College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Avishield ND, lyophilisate for suspension, for chickens and turkeys

Created: June 2016
Updated: December 2019

RMS transfer from UK to NL
Original procedure number UK/V/0553/001/DC
Current procedure number NL/V/0300/001

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0300/001
Name, strength and pharmaceutical form	Avishield ND, lyophilisate for suspension for chickens and turkeys
Applicant	GENERA Inc. Svetonedeljska 2, Kalinovica, 10436 Rakov Potok Croatia
Active substance	Live, lentogenic virus of Newcastle disease (NDV), strain La Sota $10^{6.0}$ to $10^{7.0}$ $TCID_{50}$* *$TCID_{50}$ = 50% Tissue culture infective dose
ATC Vetcode	QI01AD06
Target species	Chickens and turkeys
Indication for use	For active immunisation of chickens to reduce mortality and clinical signs due to infection with Newcastle Disease Virus. Onset of immunity: 21 days post vaccination. Duration of immunity: 35 days post vaccination. For active immunisation of turkeys to prevent mortality and clinical signs due to infection with Newcastle Disease Virus. Onset of immunity: 21 days post vaccination. Duration of immunity has not been investigated.

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	Applications with administrative, quality, safety and clinical data with known active substance submitted in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	27th January 2016
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Belgium, Croatia, Germany, Greece, Hungary, United Kingdom, Poland, Portugal, Romania, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

This was an application submitted under Article 12 (3) of Directive 2001/82/EC, as amended. The product is a live, attenuated vaccine for use in chickens, to reduce mortality and clinical signs associated with Newcastle disease virus (NDV). The onset of immunity is 21 days post-vaccination, and the duration of immunity is 35 days post-vaccination. The product is also for use in turkeys, to prevent mortality and clinical signs associated with NDV. The onset of immunity post-vaccination is 21 days. The duration of immunity has not been investigated in turkeys. Turkeys are considered MUMS (Minor Use, Minor Species) for NDV, therefore, it was permissible to extrapolate safety and efficacy data for chickens to this species, where appropriate. In the absence of data on duration of immunity in turkeys, it is indicated in the SPC that duration of immunity in turkeys has not been investigated.

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. Refer to the SPC for dosage details. 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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

II.A. Composition

The product contains live, lentogenic virus of NDV, strain La Sota, $10^{6.0}$ to $10^{7.0}$ $TCID_{50}$. The excipients are povidone K-25, bacto peptone, monosodium glutamate, potassium dihydrogen phosphate, potassium hydroxide and dextran 40000.

The container/closure system consists of colourless glass vials (type I), which are closed with rubber stoppers and sealed with aluminium caps. The product is presented in a carton or plastic box with 10 vials of 1,000 doses of vaccine,10 vials of 2500 doses of vaccine, or 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, 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 appropriate preparation of the virus strain, and freeze drying and packaging of the prepared virus.

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 a live, lentogenic virus of NDV, strain La Sota. This is an active substance not described in a pharmacopoeia, and it is prepared according to an in-house specification. The preparation specification is described in the European Pharmacopoeia.

Starting materials of non-biological origin used in production comply with relevant monographs or in-house specifications. Starting materials listed in a pharmacopoeia are SPF (specific pathogen free) hen’s eggs, povidone K-25, monosodium glutamate, potassium dihydrogen phosphate, potassium hydroxide and purified water. Starting materials not described in a pharmacopoeia are bacto peptone and dextran 40000.

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. 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 TSE (transmissible spongiform encephalopathy) declaration was provided confirming that peptone, the only relevant component of animal origin, complies with the requirements of Ph. Eur 1483 Products with risk of transmitting agents of animal encephalopathies. A valid EDQM certificate was also supplied. The risk assessment provided confirmed that the risk of transmission of TSE was very low.

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

The tests performed during production are described. Results of test runs were satisfactory.

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 include those for appearance of the lyophilised product and vacuum in the vials, residual humidity, identification, virus titre, bacterial, fungal or mycoplasma contamination, and the presence of extraneous agents. The demonstration of the batch-to-batch consistency is based on the results of 3 batches of each presentation produced according to the method described in the dossier.

