College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Avishield IB GI-13

Updated: May 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0301/001/DC
Name, strength and pharmaceutical form	Avishield IB GI-13, lyophilisate for oculonasal suspension/use in drinking water for chickens
Applicant	GENERA Inc. Svetonedeljska cesta 2, Kalinovica 10436 Rakov Potok Croatia
Active substance(s)	Live avian infectious bronchitis virus, variant strain V-173/11
ATC Vet code	QI01AD07
Target species	Chickens
Indication for use	For the active immunisation of chickens in order to reduce the detrimental effect on the ciliary activity resulting from infection by avian infectious bronchitis virus, serotype 793B (GI-13 lineage), which may be manifested in respiratory clinical signs. Onset of immunity: 10 days after vaccination. Duration of immunity: 56 days after vaccination

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	05 February 2020
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	AT, BE, CZ, DE, DK, EE, EL, ES, FR, HR, HU, IE, IT, LT, LV, PL, PT, RO, SI, 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. Qualitative and quantitative particulars

The product contains $10^{2.7}$ - $10^{4.6}$ EID_{50} (50% embryo infective dose) of live avian infectious bronchitis virus, variant strain V-173/11, and the excipients povidone K 25, bacto-peptone, monosodium glutamate, potassium dihydrogen phosphate, potassium hydroxide, dextran 40000 and sucrose.

The container/closure system consists of colourless glass vials (type I), which are closed with bromobutyl rubber stoppers and sealed with aluminium caps.

The choice of the vaccine strain is justified.

B. Method of Preparation of the Product

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

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with 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. requirements.

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

D. Control tests during production

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

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: Appearance, Vacuum test, Identity, Potency, Microbial limit, Mycoplasma and Residual moisture.

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

F. Stability

The stability of the antigens when stored under the approved conditions has been demonstrated.

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.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of an overdose in the target animal is demonstrated in two studies. The safety of the administration of a tenfold dose by spray or oral gavage in 1-day old SPF chicks was tested No clinical abnormalities or mortality occurred. In addition, a tenfold overdose safety study for the respiratory tract and kidney was performed. No mortality occurred and kidney histology scores were at most moderate, which is in accordance with the Ph. Eur. requirement. However, transient clinical signs (tracheal rales) were observed and significant average ciliary stasis scores were obtained. A warning concerning adverse reactions has been included in the SPC. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Effects on reproductive performance were examined in accordance with Ph.Eur. No macroscopic lesions attributable to vaccination were observed at necropsy. It was concluded that the vaccine is safe for the reproductive tract of SPF chickens, when applied as a single maximum dose at the youngest age for vaccination via the oculonasal route. Additional data have been provided to show the vaccine is safe for use during lay.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny, therefore a specific study was not carried out.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain. Vaccination induced mild respiratory signs. Vaccine virus take (dissemination) was confirmed from day 4 post vaccination and spread was confirmed 4 days after co-mingling. Virus colonised several tissues and organs and persisted for at least 4 weeks in caecal tonsils. An appropriate warning is included in the SPC. Three laboratory studies were performed to investigate reversion to virulence. No evidence of increase in virulence was found after 5 passages, when assessing occurrence, severity or length of clinical signs, ciliary scores, kidney histology scores or oviduct macroscopy. The biological properties of the vaccine are described. As IBV is a coronavirus and therefore a single stranded RNA virus, it has a relatively high capacity to change by spontaneous mutation. Also, homologous recombination cannot be excluded. An appropriate warning is included in the SPC to vaccinate all chickens in a flock. This is considered to mitigate the risk of passage and concurrent infection and thus of recombination events and spread of mutated strains.

The excipients used are either approved additives or outside the scope of the MRL regulation. Based on this information, a withdrawal period of zero days is considered justified.

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

Three field studies were performed in order to evaluate safety and efficacy in commercial broilers and future layers after spray and drinking water administration. It was not considered ethical to include a placebo control group, therefore trials were performed as comparative controlled studies, using a comparator vaccine (Noblis IB 4/91) with the same indication. Both safety and efficacy results of these field studies are described in detail in section IV. Clinical Assessment – Field trials.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the risk associated with the use of the product is very low . Warnings and precautions as listed in the product information are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that since IBV virus is ubiquitous and variant strains are widely used for vaccination, the use of the vaccine is not likely to increase the level of environmental exposure. The excipients in the finished product have no toxic effects in the quantities present. Since the vaccine strain does not constitute a hazard, the consequence of environmental exposure is considered negligible.

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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)

Laboratory Trials

First, laboratory studies were performed to investigate the onset and duration of immunity of the vaccine, when applied via spray, eye-nose drop or orally, in SPF birds and birds with maternally derived antibodies. Challenge with IB virus occurred on day 10, 21 and 35 . Necropsy and ciliary activity scoring occurred 5 days after each challenge.

