Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

AviPro ND C131

Zulassungsdatum:	
Zulassungsnummer:	PEI.V.03159.02.1
Datum der Erstellung des öffentlichen Beurteilungsberichts:	August 2017
Datum der Bekanntgabe beim Antragsteller der/des Zulassungsänderung/Widerrufs, Rücknahme, Anordnung des Ruhens der Zulassung:	-

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

AviPro ND C131

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0239/001/MR
Name, strength and pharmaceutical form	AviPro ND C131, lyophilisate for suspension
Applicant	Lohmann Animal Health GmbH Heinz-Lohmann Str. 4 27472 Cuxhaven Germany
Active substance(s)	Each dose contains Newcastle Disease Virus, live attenuated, strain clone 13-1 $10^{6.0}$ - $10^{7.2}$ EID_{50} *EID_{50} = 50%-embryo infectious dose: the virus titre causing infection in 50% of the embryos inoculated with the virus.
ATC Vetcode	ATCvet code: QI01AD06
Target species	Chickens and turkeys
Indication for use	Active immunisation against ND of chickens in chickens from the first day of life and in turkeys from the age of 14 days onwards

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	Mutual recognition procedure application in accordance with Article 31 of Directive 2001/82/EC as amended.
Date of completion of the mutual recognition procedure	23 May 2007
Concerned Member States for mutual recognition procedure	AT, BE, BG, CY, CZ, EE, EL, ES, FR, HU, IT, LT, LV, NL, PL, PT, RO, SI, SK, UK, DE
Date of completion of line extension	26 April 2017

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 (Summary of Product Characteristics).

The product is safe for the user and for the environment, when used as recommended. 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

A. Composition

Each dose AviPro ND C131 contains as

Active substance:

Newcastle Disease Virus, live attenuated, strain clone 13-1 $10^{6.0}$ - $10^{7.2}$ EID_{50}

*EID_{50}= 50%-embryo infectious dose: the virus titre causing infection in 50% of the embryos inoculated with the virus.

and excipients:

Peptone

Magnesium sulphate

Sucrose

Gelatine

Container/closure system:

The vaccine is filled in 6 ml glass type I containers.

The vials of the lyophilisate are closed with a vacuum stopper (type I closure) and an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulations of European Pharmacopoeia (Ph. Eur.).

The choice of the vaccine strain (Newcastle Disease virus, live attenuated, strain clone 13-1) is 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 (GMP) from a licensed manufacturing site. A corresponding manufacturing licence and GMP certificate are provided.

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

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

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with the pharmacopoeia monograph specifications 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 Ph. Eur. 2.6.24 “Avian viral vaccines: tests for extraneous agents in seed lots” and Ph. Eur. 5.2.2 “Chicken flocks free from specified pathogens for the production and quality control of vaccines”.

Seed lots have been produced as described in the relevant guideline.

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.

D. Control tests during production

The tests performed during production are described.

E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements.

The following tests are performed:

- appearance
- titre (EID_{50}/dose)
- test for absence of extraneous agents (Ph. Eur. 2.6.25)
- sterility (bacteria and fungi)/ microbiological enumeration (Ph. Eur. 0450)
- test for mycoplasmas (Ph. Eur. 2.6.7)
- identification of active ingredient
- determination of residual humidity

The demonstration of the batch to batch consistency is based on the results of three batches produced according to the method described in the dossier.

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 (1 year) when stored under the approved conditions (at 2-8°C).

The in-use shelf-life of the reconstituted vaccine (2 hours) is supported by the data provided.

III. SAFETY ASSESSMENT

AviPro ND C131 is a live attenuated vaccine containing freeze-dried Newcastle disease virus (NDV) strain clone 13-1. It initially has been licensed for the active immunization of 14 day-old chicken against Newcastle disease (ND) to reduce clinical signs and mortality.

In a grouped variation procedure, the minimum age in chickens for vaccination has been reduced to one day-old (type II variation) and with turkeys a new food producing (minor)

species has been added as target species (line extension). Accordingly, the vaccine can now be used in chickens from the first day of life by spray administration (from 14 days of life onwards administration by spray, and also by ocular use and in drinking water use is authorized) and in turkeys from the 21st day of life onwards by in drinking water use.

Laboratory trials

The trials have been performed in the target species (chickens and turkeys).

