



Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

**DRAFT PUBLICLY AVAILABLE ASSESSMENT REPORT FOR
A VETERINARY MEDICINAL PRODUCT**

HIPRAGUMBORO CW

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0162/001/DC
Name, strength and pharmaceutical form	Hipragumboro CW, Lyophilisate for oral suspension.
Applicant	Laboratorios Hipra S.A 17170 - AMER (Girona) Spain Tel. +34 972 430660 Fax. +34 972 430661 E-mail: hipra@hipra.com
Active substance(s)	Live Infectious Bursal Disease Virus, strain CH/80
ATC Vet code	QI01AD09
Target species	Chickens: broilers
Indication for use	For active immunisation of broilers with maternally derived antibodies (MDA ELISA breakthrough titre of 115) to prevent clinical signs and to reduce loss of weight and bursal damage caused by Gumboro Disease. The onset of immunity is 14 days and the duration of 30 days post vaccination.

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (<http://www.hma.eu>).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	14 June 2011 (Day 210: 22 June 2011)
Date product first authorised in the Reference Member State (MRP only)	
Concerned Member States for original procedure	AT, BE, DE, DK, FR, IT, NL, SK, UK

I. SCIENTIFIC OVERVIEW

The product is 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; the slight reactions observed are indicated in the SPC.

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 of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. *Composition*

The product contains Live Infectious Bursal Disease virus, strain CH/80, with strength $10^{3.5} 10^{5.5}$ CCID₅₀ and freeze-drying excipients: potassium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, povidone, sodium chloride, sucrose, monosodium glutamate and water for injection.

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The containers are Type I glass vials of 10 ml for all packs size. The bromobutyl stopper is incorporated to the vial and sealed together with an aluminium cap. The particulars of the containers and controls performed have been provided and conform to the regulation.

The choice of the vaccine strain CH/80 and the formulation of the vaccine are justified.

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

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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is the Live Infectious Bursal Disease virus, strain CH/80, an established and well known active substance, described in the European Veterinary Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with European Pharmacopoeia monographs or in-house specifications.

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 according to the Ph. Eur; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided

and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular titration, sterility, safety, and test for extraneous agents.

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

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

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions (24 months at 2-8°C).

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.
Shelf life after reconstitution: 2 hours

III. SAFETY ASSESSMENT

Three different vaccine batches were used.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is adequately demonstrated or justified.

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PE-2008-VR-04: Safety of the administration of one dose and an overdose

This study has been conducted in accordance to Good laboratory Practice Principles.

The study was carried out in accordance with the 2-4-2 section of the specific monograph of IBDV live vaccines. The study was conducted in three groups of one day old SPF chicks of 24 animals in each one, two vaccinated groups and a control group.

The first group of 24 SPF chickens were inoculated with an overdose of the vaccine (10 doses), and the other group with a one dose. The control group receives PBS by the same administration route (oral route).

The level of antibodies was checked in birds from the same flock to assure they were free of antibodies.

Some chicks of both groups were euthanized at 7, 14, 21, and 28 days post vaccination, as stated in the monograph of the vaccine, and samples of the bursa were taken for histological examination. Also muscular lesions, different weights and weight ratios were recorded.

Results:

The maximum level of damage to the Bursa is observed at 14 days post vaccination.

The lesion scores obtained for days 21 and 28 complied with those established at the Ph. Eur. monograph of IBDV vaccines of low virulence.

At 21 days, a notable repopulation of follicles and lymphocytes takes place, with maximum levels at 28 days post vaccination.

The results showed no statistically differences between the one dose and the overdose group. Results revealed neither systemic nor clinical signs or local reactions nor deaths attributable to the vaccine. The results supported the safety of the vaccine at one dose and an overdose in oral route.

PE-2008-VR-03: Safety of the administration of an overdose

This study has been conducted in accordance to Good laboratory Practice Principles.

The trial was conducted according to 2-4-1 section of the specific Ph. Eur. monograph of the vaccine. The overdose was administered by oral route.

Results:

The study of Bursa of Fabricius shows statistically significant mild macroscopic lesions such as loss of structure, oedemas and exudates in 8 of 21 vaccinated chickens.

These observed lesions are not different from those expected after the replication of an IBDV vaccine strain in the Bursa of Fabricius.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

In the SPC it is stated that "No effects other than those indicated in section 4.6 have been observed following administration of ten doses".