In the first study, which included chicks without maternally derived antibodies, protection from loss of ciliary activity was achieved in vaccinated birds at 10, 21 and 35 days after vaccination. The minimum vaccine dose of 2.7 EID_{50} was found to be protective (in accordance with Ph. Eur. 0442) with an onset of immunity of 10 days in SPF chicks, through each of the three proposed administration routes.

In the second study, which included chicks with maternally derived antibodies, protection from loss of ciliary activity was achieved in vaccinated birds at 21 and 35 days after vaccination. The minimum vaccine dose of 2.7 EID_{50} was found to be protective (in accordance with Ph.Eur. 0442) against homologous challenge with an onset of immunity of 21 days in chicks with maternally derived antibodies, through each of the three proposed administration routes. It can be concluded from the study that the presence of maternally derived antibodies to IBV delays the onset of protection to 21 days post vaccination, but does not affect the level of efficacy.

The onset of immunity of 10 days (in SPF chicks) is supported, and a suitable warning sentence regarding interference of maternally derived antibodies with development of immunity is included in the SPC.

Two additional laboratory studies were performed towards the duration of immunity of Avishield IB GI-13 applied via the oral route (at 7 days old) and via spray (at 1 day-old) in SPF chickens.

Challenge of orally vaccinated chicks and non-vaccinated controls occurred on day 49 or day 56 after vaccination. A significant reduction in ciliostasis scores and a reduction of the clinical signs (tracheal rales) 4 days after challenge of 7 day-old SPF chicks was observed.

Challenge of spray vaccinated chicks and non-vaccinated controls occurred on day 56. No clinical signs were observed in either group, but a significant reduction in ciliostasis scores was observed 4 days after challenge of day-old SPF chicks.

The claimed duration of immunity of 56 days is considered supported by the data presented.

Field Trials

Three field studies were performed in order to evaluate safety and efficacy in broilers and future layers. Trials were performed as comparative studies. All field studies comprised a laboratory challenge phase. Immunity was demonstrated in the field studies by protection after challenge. The chickens were vaccinated on the farm or hatchery. In the laboratory phase of the field trials, efficacy of the vaccine was proven by challenge with protection levels in broilers of 80% after spray vaccination and 90% after drinking water vaccination. In layers a protection level of 80% was achieved after spray vaccination.

The presence of maternally derived antibodies interfered with the development of immunity. A suitable warning sentence is included in the SPC.

Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results**	
Field study: Clinical field safety and efficacy after spray administration in commercial broilers					**Results**	**Conclusions**
Hybrid Ross 308 Group 1 (test group): 20,500 chicks, vaccinated with Avishield IB-GI-13 Group 2 (positive control group): 20,700 chicks, vaccinated with Nobilis IB 4/91	Commercial broiler flock	Vaccination on day 1 via spray administration. Test product: 3.8 log10 EID_{50}/dose	-	Production Blood samples Oro-pharyngeal and cloacal swabs for PCR	Feed conversion, average body weight, total animal loss and production index were better in the control group compared to the test group[a]. Both groups showed MDA titres. Antibody titres were low at Day 22 and had increased by Day 40. Antibody titres did not differ between groups on any of the sampling days[b]. 100% homology to the vaccine strain on Day 9 and 99% homology on Day 16 and 40 was found in both groups.	No adverse events were observed in both groups. The vaccine is generally safe for commercial broilers, when applied via spray at minimum age for vaccination. Production results of the test group fall within the results of four further houses at the same farm during the same period, clinical and laboratory results did not indicate that production results were related to the vaccine used. The vaccine induced antibody levels comparable with those induced by the comparator vaccine. No indications for a field challenge were observed during the study, therefore no conclusion can be drawn with respect to field efficacy of the product
Laboratory study: Laboratory challenge after spray administration in commercial broilers under field conditions					**Results**	**Conclusions**
Hybrid Ross 308, taken from field study described above.	Commercial broiler flock	Group 2: Vaccination on day 1 via spray administration (under field conditions).	Day 21: challenge of 20 vaccinated birds and 10 control birds	Clinical sings Necropsy (day 25)	No clinical signs were observed. Ciliary scores were positive	Results of the homologous challenge infection of field vaccinated animals and non-