All chickens used in laboratory trials were SPF animals, if not indicated otherwise. Turkeys were not SPF animals but had low levels of antibodies, which was justified to have no influence on the outcome of the study.

The animals in the laboratory were allocated to different groups and were administered either a single dose, an overdose or repeated single dose with an interval of several weeks. Unvaccinated animals were used as control groups. All animals were monitored for clinical reactions during the studies. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

In the initial application, the safety of the administration of one dose and an overdose (tenfold dose) administrated via eye-drop, spray and drinking water as well as the repeated administration of one dose via eye-drop (followed by i.m. injection) was demonstrated in laboratory trials in 14 day-old chickens.

For the reduction of the minimum age in chicken to 1-day-old, no special laboratory study was performed to evaluate the safety of one maximum dose of AviPro ND C131 in 1-day-old chickens, but to compromise this omission a summary of the results of the safety of the administration of one dose obtained in other safety studies has been presented. The safety of the administration of an overdose (5-fold dose, administered by spray and 10-fold dose, administered by spray or eye-drop) has been evaluated in 1-day-old SPF chickens as well as in broiler chickens.

The results of these studies are adequately reflected in section 4.10 of the SPC: “Severity and duration of adverse reactions after the administration of a 10-fold dose are dependent on the (maternal) immune status as well as the general health condition of the chickens at the time point of vaccination.”

The safety of the repeated administration of one dose has been demonstrated via spray and drinking water in day-old broiler chickens.

Studies using 1-day-old chickens with maternally derived antibodies (MDA) were carried out to consider the influence of MDA on vaccination with AviPro ND C131.

The results of the studies are satisfactorily described in section 4.6 of the SPC: “Slight reactions of the respiratory tract (coughing or sneezing) 3 – 15 days after vaccination have been reported commonly during clinical studies. This does not influence the performance of the birds. Severity and duration of adverse reactions are dependent on the (maternal) immune status as well as the general health condition of the chickens at the time point of vaccination.”

The safety of one dose was not studied for turkeys but this has been justified.

The safety of an overdose of AviPro ND C131 in turkeys has been demonstrated at 14 days of age. The results show that the vaccine administrated by crop instillation does not cause any clinical signs or mortality. Repeated vaccination per spray or drinking water also proved safe.

On the basis of current scientific knowledge, it can be concluded that the ND La Sota vaccine strains have no negative impact on the reproductive system, even if the virus can persist for about nine days post vaccination in the oviduct. To confirm the absence of any impact of the

vaccination with AviPro ND C131 on the reproductive performance in chickens, a field trial has been performed in which the vaccine was administered to (14-day-old) future laying birds. In non-primed birds ND vaccine virus was found in the oviduct after 10-fold over dosage. No egg transmission was observed in laying birds after basic immunisation. This finding is described in the SPC section 4.7. As no negative impact to the performance criteria could be observed in this trial, the safety of the veterinary medicinal product is regarded established during lay.

The safety of the veterinary medicinal product has not been established in breeders during lay. This as well is mentioned in the SPC (section 4.7).

No vaccination should be performed in turkeys in lay as indicated in the SPC.

There are no data suggesting that AviPro ND C131 might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

Specific studies in 14-days-old chickens were carried out to examine the spread, dissemination and reversion to virulence of the vaccine strain after vaccination. Biological properties, recombination or genetic re-assortment of the vaccine strain are adequately described. Specific studies on spreading of the vaccine strain were carried out in turkeys. The dissemination of the vaccine strain in turkeys after vaccination has been satisfactorily supported by bibliographic references.

In chickens, the vaccine virus is excreted with faeces up to 12 days and may spread to susceptible animals by contact infection. However, ND negative contact animals do not show seroconversion until 15 days after contact.

In turkeys, the vaccine virus is excreted for less than 14 days after vaccination.

The vaccine virus may spread to susceptible non-vaccinated turkeys without inducing any clinical symptoms.

Spread to other species, such as ducks and geese, does not induce any clinical symptoms in these species. In pigeons, slight pathological findings were observed in the respiratory tract, but no clinical symptoms occurred. The results of studies on excretion and spread of the vaccine strain are mentioned in the SPC section 4.5.

Dissemination of the vaccine virus after vaccination of 14-day-old chickens was evaluated in samples of trachea, oviduct, spleen, turbinates, stomach, intestine, faeces and eggs. Virus could be recovered in all mentioned tissues besides eggs independent on the route of vaccination. The dissemination is in line with current scientific knowledge on NDV.

