10 October 2024
EMA/489754/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Vaxxon ND Clone (EMEA/V/C/006296/0000)

Vaccine common name: Newcastle disease vaccine live

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant Vaxxinova International B.V. submitted on 31 August 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Vaxxon ND Clone, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 20 April 2023 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indication:

For the active immunisation of chickens from the age of day one to reduce mortality and clinical signs of disease caused by infection with Newcastle Disease virus.

The active substance of Vaxxon ND Clone is Newcastle disease virus (NDV), strain Clone, live. The target species is chickens.

Vaxxon ND Clone, lyophilisate and solvent for oculonasal suspension, and Vaxxon ND Clone, lyophilisate for oculonasal suspension, contains 6.0-7.5 $\log_{10}$ $ELD_{50\ of}$ NDV, strain Clone, live and is presented in packs containing 10 vials of lyophilisate (1,000 doses) and 10 bottles of solvent (30 ml) and 10 vials of lyophilisate (1,000, 2,000 or 2,500 doses), respectively.

The rapporteur appointed is Esther Werner and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 10 October 2024, the CVMP adopted an opinion and CVMP assessment report.

On 22 November 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Vaxxon ND Clone.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file, which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided, the applicant has in place a pharmacovigilance system master file (PSMF) with reference number PSMF00290823, has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

The type of record management system used for adverse event reports including the name of the database (Excel Sheet), if applicable, has been provided.

Manufacturing authorisations and inspection status

Active substance

Manufacture, quality control and storage of the active substance Newcastle disease virus strain Clone, live, takes place at Izo S.r.l., Italy.

A GMP certificate issued by the Italian Ministry of Health is available in EudraGMDP. The certificate was issued on 21st of July 2022, referencing an inspection on 29th of April 2022. The EudraGMDP document reference number is NBF/45/2022/V.

A QP declaration is provided for the active substance manufacturing site. The declaration is issued by the QP representative and states that the site was audited on 14th of December 2021.

Finished product

Manufacture, quality control, primary packaging, secondary packaging and batch release of the finished product take place at Izo S.r.l. a socio unico, Strada Statale 234 per Cremona Km 28,200, 27013 Chignolo Po (PV), Italy.

The site has a manufacturing authorisation issued on 27th November 2017 by the Italian Ministry of Health, which is available in EudraGMDP under 19/2017/V.

A GMP certificate confirming compliance with the principles of GMP for the manufacture of the finished product is provided. The certificate was issued by the Italian Ministry of Health on 21st of July 2022, referencing an inspection on 29th of April 2022. The EudraGMDP document reference number is NBF/45/2022/V.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

The GMP status of the active substance and of the finished product manufacturing site has been established and is in line with legal requirements.

Part 2 - Quality

Quality documentation (physico-chemical, biological, and microbiological information)

Qualitative and quantitative composition

The finished product is presented as freeze-dried lyophilisate containing live attenuated Newcastle disease virus strain Clone as active substance, with a potency of 6.0-7.5 $\log_{10}$ ELD_{50} per dose. The product contains a stabiliser consisting of sorbitol, disodium phosphate dihydrate, Byco C (gelatine), and pea protein GT plus. The vaccine is free of adjuvants and preservative agents.

Vaxxon ND Clone is available in multi-dose presentations of 1,000, 2,000, and 2,500 doses per 6 ml glass vial. Additionally, the 10 x 1,000 doses presentation is also available together with a box containing 10 bottles of 30 ml of solvent and 10 droppers.

The product is intended for coarse-spray administration when resuspended in water and for eye-drop administration when resuspended in Vaxxon solvent which consists of a colouring agent, Patent Blue V (E131), and water for injections.

The information regarding the composition of the product is sufficient.

Container and closure system

Vaxxon ND Clone vaccine is supplied in 6 ml heat-sterilised, type I glass vials (in accordance with Ph. Eur. chapter 3.2.1). An adequate validation report for dry-heat sterilisation of the glass vials is provided. The vaccine vials are closed with bromobutyl rubber closures (in accordance with Ph. Eur. chapter 3.2.9) and sealed with aluminium caps. The rubber stoppers are sterilised by irradiation, as confirmed by a certificate of analysis of the supplier.

