United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Avishield IB H120, Lyophilisate for Oculonasal Suspension/Use in Drinking Water, for Chickens

Date Created: April 2018

PuAR correct as of 30/10/2018 when RMS was transferred to NL.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0633/001/DC
Name, strength and pharmaceutical form	Avishield IB H120, Lyophilisate for Oculonasal Suspension/Use in Drinking Water, for Chickens
Applicant	Genera Inc. Svetonedeljska cesta 2, Kalinovica 10436 Rakov Potok Croatia
Active substance	Each dose contains Active substance: Attenuated live virus of avian infectious bronchitis, Massachusetts serotype, strain H-120 $10^{3.5}$ to $10^{4.5}$ EID_{50}* *EID_{50} = 50% Embryo infective dose
ATC Vetcode	QI01AD07
Target species	Chickens (broilers and future layers/breeders)
Indication for use	For active immunisation of chickens (broiler and future layers/breeders) in order to reduce the detrimental effect resulting from the infection by avian infectious bronchitis virus, serotype Massachusetts on the ciliary activity, which may be manifested in respiratory clinical signs. Onset of immunity: 3 weeks after vaccination Duration of immunity: 5 weeks after 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	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	20th December 2017.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

This was a full application, submitted in accordance with Article 12 (3) of Directive 2001/82/EC as amended, for Avishield IB H120, Lyophilisate for Oculonasal Suspension/Use in Drinking Water, for Chickens. The product is indicated for active immunisation of chickens (broiler and future layers/breeders) in order to reduce the detrimental effect resulting from the infection by avian infectious bronchitis virus (IBV), serotype Massachusetts, on the ciliary activity, which may be manifested in respiratory clinical signs. The onset of immunity is 3 weeks after vaccination. Duration of immunity is 5 weeks after vaccination.

The product is used as a coarse spray administered via the oculonasal route and spray from one day of age, or via drinking water from 7 days of age.

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, any reactions observed are indicated in the SPC.[1] 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 [2] 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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains attenuated live virus of avian infectious bronchitis, Massachusetts serotype, strain H-120, $10^{3.5}$ to $10^{4.5}$ EID_{50}, (50% embryo infective dose). The excipients are as follows: povidone K 25, bacto-peptone, monosodium glutamate, potassium dihydrogen phosphate, potassium hydroxide dextran 40 000 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.

Carton box with 10 vials of 1000 doses of vaccine.
Carton box with 10 vials of 2500 doses of vaccine.
Carton box with 10 vials of 5000 doses of vaccine.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain, the attenuation process and the absence of preservative are justified.

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. The manufacturing method consists of the following:

Phase I: Preparation of the virus for production, disinfection and loading of SPF eggs, embryo growth, inoculation of eggs with working dilution of seed strain, replication of bronchitis disease virus, harvesting of allantoic fuid, freezing and storage.

Phase II: Defrost of viral antigen, preparation and filling of lyophilisation mixture into vials, freeze-drying, capping, quality control testing, labelling and packaging of the product.

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

II.C. Control of Starting Materials

The active substance is an attenuated virus strain of avian infectious bronchitis, Massachusetts serotype, strain H-120**,** presented as a lyophilisate for oculonasal suspension/use in drinking water, for chickens. The active substance complies with an in-house specification. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of a non-biological origin used in production comply with the European Pharmacopoeia (Ph. Eur). Bacto-peptone is a product of biological origin, which complies with an in-house specification.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines. The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline. The packaging is appropriate for use and complies with specification.

II.C.4. Substances of Biological Origin

The applicant has provided a signed TSE/BSE declaration confirming that the peptone used in the product complies with current regulatory requirement described in Ph. Eur. 1483 Products with risk of transmitting agents of animal encephalopathies.

A valid EDQM certificate of suitability has been provided for peptone used in the vaccine. The country of origin of source materials (porcine and bovine) is the USA. Confirmation has been provided by the manufacturer that the base powder for MEM contains no substances of animal origin. 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.

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

A variety of control tests are performed during production of the product.

II.E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements. Tests include those for appearance, identification of the vaccine virus, virus titre, bacterial and fungal contamination, absence of extraneous agents, residual humidity, intact vacuum of the product and batch to batch consistency.

II.F. Stability

Data were provided for 21 months from three batches of product for each proposed presentation. 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.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf life after reconstitution: 3 hours.
Store and transport refrigerated (2 °C – 8 °C).
Protect from light.
Do not freeze.

III. SAFETY ASSESSMENT

Laboratory trials

A single safety study of the administration of one dose was not investigated. The safety of an overdose (x 10) and the repeated administration of one dose in the target animal were demonstrated in three pivotal laboratory studies, according to GLP[3] and requirements cited in Ph. Eur 5.2.6. It was concluded that the product had an acceptable safety profile based on these results.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals. Safety of the vaccine on immunological function was addressed by the submission of two pieces of published data.

Three pivotal safety studies were conducted to assess the impact of the vaccine in the respiratory tract, kidneys and reproductive tract according to Ph. Eur. 0442. These were combined with reversion to virulence of the vaccine. The studies were performed only by oculo-nasal route in one day old chicks at a suitable passage level of virus. The vaccine virus was at a suitable passage level for the study observing effects on the respiratory tract and kidneys. A single dose at maximum titre was used in the study for the reproductive tract. No adverse effects were noted.

Published data on the biological properties of the H120 strain of IBV and on genetic reassortment were provided. The strain has been used for many years, and as coronaviruses contain a non-segmented genome, reassortment does not occur.

