United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Novamune Concentrate and Solvent for Suspension for Injection for Chickens

Date Created: November 2018

PuAR correct as of 26/03/19 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PROPOSED PRODUCT SUMMARY

EU Procedure number	UK/V/0634/001/DC
Name, strength and pharmaceutical form	Novamune Concentrate and Solvent for Suspension for Injection for Chickens
Applicant	Ceva Animal Health Ltd Unit 3, Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance(s)	Live attenuated IBD virus, Serotype 1, strain SYZA26 2.65 – 4.2 $\log_{10}$ CID_{50}* * Chicken Infective Dose 50%
ATC Vetcode	QI01AD0
Target species	Chickens
Indication for use	For active immunisation of day-old future layer chickens in order to reduce clinical signs and acute lesions of bursa of Fabricius caused by very virulent Avian Infectious Bursal Disease (IBD) virus infection. Onset of immunity is expected from 30 days depending on the initial MDA level. The immunisation is influenced by the natural decline of maternally derived antibodies (MDA), and has been found to occur when MDA have reached appropriate release level. The onset of clinical protection depends on the initial MDA level. In vaccinated day old future layer chicks the release of the vaccine virus (vaccine virus take) was observed between 21-42 days after vaccination. Duration of immunity: 9 weeks. The virulent challenge tests conducted to support the claim were carried out on day old future layer chicks having an ELISA titre of

	3,000 to 5,700 (average Day 0 MDA levels). Field trials carried out showed that vaccine virus replication in the bursa of Fabricius occurs in day old future layer chicks having average MDA titre levels of 6,000 ELISA units.

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	6th June 2018.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This was an application for a full marketing authorisation, submitted in accordance with Article 12 (3) of Directive 2001/82/EC, as amended. Novamune Concentrate and Solvent for Suspension for Injection for Chickens is a vaccine containing live, attenuated infectious bursal disease (IBD) virus, Serotype 1, strain SYA26 at 2.65 – 4.2 $\log_{10}$ CID_{50} (chicken infective dose 50%), and the key excipient, bursal disease antibody (BDA) 1.3 – 2.2 log10 AB unit (antibody unit). The virus is complexed with bursal disease antibodies. Inclusion of the bursal disease antibodies ensure that release of the vaccine virus occurs once the MDA levels are relatively low, thus providing protection without MDA interference.

The product is indicated for the active immunisation of day-old, future layer chickens with maternally derived antibody (MDA), to reduce clinical signs and acute lesions of bursa of Fabricius caused by very virulent Avian Infectious Bursal Disease (IBD) virus infection. The onset of immunity is expected from 30 days, depending on the initial MDA level.

Immunisation is influenced by the natural decline MDA, and has been found to occur when MDA have reached appropriate release level. The onset of clinical protection depends on the initial MDA level. In vaccinated, day-old, future layer chicks, the release of the vaccine virus (vaccine virus take) was observed between 21-42 days after vaccination. The duration of immunity is 9 weeks. Chickens from non-vaccinated parent flocks, or having no MDA against IBDV must not be vaccinated. Vaccination in birds having no MDA may cause

immunosuppression in these animals. The vaccine is administered via the subcutaneous route, with 0.2 ml equating to one dose. The vaccine is administered once to day-old birds.

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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains live, attenuated infectious bursal disease (IBD) virus, Serotype 1, strain SYA26 at 2.65 – 4.2 log10 CID50, and the following excipients:

Vaccine:
BDA (bursal disease antibody), water for injection.

Solvent:
Sucrose, casein hydrolysate, sorbitol, dipotassium hydrogen phosphate, potassium dihydrogen phosphate, phenol red and water for injection.

The container/closure system for the vaccine consists of:
2 or 5 ml Type I glass ampoule containing 500, 1000 or 2000 doses of the vaccine. Five ampoules per cane. Canes with ampoules are stored in a liquid nitrogen container.

The container/closure system for the solvent consists of: plastic bags made of polyvinylchloride. 200 ml, 400 ml, 800 ml. The particulars of the containers and controls performed are provided and conform to the regulation. The choice and preparation of the vaccine strain is 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. Vaccine is made based on the seed lot principle, whereby batches of finished product are made. Saline solution is suitably prepared in batches.