Thirty millilitres of Vaxxon solvent are filled into low-density polyethylene bottles (LDPE, in accordance with Ph. Eur. chapter 3.1.4) of 38 ml capacity, closed with chlorobutyl rubber closures (in accordance with Ph. Eur. chapter 3.2.9), and sealed with aluminium caps. The LDPE bottles are sterilised by electron beam sterilisation according to ISO 1137 as presented by the supplier's certificate of analysis and in line with Ph. Eur. chapter 5.1.1. The stoppers are sterilised by γ-irradiation as presented by the supplier's certificate of analysis. The enclosed droppers are made of LDPE and conform to food contact regulations. A certificate of analysis is provided.

The containers and closures are in compliance with the pharmacopoeial requirements and their sterilisation is adequate.

Product development

An explanation and justification for the composition and presentation of the vaccine have been provided. The source and history of the MSV and WSVs are described satisfactorily.
Vaxxon ND Clone is intended as a prophylactic measure against Newcastle disease (ND) in chickens. ND is a highly contagious and severe disease in poultry and can cause mortality in up to 100% animals depending on the ND virus (NDV) pathotype. Thus, vaccination against ND is common in most EU countries.

The choice of NDV strain Clone as antigen is based on its high immunogenicity combined with its low pathogenicity. NDV strain Clone is a genotype II strain and was obtained after *in vitro* passaging of the lentogenic strain La Sota, which is used in other EU-licensed ND vaccines. During the

manufacturing, NDV strain Clone is propagated in SPF chicken eggs, mixed with stabiliser, filled into glass ampoules, and subsequently freeze-dried. In the course of product development, the formulation of the stabiliser changed so that the finished product does not contain components originating from pigs.
The current stabiliser is called SAKADp, which contains sorbitol, porcine-free gelatine, vegetal pea protein, and buffer. Moreover, a concentration step was introduced to increase antigen titres. Two batches of non-concentrated (previous manufacturing process) and concentrated (current manufacturing process) antigen are included in the stability program.

Each dose of Vaxxon ND Clone is comprised of 6.0-7.5 $\log_{10}$ ELD_{50} (embryo lethal dose 50%) of NDV strain Clone. The vaccine will be available in boxes of ten times 1,000-dose, 2,000-dose and 2,500-dose glass vials with an in-use shelf life of 4 hours upon reconstitution in water or Vaxxon solvent. The reconstitution agent depends on the administration method. The applicant developed a solvent that can be used for other lyophilised vaccines in the applicant's portfolio and is provided with a dropper for easy eye-drop application. The solvent contains a colouring agent so that eyes and/or beak of 1-day-old chicken turn blue confirming vaccination of the animal. In case of spray application, the vaccine is dissolved in water.

The formulation of batches used during clinical studies is the same as that intended for marketing.

Description of the manufacturing method

The manufacturing process consists of two main steps: production of the NDV antigen and production of the finished product.

The active substance is produced in SPF chicken eggs. After harvest, the allantoic fluid is filtered and concentrated by ten-fold and subsequently mixed with a stabiliser. Antigen containers are stored at 5±3 °C for up to one month or at -20 °C for up to one year. For finished product production, the antigen is mixed with stabiliser, filled in glass vials and freeze-dried. The vials are capped and stored at -20 °C for up to two years, as required.

The manufacturing method is considered as a standard manufacturing process for ND live vaccines. The process described above, including the concentration step, was completed for six production scale batches and produced consistent results.

The solvent for resuspension of the vaccine and eye-drop administration is produced by blending the two aforementioned starting materials, followed by a filtration step, aseptic filling and sealing of the bottles. Appropriate process controls are in place.

The vaccine production process is described satisfactorily.

Production and control of starting materials

All stated starting materials of animal origin used during the production of the vaccine comply with the current regulatory texts of Ph. Eur. monograph 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" and the TSE Note for Guidance (EMEA/410/01 rev.3). The master seed materials used for NDV strain Clone are in line with the "Position paper on the assessment of the risk of transmission of animal spongiform encephalopathy agents via master seed materials used in the production of veterinary vaccines" (EMEA/CVMP/019/01).
A satisfactory TSE risk assessment is provided in Part 2.C.4. of the dossier.

Starting materials listed in pharmacopoeias

Starting materials listed in a pharmacopoeia and used for production of Vaxxon ND Clone vaccine and solvent are:

Sorbitol (Ph. Eur. 0435), disodium phosphate dihydrate (Ph. Eur. 0602), water for injections (Ph. Eur. 0169), Byco C (gelatine, Ph. Eur. 0330), SPF eggs (Ph. Eur. 5.2.2), N-Z-Amine (USP), Patent Blue (E131, French Pharmacopoeia, refer to Annex 2.H.11).