A user safety risk assessment was provided. Live IBV is not known to infect humans and it is considered highly improbable that the dose and routes of administration would have impact on user/public health and safety. The SPC carries a warning with regard to the spread of the vaccine to other species. Refer to the SPC for a description of possible adverse reactions seen in the target species.

All studies supported the safety of the product as being acceptable. Suitable warnings appear on the SPC for any considerations required with regard to safe use of the product.

Field studies

Two field trials were carried out, (see Clinical Assessment Section). One trial using commercial broilers, the other on commercial layers. No adverse reactions were noted that are not cited in the SPC.

[3] GLP – Good Laboratory Practice.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required, 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 has been demonstrated in laboratory studies in accordance with the relevant requirements.

Two pivotal laboratory studies were performed. In the first study, which assessed the efficacy of the vaccine, birds were inoculated with vaccine containing the minimum antigen content of $10^{3.5}$ EID_{50}. The vaccine was administered by recommended routes, and appropriate challenge followed with IBV stain M41 via eye-drop at a dose of 10^4 EID_{50} per bird. Results from the study supported a claim of onset of immunity for 21 days.

The second study assessed the onset and duration of immunity, and the interference of maternally derived antibodies (MDA) of the propose product. The vaccine used was at the minimum titre and batch used for efficacy. Birds were appropriately challenged with IBV strain M41 by eye-drop at a dose of 104 EID50 per bird

Results from these studies contributed to the onset and duration of immunity as cited in the SPC. The onset of immunity was established as being 21 days. The duration of immunity was established as being 5 weeks.

Field Trials

Two field studies were conducted to investigate the safety and efficacy of the proposed product in commercial broilers and layers.

Study title	Evaluation of the Clinical Field Efficacy and Safety of an Attenuated Live Vaccine (IBV H120) against Infectious Bronchitis Infection in Broilers Following a Single Spray Administration to Day-old Chicks
Objectives	To study the efficacy and safety of the proposed vaccine compared to a comparator product
Test site(s)	Two farm-situated bird houses - France
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Avishield 1B H120 Lyophilisate for Oculonasal Suspension/use in drinking water, for chickens at $10^{4.4}$ EID_{50}/dose
Control product	Bioral H120 ≥3.0 $\log_{10}$ EID_{50}/dose.

Animals	Juvenile commercial broilers. 15,691 vaccinated with proposed product 15,816 vaccinated with control product
Randomisation	Birds randomised to either test or control group.
Blinding	The investigator was masked to the treatments. The technician performing daily observations was blinded to treatment allocation.
Method	Products administered via coarse spray. Single vaccination on Day 1. Blood tests performed at a variety of suitable time points. Parameters tested: Mean live weight Feed conversion European Production Index
Statistical method	The numerical values calculated for the production parameters of mean live weight, ADWG, FC and EPI were compared numerically between the two groups. Mortality data between treatments were compared using Wilcoxon rank sum tests modified for censored survival data. Antibody titre and body weight data are summarised (number, mean, median, standard deviation, minimum and maximum) by treatment and time point. In addition, for each time point separately, these data were subjected to a one-way analysis of variance. If considered necessary, the data were subjected to a suitable (e.g. logarithmic, square root, rank) transformation prior to analysis. The statistical tests were two-tailed and performed at the 5% significance level using the statistical package SAS v8.2.
RESULTS	As inconclusive seroconversion was observed during the study, the data were considered supportive.
Adverse events	No serious adverse events occurred due to treatment.

Study title	Evaluation of the Clinical Field Efficacy and Safety of an Attenuated Live Vaccine (IBV H120) against Infectious Bronchitis Infection in Layer Pullets
Objectives	To study the efficacy and safety of the proposed vaccine compared to a comparator product
Test site(s)	Two farm-situated bird houses - Slovenia
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Avishield 1B H120 Lyophilisate for Oculonasal Suspension/use in drinking water, for chickens at $10^{4.4}$

	EID_{50}/dose
Control product	Bioral H120 ≥3.7 log_{10} EID_{50}/dose.
Animals	Juvenile commercial chickens. 10,030 vaccinated with proposed product 10,560 vaccinated with control product
Randomisation	Birds randomised to either test or control group.
Blinding	The investigator was masked to the treatments. The technician performing daily observations was blinded to treatment allocation.
Method	Products administered via coarse spray Day 1. Subsequently 3 vaccinations via drinking water. Blood tests performed at a variety of suitable time points. Parameters tested: Mean live weight Feed conversion European Production Index
Statistical method	For mortality, the comparison between treatments made using Wilcoxon rank sum tests modified for censored survival data. The feed consumption for each treatment was not compared statistically but compared numerically. Antibody titre and body weight data are summarised (number, mean, median, standard deviation, minimum and maximum) by treatment and time point. In addition, for each time point separately, these data were subjected to a one-way analysis of variance. If considered necessary, the data were subjected to a suitable (e.g. logarithmic, rank) transformation prior to analysis. The statistical tests were two-tailed and performed at the 5% significance level using the statistical package SAS v8.2.
RESULTS	Although natural infection occurred during the study and some seroconversion was observed, the data were considered supportive as vaccination deviated from that proposed and correlation between antibody titres and protection was not observed.
Adverse events	No serious adverse events occurred due to treatment.

Authorisation of the product as specified in the SPC was granted in respect of results obtained from two pivotal safety studies, with supporting data from field trials.

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 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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