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

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

II.C. Control of Starting Materials

The active substance is live, attenuated IBD virus, Serotype 1, strain SYA26 at 2.65 – 4.2 log10 CID50 per dose, an established active substance not described in a Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. The master and working seeds have been produced according to the Seed Lot System, as described in the relevant guideline.

Starting materials of non-biological origin used in production comply with appropriate guidelines and are produced under relevant Certificates of Analysis. The packaging materials are produced under appropriate guidelines.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability 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.E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements: appearance, pH, identification and potency of product, BDA back assay, sterility, mycoplasma (free from), extraneous agents.

II.F. Stability

Stability data 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

Vaccine:
Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after reconstitution according to directions: 2 hours.

Solvent:
Shelf life of the solvent as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: 2 hours

Vaccine:
Store and transport frozen in liquid nitrogen (-196°C).
The liquid nitrogen containers must be checked regularly for liquid nitrogen level and must be refilled as needed.

Solvent:

Store below 25°C. Do not freeze.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the product has been demonstrated in accordance with the relevant requirements. The investigations were performed according to the recommendations of Directive 2001/82/EC as amended, and the relevant guidelines. The product is not to be used in birds in lay, nor within 4 weeks before the start of the laying period.

Specific studies were carried out to investigate the effect of the product on the immune system. Although some (expected, acceptable) levels of reversible bursal change were noted, no immunosuppressive effect occurred in the target species. Chickens from non-vaccinated parent flocks or having no MDA against IBD virus should not be vaccinated, as vaccination of such birds may cause immunosuppression. Appropriate veterinary and husbandry measures should be taken to avoid spread of the vaccine strain to susceptible birds.

Although natural reassortment is possible, no evidence of genetic reassortment is associated with IBDV vaccines.

No withdrawal period is required in accordance with Commission Regulation 37/2010. Quantities of antibiotic residues in the excipients are below the level of pharmacological activity. Based on this information, no withdrawal period is required.

Field studies

Two combined efficacy and safety field studies were conducted. Field studies showed expected and acceptable levels of reversible bursal change.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline. The live, attenuated vaccine does not show any recombination or genetic reassortment. There are no implications for pathogenesis for any other species than chickens.

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.

A study was performed on the efficacy and onset of immunity with regard to use of the proposed product. A minimum potent vaccine batch was diluted to one dose. From 78 Hyline layer chickens, a suitable number were allocated to one of the following groups: Vaccinated/challenged, control/unvaccinated, sentinel/vaccinated and sentinel/unvaccinated. Eleven birds were comingled with the vaccinated or control group on D 34 post-vaccination, (Day 4 post-challenge). Thirty days after vaccination by subcutaneous injection, birds in the vaccinated and control groups were challenged with an appropriate quantity of $_{very}$ virulent IBDV, strain MOH-94. Blood samples were collected at Day 0 from 20 hatch mate birds to evaluate MDA levels by ELISA[3]. After vaccination, birds were monitored for signs of IBD (Days 1-30), bursal samples were taken for appropriate analysis at Day 27.

After challenge, clinical observations were performed between Days 30-34, bursal samples were taken at Days 34 and 44, and pharyngeal and cloacal swabs collected at Days 34 (5 birds), and 44, (all remaining birds). Bursal scoring was conducted. All results from the study were consistent with protection being provided to the target animals as described in the SPC.

A second study analysed the duration of immunity of the proposed product. A minimum potent vaccine batch was diluted to one dose. From 48 layer Hyline chickens, a suitable number were allocated to vaccinated or control groups. Sixty-three days after vaccination by subcutaneous injection, birds were challenged with a suitable quantity of very virulent IBDV, strain MOH-94. Blood samples were collected at Day 0 from 20 hatch mate birds to evaluate MDA levels by ELISA. After vaccination, birds were monitored for signs of IBD (Days 1-63), bursal samples were taken for appropriate analysis at Day 67 (5 birds), and t Day 73, (all remaining birds).

After challenge, clinical observations were performed between Days 63-73. Bursal scoring was conducted. All supportive results from the study were consistent with protection being provided to the target animals as described in the SPC.

Two further studies on update of the vaccine were considered supportive.

[3] ELISA – Enzyme-linked immunosorbent assay.