Example certificates of analysis (CoA) have been provided for all substances listed. They conform to relevant Ph. Eur., Fr. Ph. or USP monographs.

Certificates of analysis for all suppliers of SPF eggs are provided and are satisfactory.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

NDV strain Clone:

NDV master seed virus (MSV) and working seed virus (WSV) are used for antigen production and propagated in SPF chicken eggs, which do not fall within the scope of Ph. Eur. 5.2.8. However, for dilution of the master seed virus and working seed virus, starting materials of bovine origin are used and their compliance with Ph. Eur. 5.2.8 is further described below.

The NDV Clone MSV is derived from a working seed virus produced for Izovac Clone. The absence of the extraneous agents from the master seed virus NDV-MSV has been demonstrated by performing tests for extraneous agents and providing a risk assessment in line with Ph. Eur. 5.2.5. History of the source and passaging of the material is provided.

Tryptose phosphate broth:

A certificate of analysis and adequate statement of the supplier evaluating the TSE risk are provided.

Nutrient broth:

A certificate of analysis evaluating the risk with regard to TSE is provided.

Pea protein GT plus:

Pea protein GT plus is a component of the stabiliser SAKADp (see section about media and solutions below). A certificate of analysis containing relevant information on storage and shelf life is provided. The material is plant-based and does not fall within the scope of Ph. Eur. 5.2.8.

Starting materials of non-biological origin

The only starting material of non-biological origin that is not listed in a pharmacopoeia is gentamicin. It is used during production of the viral seed material to prevent bacterial contamination. A certificate of analysis is provided.

In-house preparation of media and solutions consisting of several components

The following stabiliser solutions were used: SAKAD (original stabiliser) and SAKADp (used in the current manufacturing process). SAKADp is a version of SAKAD free of components of pig origin.

Information regarding the qualitative and quantitative composition of both stabiliser solutions, their

treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants or further assurance is given that there is no potential risk of contamination.

Control tests during the manufacturing process

During NDV antigen production, the following tests are carried out: NDV infectivity titre (50% embryo lethal dose), sterility of the stabiliser and bioburden. During production of Vaxxon solvent, a test for bioburden, filter integrity before and after filtration of the solvent, filling volume and close integrity is performed.

Test descriptions and the limits of acceptance are presented. The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing process.

Control tests on the finished product

Vaxxon ND CLONE is tested for identity (mono-specific neutralisation of NDV prior to infection of SPF embryonated eggs), potency (egg titration), bioburden, residual moisture and absence of *Mycoplasmas*. Reference to the relevant Ph. Eur. monographs is given, or a test standard operating procedure (SOP) has been provided. The tests are suitably validated. The applicant used a risk-based approach according to Ph. Eur. 5.2.5 to demonstrate absence of extraneous agents concluding for testing for freedom from *Chlamydia spp.*

A test for the sterility of the stabiliser, control of the fill volume and the visual appearance is performed during the blending of the final product.

Vaxxon solvent is tested for appearance, pH, UV-vis absorbance and sterility.

Batch-to-batch consistency

Batch analysis results based on the finished product tests are presented for three production scale batches of vaccine at the smallest (1,000 doses) and highest (2,500 doses) presentation, respectively. All batches passed the final product tests, indicating batch-to-batch consistency.

The applicant presented finished product data for three consecutive production scale batches of the solvent. The results suggest that the manufacturing process is well-controlled and consistent.

Stability

During antigen production, the applicant implemented hold times for the antigen bulk that have been adequately assessed by comparing the stability of antigen titres of two antigen batches over the proposed intermediate storage periods. The data support a storage of antigen before blending for 12 months at -20 °C or one month at 5±3 °C.

A stability of 24 months is claimed for the vaccine when stored at 5±3 °C. Moreover, prior to storage at 5±3 °C the vaccine can be stored for 24 months at -20 °C at the manufacturing site. Stability data considering antigen titre, residual humidity and bioburden for the finished product were presented for four R&D-scale vaccine batches filled in 6 ml glass vials. As outlined before, two of these batches were produced following the previous manufacturing process without a concentration step and two batches were produced according to the current manufacturing process including a concentration step. The applicant further provided 9 months' stability data for three GMP batches as 1,000 dose presentation and three GMP batches as 2,500 dose presentation, which were stored at 5±3 °C without preliminary storage at -20 °C. Both stability studies are still ongoing.

