Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

HIPRAGUMBORO G97
HIPRAGUMBORO-GM97 (BG, LT)
HIPRA GUMBORO GM97 (EE, LV)

Date Created: August 2015

Updated: May 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0191/001/E/003
Name, strength and pharmaceutical form	Hipragumboro G97
Applicant	LABORATORIOS HIPRA, SA. Avda. La Selva, 135. 17170 - AMER (Girona) Spain
Active substance(s)	Live Infectious Bursal Disease Virus, strain GM97:10^2 - 10^3 EID_{50} (embryo infective dose 50%).
ATC Vetcode	QI01AD09
Target species	Chicken: broilers
Indication for use	For active immunisation of broilers with insignificant levels of maternally derived antibodies (ELISA of 500 or below) to reduce mortality, clinical signs and bursal lesions of Gumboro disease. Such birds can be vaccinated from one day of age. The onset of immunity is 14 days post vaccination and the duration 43 days post vaccination.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Repeat Use application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the mutual recognition procedure	26 February 2018
Date product first authorised in the Reference Member State (MRP only)	26th July 2002
Concerned Member States for original procedure, and subsequently added	First Use Austria, Belgium, Czech Republic, France, Germany, Greece, Hungary, Italy, The Netherlands, Portugal, Slovakia, Spain. Repeat Use 1st wave Poland. Repeat Use 2nd wave Bulgaria, Ireland. Repeat use 3rd wave Estonia, Latvia, Lithuania

1. SCIENTIFIC OVERVIEW

This was a repeat use application submitted under Article 12 (3) of Directive 2001/82/EC as amended. The product, which contains live Infectious Bursal Disease Virus (IBDV), strain GM97:10^2 – 10^3 EID_{50}[1], was originally authorised in the UK in 2002. The data contained within this document refers to data received for the original application, along with any appropriate data submitted for variation Marketing Authorisations. The product is intended for the immunisation of broilers with an insignificant level of maternal antibody which are at risk of Gumboro disease. Vaccination may occur from 1 day of age, and the onset of immunity is 14 days post vaccination, with a duration of immunity of 43 days post-vaccination. The strain is not pathogenic.

The product was 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, any reactions

[1] EID – Embryo infective dose 50%.

observed are indicated in the SPC.[2] 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 [3] 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

II.A. Composition

The product contains Live Infectious Bursal Disease Virus, strain GM97:10^2 - 10^3 EID_{50} (embryo infective dose 50%) and the excipients disodium phosphate dodecahydrate, potassium dihydrogen phosphate, gelatin, povidone 30, sodium chloride, potassium chloride, monosodium glutamate, sucrose and water for injections.

The container/closure system consists of Type I glass vials, of 10 ml containing 1,000 doses and 5,000 doses of the freeze-dried vaccine, with Type I bromobutyl rubber stoppers and aluminium caps.

Pack sizes:
Pack with 1 vial of 1000 doses
Pack with 1 vial of 5000 doses
Pack with 10 vials of 1000 doses
Pack with 10 vials of 5000 doses

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the vaccine was justified. The vaccine does not contain preservative or adjuvant.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Production of master and working seeds has been suitably described. Eggs are prepared with virus and incubated appropriately and suitable harvesting is then performed. Viral homogenate is held for up to 7 days at 4°C prior to blending with freeze-drying excipients. Autoclaving is performed, and batches of vials produced, and storage is at 4°C.

II.C. Control of Starting Materials

The active substance IBDV, is an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

[2] SPC – Summary of product Characteristics.
[3] Efficacy – The production of a desired or intended result.

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. Any deviation from the guidelines was adequately justified.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

II.C.4. Substances of Biological Origin

A declaration of compliance and Format 3 declaration was provided. The strain was isolated from the bursa of Fabricius of an infected chicken using SPF eggs. The only materials of animal origin used in the attenuation and production of master seed and working seed stocks are SPF eggs, no material of bovine origin is used. Only gelatin of porcine origin is used in manufacture. The risk of transmission of Animal Spongiform Encephalopathies by administration of this vaccine is, therefore, extremely low.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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 the assessment of appearance of the product, macroscopic observation of the freeze-dried tablet, Dissolution of the tablet in phosphate buffered saline, residual moisture, serological identity, titre, sterility, presence of extraneous agents and additional identification tests. Safety and potency tests are also performed.

The demonstration of the batch to batch consistency was appropriately demonstrated within three consecutive batches. Other supportive data provided confirm the consistency of the production process.

II.F. Stability

Stability data on the active substance were provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided. Suitable data appears on the SPC for the storage of the product.

G. Other Information

- Do not mix with any other vaccine or immunological product.
- Shelf-life of the veterinary medicinal product as packaged for sale: 24 months.

- Shelf life after dilution or reconstitution according to directions: 1 hour.
- Store and transport refrigerated (2ºC - 8 ºC).
- Protect from light.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal was demonstrated in suitable studies. The investigations were performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals. The SPC carries suitable instruction.