Field Trials

Two combined safety and efficacy field studies were submitted.

Study title (1)	Proposed vaccine product applied by subcutaneous injection to Hyline commercial layer chickens with relevant MDA to IBDV
Objectives	To assess the safety and efficacy of a proposed IBD vaccine in layer chickens.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	A target formulated IBD vaccine batch was administered, and the product was delivered in 0.2 ml, subcutaneously.
Control	Comparator product: AviPro Gumboro Vac.
Animals	Day-old female commercial layer chickens with MDA to IBDV.
Outcomes/endpoints	(Efficacy) histology of bursa of Fabricius for vaccine virus uptake, scored according to Ph. Eur 0587. Serology for IBD, (ELISA).
Method	Birds were assigned to either group 1 (proposed product): vaccinated at hatchery prior to moving to a farm. Group2 (comparator vaccine): received a competitor vaccine on Days 20 and 29 via drinking water. Birds received a series of routine vaccinations in accordance with the farm protocol. Birds were monitored as appropriate, and samples taken.
RESULTS	Presence of the vaccine was confirmed by histology and polymerase chain reaction at appropriate time points. MDA decreased between Days 29-35 then increased between Days 32 and 72. IBD levels decreased until Day 29, then increased, peaking at Day 72. Appropriate statistical analysis provided data to support the laboratory data that the proposed product is safe and efficacious for use in the field, as described in the SPC.

Study title (2)	Proposed vaccine product applied by subcutaneous injection to Hyline commercial layer chickens with relevant MDA to IBDV
Objectives	To assess the safety and efficacy of a proposed IBD vaccine in layer chickens.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	A target formulated IBD vaccine batch was used, and the product was delivered in 0.2 ml, subcutaneously.
Control product	Comparator product: Vaxxitec HVT + IBD.

Animals	Day-old female commercial layer chickens with MDA to IBDV.
Outcomes/endpoints	(Efficacy) histology of bursa of Fabricius for vaccine virus uptake, scored according to Ph. Eur 0587. Serology for IBD, (ELISA).
Method	Birds were assigned to either group 1 (proposed vaccine): vaccinated at hatchery prior to moving to a farm. Group2 (comparator vaccine): received a competitor vaccine. Birds received a series of routine vaccinations in accordance with the farm protocol. Birds were monitored as appropriate and samples taken.
RESULTS	Presence of the vaccine was confirmed by histology and polymerase chain reaction at Days 28-34. MDA decreased at Say 25, then increased between Days 32 and 42. IBD levels decreased until Day 25, then increased, peaking at Day 42. Appropriate statistical analysis provided data to support the laboratory data that the proposed product is safe and efficacious for use in the field, as described in the SPC.

Study of proposed vaccine applied by subcutaneous injection to layer pullets

Study title	Proposed vaccine product applied by subcutaneous injection to chickens
Objectives	To assess the safety and efficacy of a proposed IBD vaccine in layer chickens.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	A target formulated IBD vaccine batch was used, and the product was delivered in 0.2 ml, subcutaneously.
Control product/placebo	Negative control.
Animals	Hyline commercial layer pullets with relevant MDA to IBDV. Birds from field study 2 above, plus day old SPF chickens, male and female.
Outcomes/endpoints	(Efficacy) histology of bursa of Fabricius for vaccine virus uptake, scored according to Ph. Eur 0587. Serology for IBD, (ELISA).
Method	Forty day-old vaccinated chicks from a previous study were vaccinated with one dose (0.2 ml) of Novamune. Fifty-one day-old were kept as unvaccinated controls. Twenty day-old chicks were used as SPF challenge controls. Birds were transported to a laboratory facility where chickens of the three groups were challenged with a

	virulent IBD strain (MOH-94 in 0.2 ml oculonasally), on D42 and D56 after vaccination.
RESULTS	The vaccine is efficacious 10 days after challenge, all the vaccinated birds survived. The overall clinical scores, (average daily scores), were compared between the vaccinated group and the non-vaccinated control via suitable statistical analysis. The mean clinical scores were significantly lower in the vaccinated group (group 1) compared to the controls (group 2) at day 42 and day 56 after challenge ($p<0.001$). The data support the laboratory results, and therefore the claims cited in the SPC.

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.

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