However, based on the presented data so far and the applicant's agreement on the proposed post-authorisation measure, stability at 5±3 °C for up to 24 months is supported for the finished product. The applicant committed to report any out-of-specification data and to update the dossier with outstanding stability data once the stability studies are completed (Post-authorisation recommendation).

Stability data on the finished product stored at 30 °C for 72 hours support the applicant's conclusion that the antigen is not stable at elevated temperatures and should be stored and transported refrigerated.
An appropriate statement is included in the product information.

Stability data on the finished product resuspended in either sterile water or Vaxxon solvent and stored at room temperature were provided and are considered acceptable for the claimed 4 hours of in-use shelf life.

Stability data on three production-scale batches of Vaxxon solvent are presented. The results support the proposed shelf life of 60 months at room temperature.

Overall conclusions on quality

Information regarding the qualitative and quantitative composition, the starting materials, production method, quality controls, and stability is provided in this part of the dossier. Consecutive batches at production scale were provided in order to demonstrate batch-to-batch consistency for the vaccine and the solvent.

The rapporteur considers the presented analytical dossier as adequate. Therefore, the quality of Vaxxon ND Clone has been adequately demonstrated.

Recommendations:

The applicant is recommended to provide the following data post-authorisation:

Stability of the finished product:

The stability testing of all vaccine batches included in the R&D and GMP stability program should be completed by the applicant and the results provided. The applicant will inform the Agency if any OOS result is observed during the stability studies.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Vaxxon ND Clone is a freeze-dried vaccine that contains the live attenuated Newcastle disease virus (NDV) strain Clone intended for oculonasal use (coarse-spray or eye drop). The virus titre range will be 6.0 to 7.5 $\log_{10}$ ELD_{50} (embryo lethal dose 50%). The excipients are sorbitol, gelatine, pea protein GT plus, disodium hydrogen phosphate dihydrate and water for injections. For eye drop administration, the vaccine is reconstituted in a solvent (Vaxxon solvent) consisting of Patent Blue V (E131) and water for injections.

The vaccine is intended for the active immunisation of chickens from the age of day one to reduce mortality and clinical signs of disease caused by infection with Newcastle disease virus.

A full safety file in accordance with Article 8(1)(b) has been provided. Studies to determine the safety of the vaccine were performed in accordance with Regulation (EU) 2019/6, Annex II, section IIIb, Ph. Eur. monograph 0062 on vaccines for veterinary use, Ph. Eur. chapter 5.2.6 on evaluation of safety of veterinary vaccines and immunosera, Ph. Eur. monograph 0450 'Newcastle disease vaccine (live)', and VICH GL 41 Target animal safety: examination of live veterinary vaccines in target animals for absence of reversion to virulence.

One hydrolytic type I glass vial contains 1,000, 2,000 or 2,500 doses. The solvent is provided in polyethylene bottles with a dropper containing 30 ml. Both containers are closed with rubber stoppers and aluminium caps. The product will be marketed in cardboard boxes with 10 vials of vaccine or 10 vials of vaccine with 10 bottles of solvent.

Safety documentation

Ten safety studies were conducted to investigate the safety of the product. They comprised eight pre-clinical studies and two clinical trials. The pre-clinical studies included a single dose plus overdose study, a tenfold overdose study, a study to investigate the dissemination, excretion and spread and five studies for reversion to virulence (2 reversion to virulence passage studies, intracerebral pathogenicity index (ICPI) study, sequencing of the cleavage site, and a comparative study MSV versus MSV+5). One additional study assessing especially the safety of a single maximum dose and a tenfold overdose in SPF broiler chickens was provided upon request during the procedure.

The vaccine was administered in the pre-clinical studies by the oculonasal route via eye drop and in the clinical studies via coarse spray. Eye-drop application was chosen in the pre-clinical studies to assure that the complete dose was administered to the birds.

All pre-clinical studies provided in the dossier of Vaxxon ND Clone were reported to be GLP-compliant. All studies were carried out in chickens (broilers or layers) of the minimum age recommended for vaccination using pilot batches or the MSV except for the two reversion to virulence passage studies, where 14-day-old chickens were used in accordance with Ph. Eur. monograph 0450. The two randomised and double-blinded clinical studies were GCP (Good Clinical Practice)-compliant and were provided to assess both the safety and efficacy of Vaxxon ND Clone under field conditions. One study was carried out in layer chickens and one in broiler chickens.