Group 1 (control group): 20 non-vaccinated hatch mates Group 2 (test group): 25 chicks vaccinated with Avishield IB-GI-13		Test product: 3.8 log10 EID_{50}/dose	with IBV by eye drop.		(>1 ring affected) in 4/20 vaccinates and 8/10 controls.[a].	vaccinated hatch mates with maternally derived antibodies support the claimed efficacy.
Field study: Clinical field safety and efficacy after drinking water administration in commercial broilers					**Results**	**Conclusions**
Hybrid Ross 308 Group 1 (test group): 20,500 chicks, vaccinated with Avishield IB- GI-13 Group 2 (positive control group): 20,300 chicks, vaccinated with Nobilis IB 4/91	Commercial broiler flock	Vaccination on day 7 via drinking water administration. Test product: 3.8 log10 EID_{50}/dose	-	Production Blood samples Oro-pharyngeal and cloacal swabs for PCR	No difference in body weight.[b] Test group had a lower total animal loss. Control group had a slightly better production index. Both groups showed MDA titres. Antibody titres were slightly lower at Day 29 and had increased by Day 40. Antibody titres did not differ between groups on day 8[b] and 29[b], but were higher in the control group on Day 40[a]. 99% homology to the vaccine strain on Day 16, 23 and 40 in the test group. In the control group homology was 99% on Day 16 and 41 and 100% on day 23.	No adverse events were observed in both groups. Results of the field study confirm the vaccine is generally safe for broiler chicks, when applied via drinking water at 7 days of age. Overall production results were good in both groups. Serology showed higher antibody titres in the control group at Day 40. No field challenge occurred, therefore no clear conclusions with respect to field efficacy can be drawn.
Laboratory study: Laboratory challenge after drinking water administration in commercial broilers under field conditions					**Results**	**Conclusions**
Hybrid Ross 308, taken from field study described above.	Commercial broiler flock	Vaccination on day 7 via drinking water administration (under field conditions).	Day 21: challenge of 20 vaccinated birds and 10 control birds	Clinical sings Necropsy (day 25)	No clinical signs were observed. Ciliary scores were positive (>1 ring	Results of the homologous challenge infection of field vaccinated animals and non-vaccinated hatch

Group 1 (control group): 20 non-vaccinated hatch mates Group 2 (test group): 25 chicks vaccinated with Avishield IB-GI-13		Test product: 3.8 log10 EID_{50}/dose	with IBV by eye drop.		affected) in 2/20 vaccinates and 9/10 controls.[a]	mates with maternally derived antibodies support the claimed efficacy.
Field study: Clinical field safety and efficacy after spray-on administration in commercial layers					**Results**	**Conclusions**
Hybrid Lohman Brown Group 1 (test group): 26,000 chicks, vaccinated with Avishield IB- GI-13 Group 2 (positive control group): 26,000 chicks, vaccinated with Nobilis IB 4/91	Commercial layer flock	Vaccination on day 1 via spray administration. Test product: 3.8 log10 EID_{50}/dose	-	Production Blood samples Oro-pharyngeal and cloacal swabs for PCR	Body weights were generally higher[a] and food conversion was lower in the test group. No differences in antibody levels between groups, MDA were present.[b] 99-100% homology to the vaccine strain on Day 9 and 18 in both groups.	The study shows the vaccine is safe when applied by spray under field conditions in layer pullets from 1 day of age. No field challenge occurred, therefore no clear conclusions with respect to field efficacy can be drawn.
Laboratory study: Laboratory challenge after spray-on administration in commercial layers					**Results**	**Conclusions**
Hybrid Lohman Brown, taken from field study described above. Group 1 (test group): 25 chicks vaccinated with Avishield IB-GI-13 Group 2 (control group): 15 non-vaccinated hatch mates	Commercial layer flock	Vaccination on day 1 via spray administration (under field conditions). Test product: 3.8 log10 EID_{50}/dose	Day 21: challenge of 20 vaccinated birds and 10 control birds with IBV by eye drop.	Clinical sings Necropsy (day 25)	Tracheal rales were observed in 2/20 vaccinates and 5/10 controls after challenge. Ciliary scores were positive (>1 ring affected) in 4/20 vaccinates (including the two with tracheal rales) and 7/10 controls.[a]	Results of the study support the efficacy in commercial future layers when applied via spray (worst case) under field conditions.

[a]: significant difference between vaccinates and controls
[b]: no significant difference between vaccinates and controls

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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.

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

Summary of change	**Section updated**	**Approval date**
Addition of a supplier for an excipient (NL/V/0301/001/IA/001)	N/A	15 APR 2020
Update CEP for bacto peptone. (NL/V/0301/001/IA/004/G)	N/A	29 NOV 2021
Lowering the lower virus titre limit of the WSV (NL/V/0301/001/IB/005)	N/A	10 DEC 2021
Deletion of AE tests from finished product specifications (NL/V/0301/001/WS/002)	Module 3, Quality Aspects, Control Tests on the Finished Product	05 JAN 2022
Addition of safety data for use during lay (NL/V/0301/001/II/003)	Module 1 and Module 3, Safety Assessment, Laboratory trials	03 MAR 2022