In studies on reversion to virulence, virus isolation was possible until the fourth chicken passage. The differences in ICPI before and after passaging are regarded as acceptable and comply with Ph. Eur. provisions.

NDV contains a single stranded RNA. Based on the characteristics of this virus neither recombination nor genomic re-assortment are to be expected. No reports from the field, which could give an indication on recombination or genomic re-assortment, are known.

In the final product the used excipients and starting materials do not have a natural potential and concentration to induce MRL-relevant residues. 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 under section 4.8: “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

The safety of the vaccine was tested under field conditions in 14-day-old SPF-chickens, commercial broilers and layers. All routes of application were used. The performance parameters were serological response, resistance to challenge, weight development, feed conversion rates, laying activity, hatchability of eggs from vaccinated hens, egg weights and mortality not related to ND. The safety of the vaccine applied to chickens during rearing and laying periods was proven.

If animals were vaccinated at day-old under field conditions, performance parameters were reduced in comparison to the standard values provided by the breeding company. This might possibly be a result of the physically demanding effect of the ND vaccination on the first day of life. The adverse reactions observed in laboratory also were found in the field and are mentioned in the SPC (section 4.6). A risk-benefit evaluation on vaccination at day-old in comparison to vaccination at 14 days of age for chickens has been performed and is regarded to be in favour of the benefit of vaccination of chickens at day-old.

Overall, the vaccine proved to be well tolerated in the target species chickens and turkeys. The results from field trials basically confirm the observations made in the laboratory studies. The systemic reactions observed after vaccination are described in the SPC and package leaflet under “adverse reactions”.

Environmental Risk Assessment

The applicant provided an environmental risk assessment in compliance with the relevant guideline which showed that the risk for the environment and other animals and species posed by this vaccine can be considered as very low.

No warnings are therefore required in the SPC and package leaflet.

IV. EFFICACY

IV.B Clinical Studies

Laboratory Trials

AviPro ND C131 is a live attenuated vaccine containing freeze-dried Newcastle disease virus (NDV) strain clone 13-1. It initially has been registered for the active immunization of chickens from 14 days of age onwards against Newcastle disease (ND) to reduce clinical signs and mortality.

In a grouped variation procedure, the minimum age for vaccination in chickens has been reduced to 1-day-old chickens and a new food producing target species (turkeys) has been added to be vaccinated at 21 days of age.

The following routes of administration are applicable for the different species and age categories according to section 4.9 of the SPC:

Species	Vaccination age	Administration route
Chickens	from 1 day onwards	nebulisation
	from 14 days onwards	nebulisation, ocular use, in drinking water use
Turkeys	from 21 days onwards	in drinking water use

Onset and duration of immunity in chickens

In chickens, the onset of immunity is determined with 3 weeks after vaccination (7 days in seronegative chickens when vaccinated at 14 days of age).

The duration of immunity is 8 weeks after vaccination.

For the initial application, efficacy of vaccination with AviPro ND C131 has been demonstrated in 14-day-old chickens which vaccinated via drinking water, by spray or eye-drop with 1 dose of vaccine. The influence of maternal antibodies has been determined in layer as well as broiler type chickens. The influence of the repeated application on the development of immunity also was determined. The results of the field trials confirmed the results of the laboratory trials.

Since the minimum age for vaccination of chickens has been reduced to one day of age, the efficacy of vaccination with AviPro ND C131 had to be re-established in 1-day-old chicks as the minimum age category for vaccination.

In addition, the efficacy of AviPro ND C131 in 21-day-old turkeys had to be demonstrated.

All clinical trials were conducted in accordance with a trial protocol and carried out in conformity with the principles of good clinical practice laid down in Council Directive 2001/82/EC. The welfare of the animals was subject to veterinary supervision.

Efficacy trials performed in turkeys or in 1-day-old chicks in the laboratory were controlled trials and included untreated control animals.

For efficacy in 1-day-old chicks, controlled laboratory studies were performed, in which day-old SPF birds, which were vaccinated via spray with a (0.5x) minimum dose of the vaccine and challenged 21 or 28, 42 and 56 days later, were used to demonstrate onset and duration of immunity. The animals were observed until 14 days after challenge for clinical signs. The protection rates in vaccinated SPF animals in all studies and at all times of challenge were between 95-100% while unvaccinated controls were completely unprotected. Based on the results of these studies, onset of immunity at 21 days p.v. can be regarded as demonstrated. It also can be concluded that immunity after a single application of the vaccine on the 1st day of life via spray lasts for at least 8 weeks (56 days) p.v.