In the tenfold overdose study, the vaccine Vaxxon H120-Clone from the same company was used that contains the same NDV strain and the same excipients Vaxxon ND Clone, but contains in addition the live attenuated infectious bronchitis virus (IBV) strain Massachusetts H120.

Throughout the study reports, the vaccine is referred to as Vaxxon Clone.

Study reference	*Study title (shortened)*	*Product used*
Preclinical studies		
	Safety of a 10x overdose of Vaxxon Clone in day-old SPF broiler chickens	Vaxxon ND Clone
	Safety of a 10x overose of Vaxxon H120-Clone in day-old SPF layer and broiler chickens	Vaxxon H120-Clone*
	Study to assess the safety of one dose and an overdose of Vaxxon ND Clone in day-old SPF broiler chickens.	Vaxxon ND Clone
	Investigation of dissemination, shedding and spreading	Vaxxon ND Clone
	Virulence profile of a live NDV candidate vaccine by sequential passaging in chickens	MSV
	Virulence profile of a live NDV candidate vaccine by sequential passaging in chickens	MSV
	Determination of the F0 cleavage site of the MSV and the 5x passaged MSV	MSV
	Determination of the intracerebral pathogenicity index of the MSV and the 5x passaged MSV	MSV and 5th passage of MSV
	Comparison of the safety profile of the MSV and the 5x passaged MSV	MSV and 5th passage of MSV
Clinical studies		
	Safety of Vaxxon Clone in one-day-old commercial layer chickens under field conditions in Hungary	Vaxxon ND Clone
	Safety of Vaxxon Clone in one-day-old commercial broiler chickens under field conditions in The Netherlands	Vaxxon ND Clone

* In this study, the vaccine Vaxxon H120-Clone was used that contains the same NDV strain and the live attenuated IBV strain Massachusetts H120.

** Additional study provided during the procedure upon request.

Pre-clinical studies

For all pre-clinical studies SPF chickens of the broiler type or of the layer type were used. SPF certificates to confirm their status were provided. The applicant has established relevant clinical signs and humane endpoint criteria to maximise animal welfare during the studies. It should be noted that it may be beneficial to establish scoring systems in future studies. Study protocols for all study types were provided.

Safety of the administration of one dose

One pivotal single dose study, which was combined with an overdose study, is provided. In this study, the safety of a single maximum dose of 7.5 $\log_{10}$ ELD_{50} and a tenfold overdose of 8.5 $\log_{10}$ ELD_{50} of Vaxxon ND Clone was administered to SPF broiler chickens. The study was performed according to the requirements of Ph. Eur. monograph 0450.

One group of SPF broiler chickens of the minimum age was vaccinated with a single maximum dose (G1) and one group with a tenfold overdose (G2) and observed for clinical signs for 14 days. A placebo group inoculated only with solvent was also included. Seven out of 10 birds in G1 were coughing for at least one day on the first 10 days after vaccination. Two of them were coughing for 4 consecutive days. These findings were transient and interpreted by the applicant as normal vaccine reactions. In G2, 8 out of 10 birds were coughing at least for one day in the same period. Five of them were coughing for at least 3 consecutive days (maximum 4 days), and 2 of these chickens developed a dyspnoea and were euthanised. The euthanised birds were necropsied and histological examinations were performed on the trachea and larynx. A tracheitis with free blood

cells in the lumen was found explaining the severe respiratory signs, which were considered to be related to the vaccination. Therefore, the overdose test was not considered valid by the applicant. According to Ph. Eur. monograph 0450, the study complies if no bird shows abnormal signs of disease or dies from causes attributable to the vaccine.
In summary, the majority of the birds used was affected with transient adverse reactions in both groups (more severe in G2), and in G2 two of them had to be euthanised. In the placebo group, one chicken was coughing for one day.

In conclusion, the safety of a single maximum dose of Vaxxon ND Clone was questionable in one-day-old SPF broiler chickens when used according to the recommendations, whereas a tenfold maximum dose was not regarded as safe in SPF broiler chickens. The applicant had to justify the proposed maximum titre and consider lowering the proposed maximum dose of 7.5 $\log_{10}$ ELD_{50} to avoid possible clinical signs. It was noted that the proposed maximum virus titre is high comparing the already authorised NDV vaccines in Europe. Following this request, a new study was provided during the procedure and is summarised below. The relevant SPC sections were updated accordingly.