Studies were also performed which assessed the spread of the live Gomboro G97 vaccine to unvaccinated birds, and to other species. The SPC carries suitable information with regard to care of use:

Due to its residual pathogenicity to the bursa the vaccine should be used only in areas contaminated with vvIBDV, except for infected flocks showing clinical signs.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain. The excipients used are applicable for the product. No withdrawal period is required. The product contains no adjuvant or preservative, therefore no residue studies were required. The vaccine is not immunosuppressive.

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

Refer to Efficacy Section.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that spread of the vaccine does not cause adverse effects in infected birds and does not spread to other species. There is no reversion to virulence and the product does not contain components subject to maximum resides limits. The procedure for using the vaccine will not cause undue spread of the virus. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product was demonstrated in laboratory studies. These included titration of the pathogenic vvIBDV to be used in challenge infections, a pathogenicity comparison of the inoculation route using the pathogenic vvIBDV strain, which assessed any differences in pathology caused by ocular or oral administration. Results were similar.

Determination of the minimum vaccine dose of the product required was performed. The assays were also used to determine the effectiveness of the vaccine via the oral route, which was found to be comparable to the ocular route described for the active substance in the Ph. Eur. 5 groups of 10 young birds were given a minimum dose of 10^2 EID_{50}/bird, or 3 x10^2 EID_{50}/bird, 10^3 EID_{50}/birds or 3 x 10^3 EID_{50}/bird. A final group of negative controls received no vaccine. Vaccine with working seed at 0.2 ml dilutions occurred, with observation taking place for fourteen days. Blood sampling was performed, then birds were challenged with pathogenic virus diluted 1/100, strain VG-248. Observations were made, and any deceased birds subjected to post-mortem analysis. On day 28 all birds were culled and post-mortems performed. Results indicated that a minimum dose of 10^2 EID_{50} in seventeen day old birds was supported.

The innocuousness and potency of a single dose in one day old birds was assessed. 60 birds were divided into two groups. From each flock, 10 birds were euthanased and levels of IBDV antibodies tested. Remaining birds were then vaccinated orally with 10^2 EID_{50}/bird in 0.2 ml. No birds were inoculated from the second group. 10 birds in each group were necropsied after 14 days. Vaccinated birds had a slight reduction in size of bursa and a score was seen of 2.0 for lymphoid depletion. This was slightly less for the unvaccinated birds. After 60 days, 20 birds from each group were orally challenged with the strain Girona. 4 birds were added as a challenge control group. Observations were performed until day 70, with suitable blood tests occurring, when all birds were euthanased. No adverse reactions associated with the disease assessed were recorded. The study supported the efficacy of a single dose of the product given at one day of age and that protection was exhibited up to 60 days post-vaccination.

A GLP-compliant study was performed to assay the immunity and efficacy of the product in one day old birds. 75 birds were divided into 2 groups, the first group was vaccinated orally at a dose of 10^2 EID_{50}/bird, and the second group acted as controls. Birds were pre-tested for IBDV antibodies. The groups were further sub-divided at days 7 and 14, and birds from both groups were challenged with the Girona strain via the ocular route at either of these time points. Daily observations were performed and dead birds necropsied. Blood tests were performed on day 18, and all remaining birds, culled and necropsied on day 24. Adverse clinical signs were recorded only for the unvaccinated groups, but were seen as expected in the unvaccinated groups. The assay confirmed the immunity and effectiveness of the products against challenge at days 7 and 14 post-vaccination.

A trial assessed protection in birds with passive immunity, in order to determine duration of immunity. The minimum dose was given to 100 farm-bred young birds with varying levels of maternally derived IBDV antibody. A proportion of birds from both premises were tested via culling and necropsy for antibody status, and the remainder were then divided into 4 groups, exhibiting low or high maternally-derived IBDV. On day 15, dependent on maternally-derived antibody, one group of low MD antibodies was vaccinated orally with 10^2 EID_{50} of the product, and another group inoculated with phosphate buffered saline as negative controls. On day 20 the 2 high MD antibody groups were likewise vaccinated with $10^{2.2}$ $EID_{50,}$ or given PBS. Birds were observed, then on day 43 10 additional birds were added as non-vaccinated pre-challenged controls. A sample of all birds were placed together, and all animals were then euthanased on day fifty-four for analysis. Results showed that a duration of immunity was established of 33 days for chickens vaccinated at 15 days of age and that vaccination when maternal antibodies have declined is satisfactory.

A further study observed the efficacy, onset and length of immunity of the product in 1 day old broiler chicks. 145 birds were divided into 3 groups. The first group were blood sampled and vaccinated on day 0 at 15 days old. 20 birds were culled and necropsied to establish the level of maternally derived antibodies to IBDV, a further group of 60 birds was not vaccinated. On day 7, both remaining groups were divided into four groups and one group subjected to viral challenge. Another group were kept as negative controls. Birds were observed daily and dead birds necropsied. On day 14, the other remaining groups were further subdivided, and a proportion of vaccinated and non-vaccinated birds were blood sampled and subjected to challenge with the vvIBDV Girona strain. Futher non-challenged groups were added as controls. On day 17, the two groups challenged on day 7 (one vaccinated, one not vaccinated), were euthanased and necropsied, and on day 24 the two groups challenged on day 14 were euthansed and necropsied. On day 58 remaining birds were challenged, with further non-challenged birds being added. On day 68, all remaining animals were culled and necropsied. The study supported the onset of immunity as being 14 days post-vaccination, with a duration of immunity of 58 days, and demonstrating a reduction in adverse reactions.