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

In the SPC it is stated that: “A notable transient lymphocyte depletion can be observed in birds on day 7 post-vaccination. The repopulation of the follicles by lymphocytes starts after day 7 post-vaccination, being especially evident on 21 days post-vaccination. By day 28 postvaccination only mild lesions remain in some birds. This does not result in an immunosuppressive effect”.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain(s). In the SPC is stated that “The vaccine strain is excreted up to a maximum of 10 days; thus, during this time, it may spread to unvaccinated chickens”.

No adjuvant is used, and excipients are widely known as safety. Based on this information, no withdrawal period is proposed.

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

One multicentric field trial, referenced as **EC-2008-VR-04** has been carried out to assess both the safety and efficacy under field conditions.

EC-2008-VR-04

See IV efficacy

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

The very low pathogenicity of the strain, its no reversion to virulence (demonstrated in laboratory trials), the no spread to species different that chickens (as stated in bibliography) and in case it occurs, the low pathogenicity of the strain, support its null environmental risk, although its long and persistent survival in nature.

In case of improper use of the vaccine, none of the components of the formulation is known to cause environmental problems.

The cleaning and disinfection measures on the poultry houses are appropriate to avoid its spread to the environment.

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)

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IV.B Clinical Studies Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that this vaccine stimulate active immunity against Infectious Bursal Disease (Gumboro disease) Virus to prevent clinical signs and to reduce loss of weight and bursal damage caused by Gumboro Disease.

The onset of protection and the duration of protection were studied in the following trials:

- PE-2009-VR-02. Study of the efficacy of the vaccine PB-114 live vaccine against Infectious Bursal Disease in SPF birds.

22 one day old chickens were vaccinated with the minimal titre by oral route, and 22 inoculated with PBS. Both groups were challenged by eye drop with IBDV at 14 days after vaccination. A third group was vaccinated and inoculated with PBS as control.

The chickens were observed daily for 10 days after challenge for clinical signs, or deaths. No clinical signs were observed in the chicks during 14 days post vaccination in any group. After the challenge, the vaccinated group did not show clinical signs. The non vaccinated and challenged show, in more than a 50% of animals, clinical signs. The other parameters confirm the immunogenicity of the vaccine administered to one day old chickens.

The vaccine complies with the test (section 2-4-5 of monograph 0587).

- PE-2009-VR-03. Study of the efficacy and duration of protection of the vaccine PB114 (live vaccine against Infectious Bursal Disease) in broilers.

80 broilers were vaccinated and challenged, and other group of 80 broilers were not vaccinated but challenged. There were three challenges at different times: 14, 21 (in order to asses the onset protection) and 50 days post vaccination (in order to asses the duration of immunity). The age of vaccination was considered: maternally antibodies protect chickens against field infection, but neutralizes the IBD vaccine viruses and blocks the development of a suitable active immune response against disease.

In absence of MDA vaccines could be administered at one day old (as it was in most of the laboratory trials included in the dossier). But when MDA are present at birth, vaccination should be delayed until MDA has waned in most of the flock.

The Applicant proposes calculate the appropriate age to vaccination by serological testing of the birds within the first day post hatching.

The animals were vaccinated by drinking water with one dose of vaccine with the minimum titre. Clinical signs, damage to the bursa, and performance measures were observed. And a protective ELISA titre of antibodies was established.

The optimal day of vaccination is calculated according to the Deventer's formula, using 115 as

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the ELISA breakthrough titre value.

The results support the onset of immunity at 14 days before vaccination, and the duration of immunity of 30 days post vaccination.

Field Trials

EC-2008-VR-04: Safety and efficacy under field conditions.

The applicant has conducted field studies to demonstrate the safety and efficacy of the vaccine administered in broilers under field conditions.

A total of 82730 broilers were used, distributed in three farms. From them, 41490 were vaccinated with Hipragumboro CW and 41240 were vaccinated with a similar licensed vaccine, in order to have a positive control group.

The vaccine for the positive control group was administered by the same administration route and at the same frequency as the trial product.

The vaccines were administered by oral drinking water, one single administration. Vaccination day was calculated according the Deventer formula, and was 21 days old in farms A and C, and 22 days old at farm B.

As long as the farm C was the only one with a natural outbreak of Gumboro disease, this is the only widely described in the efficacy section

The parameters studied were mainly mortality, and secondary serology, the European Factor of Production Efficiency (EFPE, provides information about fattening process) and FTA cards (a method of sampling and processing nucleic acids).

The outbreak of Gumboro took place two weeks after vaccination in farm C.

Results:

The mortality rate in the vaccinated group with Hipragumboro CW was statistically lower than in control group.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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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 veterinary Heads of Agencies website (www.hma.eu).

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