Nevertheless, from the data provided in further studies (spread + dissemination and comparison safety MSV and MSV+5), a single maximum dose is considered safe in chickens of the layer type.

Safety of one administration of an overdose

One pivotal overdose study was provided to evaluate the safety of Vaxxon H120-ND Clone (vaccine of the same company with the same NDV strain and additionally with an IBV H120 strain), when applied at a tenfold overdose to 1-day-old SPF chickens of both types. According to Guideline EMA/CVMP/IWP/594618/2010, data from laboratory safety studies carried out on a combined vaccine may be acceptable to demonstrate the safety of a vaccine containing one of the active substances provided the components are identical. Furthermore, this approach is considered as worst-case scenario as a second respiratory virus is included. Therefore, this study is accepted to be relevant also for the marketing authorisation procedure of Vaxxon ND Clone.

The study was performed according to the requirements of Ph. Eur. monograph 0450. One group of SPF layer chickens (G1) and one group of SPF broiler chickens (G3) were vaccinated with a tenfold overdose of 8.5 $\log_{10}$ ELD_{50} and observed for clinical signs for 14 days. A placebo group for each chicken type was also included (G2 and G4; only inoculated with solvent). The volume at which the vaccine was applied was higher than the intended volume for Vaxxon ND Clone (0.1 ml instead of 0.03 ml) because of the second vaccine strain. The higher volume was divided between both eyes of each chicken.

Four out of 10 layers in G1 showed transient coughing and/or buccopharyngeal flutter for 1-3 days. These findings were interpreted by the applicant as normal vaccine reactions. In G3, all 10 birds showed coughing and/or buccopharyngeal flutter for 1-3 days and 4 of these chickens for 6-7 consecutive days. Additionally, signs of dyspnoea were noted in 4 chickens on 1-2 days. One of them developed a severe dyspnoea and was euthanised. Another one of them exhibited also nasal discharge on 2 days. The clinical signs noted are in line with the results of the single dose (overdose) study. In the control groups, no anomalies were detected.

In the euthanised bird, a tracheitis with a large fibrinous plug partly blocking the trachea lumen was detected during the pathological and histological examination (no record is provided). This finding was considered to be related to the vaccination by the applicant and is in line with the results in study RD-REP-2023-0001 (single dose + 10x dose) where a tenfold overdose of Vaxxon ND Clone applied to 1-day-old SPF broiler chickens also led to abnormal vaccine reactions and the euthanasia

of two birds. Nasal discharge was also noted and added to SPC section 10. According to Ph. Eur. monograph 0450 the study complies if no bird shows abnormal signs of disease or dies from causes attributable to the vaccine.

In conclusion, the administration of a tenfold overdose of Vaxxon ND Clone is regarded as safe in 1-day-old SPF layer chickens when used according to the recommendations.

Upon request, an additional was provided to examine especially the safety of a maximum single dose and an overdose in SPF broiler chickens and evaluating a decrease of the maximum titre. For this aim, six groups of SPF broiler chickens were vaccinated with Vaxxon ND Clone per eye drop or via spray (two groups). The chickens received doses of 7.2 ELD_{50} or 8.2 ELD_{50} or 7.5 ELD_{50} or 8.5 ELD_{50}.
In the groups vaccinated per eye drop with a single dose of 7.2 or 7.5 ELD_{50}, no clinical signs were noted, except for one bird that showed buccopharyngeal flutter for one day in the second group. In the groups vaccinated per eye drop with an overdose of 8.2 or 8.5 $ELD_{50,}$ also buccopharyngeal flutter in one or two chickens was detected. In the groups vaccinated via spray (7.2 ELD_{50} or 8.2 ELD_{50}) a greater variety of minor respiratory symptoms was evident: In the first group one chick showed accelerated breathing and two days the chicks appeared sluggish with reduced activity levels. On one day, the birds were shaking their heads. In the second group (8.2 ELD_{50}), buccopharyngeal flutter, coughing, head shaking, and dyspnoea were noted in single animals lasting for one or two days. Two chickens reached the humane endpoint and were euthanised. One of them was depressed and dehydrated due to lack of water intake (not vaccine related), and one exhibited a heart failure and a chronical airsacculitis and pneumonia of the right lung (probably related to an earlier infection). The applicant clarified that no bacterial examination was performed. Furthermore, the applicant justified further how it can be considered that the reactions observed in SPF broiler chickens vaccinated by the spray route comply with the requirements of Ph. Eur. 0450, in which the requirement at 10x dose is that no bird shows abnormal signs of disease or dies from causes attributable to the vaccine.
Considering these results, the applicant decided to keep the single maximum dose at 7.5 ELD_{50} and concluded that the vaccine is safe in SPF broiler chickens. Indeed, this new study provides additional assurance that the vaccine will also be safe in broiler chickens without or with a low amount of MDAs when given according to the recommendations of the SPC. However, the incidence of minor respiratory signs is clearly higher in chickens of the broiler type compared to layer chickens taking the results of all studies together. The SPC has been revised accordingly.