Field Trials

Three field trials were performed, which provided safety and efficacy data to support the authorisation of the product. In the first trial, 11,500 birds were divided into two groups, the first intended to be inoculated with the proposed product, the second intended to be inoculated with Hipra Gumboro Clone CH80, a live vaccine authorised in Spain. Birds were also vaccinated against infectious bronchitis virus (IBV) prior to the trial. The criteria for testing for efficacy were:

- In the case of a natural outbreak of Gumboro disease, the presence of clinical disease or mortality will not be higher in the group inoculated with the proposed vaccine as compared to those inoculated with the reference vaccine.
- If there were no outbreaks of clinical disease, the development of antibodies against IBD to be observed in at least 80% of birds vaccinated with the proposed product.

On day 1, 10 birds from each group were tested for infectious bursal disease (IBD) antibodies. This was repeated on day 16, and birds in the first group were

were vaccinated with the proposed product, when the level of IBD antibodies was seen to drop from 4141 to 675. Serological analysis carried out at culling showed that the antibody level in the vaccinated group was then 6024. It was not stated that a challenge from Gumboro disease occurred during the trial, so there is no direct evidence of protection. However, the level of antibodies at the time of culling was at a protective level, based on laboratory studies.

In a second trial 31,020 birds were divided into two groups at 1 day of age. The criteria set for the efficacy of the vaccine were:

• In the case of a natural outbreak of Gumboro disease, the presence of clinical disease or mortality will not be higher between the two groups of birds intended for treatment with the proposed or reference vaccines.
• If no outbreaks of clinical disease occurred, the development of antibodies against IBD was to be observed in at least 80% of birds vaccinated with the proposed vaccine.

The first group consisted of 15,840 chicks intended for vaccination with Hipra Gumboro GM97. The second group consisted of 15,180 chicks intended for vaccination with Hipra Gumboro clone CH80. All birds were also vaccinated against IBV. 10 chicks were randomly selected from each group and were bled for the testing of IBD antibodies. On day 13, this was repeated. The first group was vaccinated against Gumboro disease on day 16. The method of administration was oral, in drinking water. The birds were observed daily for clinical signs attributable to Gumboro disease, and any mortality occurring. Any birds suspected of dying from Gumboro disease were sent for necropsy. On day 40, both groups were culled and weighed, and the data used to calculate the European Factor of Production efficiency (EFPE).

No clinical signs of Gumboro disease were noted in either group. Overall mortality was similar in both groups. The EFPE for the group vaccinated with the proposed product was 294, and was 276 for the group vaccinated with the reference product. (This was considered normal for the intensive rearing of broilers). The antibody level in the first group of birds on day 1 was 3458 ELISA units. Using Kouwenhoven's formula to calculate the day on which antibody levels would have waned to an acceptable level, day 14 was indicated. On day 14, the antibody levels were 2155 in the first group and 2258 in the second group. The trial demonstrated that the proposed vaccine was safe during field use, and that an effective level of protection was reached, as had been supported by laboratory trials.

During the trial no clinical disease was reported, so direct assessment of efficacy could not be made. Serological analysis during the trial showed that on the day of vaccination with the proposed product at day 14, the antibody levels had dropped to 2155 from 3458. These levels were higher than expected, and higher than that recommended by the Kouwenhoven formula. Antibody levels at cull (day 38), showed a mean antibody titre of 4060, indicating that vaccination had persisted until culling.

In a third trial, 56,700 birds were divided into two groups (31,200 in the first group, 225,000 in the second group). The first group was intended for vaccination with Hipra Gumboro GM97, and the second group with Hipra Gumboro CH80. On days 1 and 16, randomly selected birds from each group

were blood sampled. Kouwenhoven's formula gave day 16 as the appropriate day for vaccination. Both groups were also inoculated with IBV vaccine. The birds were observed for clinical signs and/or death. In the case of deaths possibly attributable to Gumboro disease, corpses were sent for necropsy. On day 49, both groups were culled and the appropriate measurements made to calculate the EFPE. No adverse reactions to the vaccine were recorded, and no clinical signs of disease were recorded in either group. The overall mortality rates between the two groups were similar.

The EFPE for the first group was 216, and was 208 for the second group. These data were considered satisfactory. The ELISA titre had fallen to 551 on the day of vaccination in birds receiving the proposed product. By the time of culling, it had risen to 6863. This study did show direct support of efficacy, because there was no natural challenge. However, the serological data indicated that a protective titre was present at the end of the study, when compared to efficacious laboratory challenge results.

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 of the product(s) is favourable.

MODULE 4

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 Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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