merial panel of inactivated viral vaccines for poultry. The dose and the composition of excipients and adjuvants is standardised throughout the Gallimune panel as stated by Merial.

A study on the safety of the administration of a dose, an overdose and a repeated dose of the Avian Influenza H5N9 vaccine in 21-day-old SPF-chickens has been provided**.**

The safety of Gallimune Flu H5N9(i) was evaluated considering the local and systemic reactions of the vaccine in chickens after administration of a dose, an overdose and a repeated dose of Gallimune Flu H5N9(i). The trials are performed with chickens at day 21 of age, which is the recommended vaccination age. In each trial, the vaccine was applied i.m., the recommended route of administration. The study demonstrates the safety in chickens at the minimum age of vaccination.

Supportive studies were provided for the application of one dose and of an overdose. These studies were performed with Gallimune 407 ND+IB+EDS+ART (Inactivated vaccine in an oily adjuvant against Newcastle Disease, Infectious Bronchitis, Egg Drop Syndrome (EDS76) and Avian Rhinotracheitis). This vaccine is an inactivated vaccine from Merial's panel of inactivated oil-emulsion vaccines for poultry.

The major concern covers the comparability of Gallimune Flu H5N9(i) with the vaccines used in the supportive studies. As long as the composition of the vaccines Gallimune Flu H5N9(i) and Gallimune 407 ND+IB+EDS+ART, which are subject of the supportive studies, is not fully demonstrated the supportive studies cannot be considered as being relevant for the safety assessment of Gallimune Flu H5N9(i).

The examination of reproductive performance was demonstrated by a study performed with Gallimune 407 ND+IB+EDS+ART.

The original purpose of the study was to demonstrate the duration of immunity for Gallimune 407. As the study covers the possible impact of the vaccination to the reproductive performance as well and as the vaccine under evaluation is pretended to have the same composition as Gallimune Flu H5N9(i), the results of this study can be used to assess the safety of Gallimune Flu H5N9(i) with respect to the impact of the reproductive performances as well. It can be concluded that the vaccination of 18 weeks old future layers is safe. This is of major importance as in an event of emergency, the whole chicken population from the minimum age of vaccination onwards will be vaccinated.

Examination of immunological functions:

The vaccine induces specific antibodies against Avian Influenza H5N9 strain. It does not contain any substances known to induce adverse effects on the immunological response. Therefore, the examination of the immunological function was not investigated.

Interactions with other vaccinations have not been reported. This is reflected in the proposed SPC.

Field trials are not required for emergency vaccination. As supportive data, a PSUR for Gallimune 407 ND+IB+EDS+ART was provided.
The major concern covers the comparability of Gallimune Flu H5N9(i) with the vaccines used in the supportive studies. As long as the composition of the vaccines Gallimune Flu H5N9(i) and Gallimune 407 ND+IB+EDS+ART, which are subject of the supportive studies, is not fully demonstrated the supportive studies cannot be considered as being relevant for the safety assessment of Gallimune Flu H5N9(i).

The safety data submitted do not currently support the full vaccination regime recommended for future layers. Only two doses, corresponding to the primary vaccination schedule, were administered. Justification for the recommended booster dose 2-4 weeks before the onset of lay is therefore required.

The excipients and adjuvants are either allowed substances for which Table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as

not falling within the scope of Regulation (EC) No 470/2009 when used as in this product. As a result of the composition of the vaccine no specific residue studies were considered necessary.

Gallimune Flu H5N9(i) is an inactivated vaccine; therefore, there is no risk of transmitting live antigens. The components used in this vaccine are classical components for this type of product, which do not have any known action on the environment. Besides, the product is administered individually, in a small quantity (0.3ml), via the parenteral route; the product is not conveyed directly in the ecosystems.

Concerning User Safety, no additional warnings or precautions are regarded as necessary, except the standard texts for mineral oil adjuvanted products for user safety purpose. These remarks are already included in the proposed SPC.

Part 4 – Efficacy

As the vaccine is intended for use in chickens only, the efficacy trials were carried out in SPF-chickens of the youngest age recommended for vaccination (3 week old chickens). The chickens are injected i.m., the batches tested had the minimum antigen content or even less and were manufactured in compliance with the production described in the analytical part of the dossier.

Three studies performed with different vaccine preparations of Gallimune FLU H5N9(i) were presented.

Efficacy assessed by serology of different Avian Influenza H5N9 experimental inactivated vaccines in 3-week-old chickens

The minimum age of vaccination is applied to be 21 days. This study was performed with chickens of 22 days of age. It is not expected that this day of age has an impact on the evaluation of the efficacy of the vaccine. It has been demonstrated that a vaccine preparation containing a minimal quantity (50µl) of antigen meets the defined threshold for the potency test. The major concern covers the statistical analysis of the trial. The statistical analysis requires further evaluation.