II.F. Stability

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.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after reconstitution: 3 hours.
Do not refrigerate or freeze.
Store in a refrigerator (2 ºC - 8 ºC). Protect from light.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of an overdose (10 x overdose, all routes of administration), in each of the target species, and the repeated administration via the oculonasal route of one maximum dose of $10^{7.0}$ $TCID_{50}$ chickens were demonstrated. The investigations were performed according to the recommended guidelines. Tracheal rales (open-mouthed breathing), were noted in some assays, and Section 4.9 of the SPC carries suitable warnings with regard to this symptom. Revaccination in turkeys has not been investigated. The SPC reflects this.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals. 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 in chickens to investigate the spread, dissemination, reversion to virulence, biological properties, recombination or genetic re-assortment of the vaccine strain. All results were satisfactory. In common with other live NDV vaccines, the vaccine was shown to disseminate in vaccinated chickens and spread to in-contact naïve birds. A relevant warning is included in the SPC. The adjuvant and excipients used are in accordance with specified MRL regulations and based on this information, no withdrawal period is proposed. The product must not be used in birds in lay.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

Field studies

Three field trials were performed. In one trial, commercial broiler birds were used, and in two, layer birds, (all chickens). Birds used in the studies were >18 days of age and were inoculated by coarse spray and oral route administration, (in some studies up to four vaccinations), for up to 24 weeks. No significant safety concerns were noted. Turkeys are considered a MUMS species for NDV, and field studies were not required as laboratory studies showed no safety risk.

User Safety

A satisfactory User Risk Assessment was submitted. The SPC carries suitable warnings:

- Care should be taken when handling and administering the vaccine
- NDV can cause a mild transient conjunctivitis in the person administering the vaccine.
- Well-fitting masks and eye protection to European standards should be worn when handling the product.

- Hands should be washed and disinfected after vaccinating.

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 was demonstrated in laboratory studies in accordance with the relevant requirements.

Efficacy of administration of the minimum dose of vaccine (10^6 EID_{50}/dose), was tested in one day old SPF chickens and 14 day old SPF turkeys, via oculonasal, oral and spray administration.

Additional studies examined the influence of MDA (maternally derived antigens) in one day old SPF chicks and broiler chicks having different levels of MDA when vaccinated by each of the recommended routes of administration.

Chickens: It was concluded from the results of these studies that an onset of immunity of 21 days post vaccination and duration of immunity of 35 days post vaccination in chicks from one day of age following vaccination by the oculo-nasal, oral or spray route is supported with the clear warnings in Section 4.5 of the SPC that MDA can interfere with the development of active immunity and that where it is likely that recent field infection or vaccination of the parent flock has stimulated a high antibody titre and consequently a light level of MDA, vaccination should be planned accordingly. An additional warning is included in the SPC that it has been shown in laboratory studies that MDA interferes with vaccination by the spray and oral route and can result in up to 55% unprotected birds 3-4 weeks post vaccination. Better protection in these studies was seen by oculonasal delivery but the onset of immunity is delayed by a week.

Turkeys: It was concluded from the results of these studies that an onset of immunity of 21 days post vaccination in turkeys from 14 days following vaccination by the oculonasal, oral or spray route is supported. The duration of immunity and influence of MDA in turkeys has not been investigated and the SPC carries appropriate warnings.

Field Trials

Efficacy in chickens was tested in three field trials. One trial was conducted using commercial broilers and two trials conducted using commercial layers. There was some evidence of an active immune response to vaccination as assessed by antibody responses three weeks following vaccination of 18 day old commercial broilers with MDA by the oral route of administration and three weeks following vaccination of 21 day old commercial layers with MDA by spray vaccination. However, the studies do not represent the use of the vaccine as recommended in one-day-old chicks and repeated vaccinations were administered in two of the studies. In light of the fact that vaccinated birds did not receive challenge with Newcastle disease virus in the field trials, a statement is included in Section 5 of the SPC that: "In the absence of a field infection with Newcastle Disease, efficacy by challenge was not demonstrated in field conditions".

Efficacy in turkeys was not investigated in the field. The laboratory trials and field trials together supported the authorisation of the application.