Safety of the repeated administration of one dose

No specific study assessing the administration of a repeated dose was performed as the vaccine is not intended for repeated administration. Nevertheless, some data regarding a repeated administration of Vaxxon ND Clone were generated during the clinical studies in Hungary and The Netherlands:

In Hungary, one group of layer chickens was vaccinated with a commercial dose of 7.1 $\log_{10}$ ELD_{50} with coarse spray at 1 day of age and a further group at 1 day of age and additionally at 21 days. Another group remained unvaccinated. The birds were followed up until day 70 p.v. No systemic clinical signs were noted. Thirty chickens per group were sacrificed on day 70 p.v. Mortality rates were low.

In the Netherlands, the same vaccination scheme was applied to broiler chickens and a control group including a comparator product. Likewise, no systemic clinical signs were noted during the observation period of 56 days (only transient sneezing/coughing for two days in the group that was revaccinated twice) and the mortality rates were low. These results give some assurance that no

safety concerns are to be expected after an accidental revaccination with Vaxxon ND Clone.

Examination of reproductive performance

No dedicated study assessing the reproductive performance after vaccination was performed as the vaccine is not intended for use during the laying period. The standard warning sentence was included in SPC section 3.7: 'The safety of the veterinary medicinal product has not been established during lay.'

However, the safety for the developing reproductive tract was investigated during the clinical study in Hungary: One group was vaccinated on the first day of life with a commercial dose of Vaxxon ND Clone and another group was vaccinated on the first day of life and again at 21 days of age also with a commercial dose of Vaxxon ND Clone. An unvaccinated negative control group was included in the study as well. Thirty chickens per group were sacrificed on day 70 p.v. During macroscopic examination of the reproductive tract, none of the reproductive tracts showed any abnormal findings. These results provide some assurance that no safety concerns are to be expected after vaccination with Vaxxon ND Clone.

Examination of immunological functions

No further studies were conducted to investigate the effects of the product on immunological functions. However, no adverse effects were observed in any of the safety or efficacy studies. It is therefore unlikely that this vaccine will have an adverse effect on immunological functions due to the nature of the live vaccine without any known immunosuppressive effects. However, an influence of maternally derived antibodies can be noted when comparing the results of the pre-clinical and clinical studies in broiler chickens.

Special requirements for live vaccines

The applicant has provided one study investigating the dissemination, excretion and spread of the vaccine strain and five studies to examine a possible reversion to or increase in virulence considering Ph. Eur. monograph 5.2.6 and VICH GL41 Target Animal Safety: examination of live veterinary vaccines in target animals for absence of reversion to virulence.

Spread of the vaccine strain

Dissemination, excretion, and spread of the vaccine virus from vaccinated SPF chickens to naïve SPF chickens was investigated. Thirty one-day-old SPF layer chickens were vaccinated via eye drop with a single maximum dose of 7.5 $\log_{10}$ ELD_{50}. On the same day, 5 hatch mates were sacrificed to verify the negative serological NDV status. A group of unvaccinated sentinels of the same number was included and mingled with the vaccinated chickens.

On days 2, 4, 7, 10, and 14 p.v., 5 chickens from each group were sacrificed and blood, trachea, proventriculus, brain, bursa and cloacal swab samples were collected. From day 7, all vaccinated chickens and 3 out of 5 sentinels had developed antibodies against NDV. From day 10, all sentinels were serologically positive, indicating a fast spread to the non-vaccinated group. The first cloacal swabs from vaccinates were positive on day 2 and from two of the sentinels as well. The virus detection increased until day 7 and then decreased again slowly. On day 14, still 3 out of 5 cloacal swabs from the vaccinates and 2 out of 5 cloacal swabs from the sentinels were positive for NDV.