Efficacy of 2 different Avian Influenza H5N9 inactivated vaccines against a highly pathogenic H5N1 Avian Influenza challenge in 3-week-old SPF chickens

The onset of immunity after one vaccination can be regarded as demonstrated, provided the relevance of the AI-strains used for the serological testing and the relevance of the challenge strain towards the current epidemiological situation in Europe is justified. The efficacy is demonstrated for protection against mortality, reduction of clinical signs and reduction of virus shedding after infection, provided the outstanding concerns will be solved. The major concerns cover the validation of the techniques used for serology and virus detection and the statistical analysis of the test results.

Duration of immunity conferred by the Avian Influenza H5N9 inactivated vaccine in SPF chickens

The duration of immunity for laying birds after three vaccinations is not confirmed. The serological data do not comply with those presented in the other two studies. The data presented can therefore not be interpreted. One of the vaccine preparations was used in all three studies and induced significantly different levels of antibodies against the same antigen in the HI. The major concern covers the lack of consistency between the three studies. As the vaccine is not intended for use before the decline of maternal antibodies and is also not intended for use during lay, relevant investigations were not performed and are not regarded as being necessary. Field trials are not required for an authorisation under exceptional circumstances.

The antibody levels induced in vaccinated animals differ from trial to trial. The antibody levels after three injections are lower than those induced after one vaccination in another trial. Therefore no conclusion on the induction of efficacy can currently be made. Major objections remain regarding the establishment of the challenge model and onset of protection, the duration immunity and the discrepancy in the serological titre results in the study reports.

Part 5 – Benefit Risk Assessment

Benefit assessment

Direct therapeutic benefit

Concerning efficacy, the benefits of Gallimune Flu H5N9(i) are the reduction of mortality, clinical signs, and viral excretion.

The proposed indication is as follows:

For active immunisation of chickens to reduce mortality, clinical signs and viral excretion caused by Avian Influenza Virus type A, Highly Pathogenic subtype H5N1.

Onset of immunity has been demonstrated 3 weeks after one injection.

50 weeks duration of immunity has been demonstrated after the primary vaccination course followed by a revaccination before the onset of lay.

Additional benefits

Gallimune Flu H5N9(i) has the Neuraminidase subtype N9 which allows distinction from the field strains, which up to now have the Neuraminidase subtype N1. Therefore it would be possible to differentiate infected birds from vaccinated ones (DIVA strategy), if a suitable test for differentiation would be available.

Risk assessment

Quality

The starting materials comply with the requirements on purity as defined by Ph.Eur. No products of ruminant origin are used. Therefore, a risk from TSE can be excluded up to current scientific knowledge. The manufacturing of the vaccine (production and control) complies with GMP and are certified accordingly. Protocols for MSV and WSV and different batches concerning active ingredient and final product are provided.

The inactivation is not yet adequately validated.

The tests performed comply with the current legislation. All tests performed in process and on the final product are well described and, with the exception of the potency test, validated.

The stability of the final product cannot yet be finally assessed as no data on the quantitative composition of the vaccine have been provided. Therefore the additional data from another vaccine with the same composition cannot yet be regarded as supportive. Stability data on the vaccine itself are missing.

The company was sent major objections and other concerns regarding the quality part and asked to address them.

Safety

Concerning safety, data on birds, vaccinated once, twice or once with a double dose were presented. The most common side effects are a very moderate and transient local reaction in a small percentage of vaccinated chickens which resolves spontaneously within 3 to 4 weeks at the most. After the second injection, and subsequent administrations, this reaction is markedly reduced.

As no comparable data on the quantitative composition of the vaccine have been provided, the additional data from another vaccine with the same composition cannot yet be regarded as supportive. Therefore a final conclusion on the safety of the vaccine currently cannot be made and the company was sent major objections on this issue.

Concerning User Safety, no additional warnings or precautions are regarded as necessary, except the standard texts for mineral oil adjuvanted products for user safety purpose. These remarks are already included in the proposed SPC.

The excipients and adjuvants are either allowed substances for which Table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product. As a result of the composition of the vaccine no specific residue studies were considered necessary.

A negative impact on the environment is not expected.

The company was sent major objections and other concerns regarding the safety part and asked to address them.

Efficacy

The antibody levels induced in vaccinated animals differ from trial to trial. The antibody levels after three injections are lower than those induced after one vaccination in another trial. Therefore no conclusion on the induction of efficacy can currently be made. Major objections remain regarding the establishment of the challenge model and onset of protection, the duration immunity and the discrepancy in the serological titre results in the study reports.

The company was sent major objections and other concerns regarding the efficacy part and asked to address them.

Evaluation of the benefit risk balance

The benefit risk balance for Gallimune FLU H5N9 (i) cannot currently be considered positive since **"major objections"** have been identified which preclude a recommendation for marketing authorisation.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considered at the April 2010 meeting that the application for the Gallimune FLU H5N9(i) is not approvable at the present time since **"major objections"** have currently been identified which preclude a recommendation for marketing authorisation. The details of these major objections were provided to the applicant in the List of Questions. Major objections are critical points requiring resolution before recommendation for a marketing authorisation. In addition, satisfactory answers must be given to the **"other concerns"** as detailed in the List of Questions.

Merial informed the European Medicines Agency on 30 September 2010 that it withdraws the application for Gallimune Flu H5N9(i).