Study title	Field trial of a live, attenuated NDV (La Sota) vaccine in commercial broilers
Objectives	To evaluate the proposed vaccine under field conditions
Test site(s)	multi-centre, farms, EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	The proposed product was given at one dose per bird via drinking water.
Control product/placebo	A comparator product was used as a positive control: Nobilis ND Clone 30.
Animals	38,800 commercial broilers (hybrid line Ross).
Outcomes/endpoints	Efficacy of a proposed product as compared to a reference product, by means of statistical analysis. Parameter tested: serology. Additional observations were made on mortality, bodyweight and feed consumption.
Randomisation	Performed before start of the in-life phase on Study Day 1.
Blinding	Not blinded.
Method	Birds divided in to four flocks. Cloacal swabs taken from a proportion of birds in each group to ascertain presence of NDV. All negative. Inoculation (one $10^{6.0}$ – $10^{7.0}$ $TCID_{50}$ dose at reconstitution), occurred on Day 18. Birds additionally vaccinated against infectious bursal virus (IBV) and infectious bursal disease (IBD) at Day 13. Management practices were the same for all flocks. Two flocks treated with the proposed product, two with the control product, via drinking water. Clinical observations were carried out at suitable time points. Birds culled on days 39 to 43. Birds were not challenged with NDV.
Statistical method	General linear model (GLM) was used to analyse data on body weight, mortality, culling and antibody titres

	according to tested vaccines. Data were analysed using software IBM SPSS Statistics 17.0; values of P<0.05 were considered significant for all analyses.
RESULTS	
Duration of follow-up	From days 0 to 39-43.
Outcomes for endpoints	Differences in MDA were noted between flocks 1 and 2 and 3 and 4. This was believed to be due to the birds being sourced from two broiler sites. No significant differences were noted between the effects of the two vaccines, (P<0.05 all parameters, as measured by serology). Similar profiles were seen for MDA effect, mortality, culling and bodyweight.
Adverse events	No significant adverse reactions were noted.
DISCUSSION	There was evidence of an active immune response to vaccination as assessed by antibody responses against both vaccines three weeks following vaccination of 18 day old commercial broilers with MDA, via the oral route of administration. It was noted that MDA has an effect on the efficacy of the proposed product. Refer to the SPC for further information.

Study title	Field trial of a live, attenuated NDV (La Sota) vaccine in commercial layers. THE PRODUCT MUST NOT BE USED IN BIRDS IN LAY.
Objectives	To evaluate the proposed vaccine under field conditions
Test site(s)	multi-centre, farms, EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	The proposed product was given at one dose per bird via spray.
Control product/placebo	A comparator product was used as a positive control: Nobilis ND Clone 30.
Animals	13,850 commercial layers (hybrid line Lohmann Brown).
Outcomes/endpoints	Efficacy of a proposed product as compared to a reference product by means of statistical analysis. Parameter tested: serology. Additional observations were made on mortality, bodyweight, egg production and feed consumption.
Randomisation	Performed before start of the in-life phase on Study Day 1.
Blinding	Not blinded.
Method	Birds divided in to two flocks. Cloacal swabs taken from a proportion of birds in each group to ascertain presence of NDV. All negative. Inoculation of the proposed product was provided at $10^{6.0}$ – $10^{7.0}$ $TCID_{50}$ dose at reconstitution. Chickens from both groups were vaccinated against NDV four times. First vaccination was conducted at the age of 3 weeks and birds were revaccinated at 8, 16 and 24 weeks of age. The last revaccination was performed in production period