Commercial broilers with high levels of MDAs were used to examine the efficacy of the vaccine in the presence of MDAs in 1-day-old chicks. These broilers as well were completely protected in challenge at 21 days after vaccination. In the control group with unvaccinated commercial broiler chickens, only 25% of the animals were susceptible to challenge infection. This result shows that commercial birds are still partly protected in challenge by MDAs, but that vaccination is well effective in presence of MDA and results in full protection. Based on the results of this study, it can be concluded that vaccination of 1-day-old commercial broiler chicks under laboratory conditions prevents clinical symptoms and mortality after infection with a virulent NDV strain.

Field trial

One field trial was performed to confirm the efficacy of vaccination with AviPro ND C131 in 1-day-old chicks under field conditions. The results in serology in connection with this study can be regarded as indicative of a tendency to seroconversion after vaccination. In regards to protection after challenge infection, the efficacy of the vaccine under field conditions has been satisfactorily justified referring to the laboratory study performed in commercial broilers. The justification of the applicant that the expected additional benefit of a challenge performed in commercial broilers kept under field conditions does not bear relation to the severe pain and distress of the unvaccinated control birds after challenge is accepted.

The performance parameters in the flock vaccinated with AviPro ND C131 (and basically a competitor vaccine as well) were reduced in comparison to the standard values provided by the breeding company. The applicant states that this might possibly be a result of the physically demanding effect of the ND vaccination on the first day of life. Also taking into account the observed adverse reactions mentioned in Part III, a benefit-risk evaluation on vaccination at 1-day-old chickens in comparison to vaccination at 14 days of age for chickens has been performed.

The overall benefit-risk evaluation for the administration of AviPro ND C131 to 1-day-old chicks is deemed positive. Although circulating maternal antibodies against ND are providing some protection in the early life phase, the data obtained show that 25% of non-vaccinated broilers died after being challenged with a virulent strain of NDV at day 21, showing the importance of vaccination at day-old in case of early exposure to NDV. Even if ND vaccination on the first day of life may be physically demanding as stated above, the lower performance in the field trial after vaccination with a single dose cannot be clearly attributed to the vaccination.

The onset of immunity claim “7 days in seronegative chickens” has been specified not to be applicable for use in 1-day-old chicks in the SPC.

The duration of immunity has been adapted from 4 weeks (as mentioned in the currently authorised SPC) to 8 weeks according to studies in 1-day-old chicks (youngest age of vaccination) provided with this application.

Onset and duration of immunity in turkeys

In turkeys, the onset of immunity is claimed with 2 weeks after vaccination and the duration of immunity with 8 weeks after vaccination.

The following trials were performed to demonstrate the efficacy of AviPro ND C131 in 21-day-old turkeys when administered via drinking water.

For efficacy of AviPro ND C131 in 21-day-old turkeys, controlled laboratory studies were performed, in which commercial broilers were vaccinated via drinking water with a (close to) minimum dose or even tenfold lower dose. The turkeys were challenged 7, 14, 21, 35, 42 and 56 days after vaccination and observed for 14 to 21 days afterwards for clinical signs of ND. The achieved protection rates were between 90 and 100 % for animals vaccinated with a (close to, less than) minimum dose, while controls were unprotected at a ratio between 95 and 100%. The onset of immunity was determined to be 14 days p.v. and the duration of immunity can be defined as 56 days p.v. according to the results in challenge studies. As the antibody titre of the turkeys at the time of vaccination is very low, the use of commercial broilers can be accepted even if not in line with the requirements of Ph. Eur.

No field trials were performed to confirm the efficacy of the vaccination with AviPro ND C131 in turkeys under field conditions. This can be accepted, as field trials are not mandatory for application for minor species. The omission of field trials has been justified according to concept paper EMA/CVMP/505827/2014. In this context, it was discussed and justified that

animals with very low titers of MDAs were used in the presented laboratory studies as it is expected that commercial turkeys will have comparable levels of maternally derived antibodies against ND on day 21 of life. In order to take into account potential situations with unexpectedly high MDA levels at day 21 of life, the sentence “Maternally derived antibodies (MDA) may interfere with the development of a protective immune response following vaccination” has been added under point 4.4. of 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.