	where 500 birds of Group 1 were vaccinated with Pestikal La Sota SPF and 1000 birds of Group 2 were vaccinated with Nobilis ND Clone 30. Management practices were the same for both flocks. Birds additionally vaccinated against Marek's disease, IBV, IBD, *Salmonella Enteritidis*, fowl pox and avian encephalomyelitis. One flock treated with the proposed product, one with the control product, via spray. Clinical observations were carried out at suitable time points. Birds were not challenged with NDV.
Statistical method	General linear model (GLM) was used to analyse data on body weight, mortality, culling and antibody titres according to tested vaccines. Data were analysed using software IBM SPSS Statistics 17.0; values of $P<0.05$ were considered significant for all analyses.
RESULTS	
Duration of follow-up	Three weeks after each vaccination.
Outcomes for endpoints	There was statistically significant evidence of an active immune response to vaccination as assessed by antibody responses against both vaccines, three weeks following vaccination of 3 week old commercial layers with MDA, via the spray route of administration. There was no significant difference in MDA levels between the flocks. No significant differences were noted between the effects of the two vaccines, ($P<0.05$ all parameters, as measured by serology). Similar profiles were seen for MDA effect, mortality, culling and bodyweight. Egg production data were not fully available, and were not considered for the study.
Adverse events	No significant adverse reactions were noted.
DISCUSSION	An NDV antibody response was noted following vaccination of 3 week old commercial layers via the spray route of administration. There was no challenge with NDV. It was noted that MDA has an effect on the efficacy of the proposed product. Refer to the SPC for further information.

Study title	Field trial of a live, attenuated NDV (La Sota) vaccine in commercial layers – additional trial. THE PRODUCT MUST NOT BE USED IN BIRDS IN LAY.
Objectives	To evaluate the proposed vaccine under field conditions.
Test site(s)	multi-centre, farms, EU
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	The proposed product was given at one dose per bird via spray administration.
Control product/placebo	No control.
Animals	18,000 commercial layers (hybrid line (Lohmann Brown).

Outcomes/endpoints	Efficacy of a proposed product as compared to a reference product by means of statistical analysis. Parameter tested: serology. Additional observations were made on mortality, bodyweight, feed conversion and egg production.
Randomisation	None. No control group.
Blinding	Not blinded.
Method	Cloacal swabs taken from a proportion of birds in each group to ascertain presence of NDV. All negative. Inoculation ($10^{6.0}$ – $10^{7.0}$ $TCID_{50}$ dose at reconstitution), occurred on Day 24. Birds additionally vaccinated against NDV, Marek's disease, *Salmonella enteritidis*, fowl pox, avian encephalomyelitis, IBV and IBD at 16 weeks of age. Clinical observations were carried out at suitable time points. Management practices were standard. No evidence of natural challenge to NDV.
Statistical method	General linear model (GLM) was used to analyse data on body weight, mortality, culling and antibody titres according to tested vaccines. Data were analysed using software IBM SPSS Statistics 17.0; values of $P<0.05$ were considered significant for all analyses.
RESULTS	
Duration of follow-up	up to day 29 post-vaccination.
Outcomes for endpoints	A statistically significant increase in levels of NDV antibody was observed.
Adverse events	No significant adverse reactions were noted.
DISCUSSION	There was evidence of an active immune response to vaccination as assessed by antibody responses.

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 Heads of Vetrinary 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 (Application number)	**Section updated in Module 3**	**Approval date**
Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS) (UK/V/0553/IA/002/G)	N/A	9 March 2017
Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product (storage for 12 months at ≤20˚C before start of shelf life) (UK/V/0553/001/II/001)	N/A	30 June 2017
Change in the pack size of the finished product: addition of 5000 doses presentation form (UK/V/0553/001/II/003)	N/A	12 January 2018
Change address of the marketing authorisation holder, manufacturer of the active substance and manufacturer of the finished product (Genera Inc.) (UK/V/0553/IA/004/G)	Module 1 updated	10 May 2018

Deletion of nonsignificant specification parameters of an excipient. Deletion of nonsignificant specification parameter of glass vials and rubber stoppers of the immediate packaging of the finished product. Addition of two suppliers for packaging materials. (UK/V/0553/IA/005/G)	N/A	3 May 2018
Change RMS from UK to NL. Procedure number changed from UK/V/0553/001 to NL/V/0300/001	Module 1: procedure number Module 3: UK > CMS	December 2018
Change in the QPPV (NL/V/xxxx/IA/034/G)	N/A	10 March 2019
Change in test procedure for WSV of Newcastle disease virus (NL/V/0300/IB/008/G)	N/A	26 March 2019
Extension of the shelf life of the semi-finished product at ≤ -20°C from 12 to 24 months (NL/V/0300/001/IB/009)	N/A	25 June 2019