The virus disseminated to all tested organs in both groups and was most often isolated from the trachea and proventriculus also indicating an excretion over the oropharyngeal route, which was

unfortunately not tested in this study although it is common knowledge that NDV is transmitted via infected saliva. The range of tested organs is considered as relevant for NDV. No clinical signs were noted in any chicken.

No study is provided to assess the spread of the vaccine strain to non-target species. This is not obligatory but was considered for the warnings included in the SPC.

Dissemination in the vaccinated animal

Dissemination and spread of the vaccine strain were evaluated in one study. See chapter 'Spread of the vaccine strain'.

Increase in virulence of attenuated vaccines

A possible reversion to or increase in virulence was also evaluated as well as the intracerebral pathogenicity index (ICPI) and the sequence of the cleavage site of the vaccine virus.

The reversion to virulence of the vaccine strain of Vaxxon ND Clone was assessed with two studies: the first study is regarded as only supportive as the MSV was not used at the proposed maximum dose. Only 6.0 $\log_{10}$ ELD_{50} were used to inoculate the first group of chickens instead of 7.5 $\log_{10}$ ELD_{50}. Five subsequent animal passages were performed and each group was sacrificed 4 days p.i., necropsied and the tracheal mucosa and brains were collected. Suspension pools per organ type were made from each group and examined via RT qPCR. When NDV was confirmed to be present in the suspension, the organ pools were mixed and applied via eye drop to the next group of birds. The virus was detected in each pool over all 5 animal passages. No clinical signs were noted throughout the study. However, RNA concentrations were too low in the samples to use them for further studies such as the sequencing of the cleavage site or the ICPI test.

The second study was performed with the correct dose of 7.5 $\log_{10}$ ELD_{50} of the MSV in a slightly higher volume of 0.05 ml, which is of no concern. Again, the vaccine virus was passaged over several chicken groups. In each passage, the presence and also the viability of the virus was verified by RT qPCR or egg titration. In the fourth passage, no virus was detectable. Therefore, this passage was repeated with twice the number of birds per group. This time viable virus was found and, according to the requirements of the Ph. Eur. monograph 5.2.6, in the last passage also a higher number of animals was used and NDV was re-isolated as well. No clinical signs were detected and no indications were found that the vaccine strain would reverse to or increase in virulence. Data on the methods used were provided upon request.

The intracerebral pathogenicity index (ICPI) of the NDV vaccine strain was tested to investigate its capacity for virulence. For this aim, both the MSV and the MSV+5 (brain/tracheal mucosa-suspension originating from the second reversion to virulence study) were propagated once in SPF chicken eggs in the first phase of the study to gain more material at a higher virus titre. In the second phase of this study, two groups of 1- to 2-day-old chicks were inoculated intracerebrally with 8.0 $\log_{10}$ ELD_{50} of either the reference item (MSV+1) or the test item (MSV+6). The chickens were scored daily for 8 consecutive days. All noted abnormalities were considered as NDV-related. For the reference item an ICPI of 0.3 and for the test item an ICPI of 0.2 was determined indicating that both virus isolates are of low pathogenicity and comply with the requirements of Ph. Eur. monograph 0450.

Initially, it was intended to determine the sequence of the cleavage site of the vaccine virus strain in the MSV and in the organ pools originating from the first reversion to virulence study. However, RNA concentrations were too low and the study was repeated. But also, the RNA content in the sample originating from this study was too low. Therefore, the allantoic fluid from the ICPI study was used

for the sequencing of the cleavage site and compared to the MSV. The two virus samples showed identical results and complied with the requirements of Ph. Eur. monograph 0450.

The MSV was compared to the MSV+5 (brain/tracheal mucosa-suspension, obtained in the second reversion to virulence study) to evaluate the safety of the two passages. An observation period of 21 days was chosen in this study to be compliant with both the Ph. Eur. and the VICH GL 41. One group of chickens was inoculated with the MSV and another group with the MSV+5. No clinical signs or deaths were noticed during the observation period after inoculation. Therefore, both virus samples complied with the test.

It is concluded that no reversion to or increase in virulence was observed following five passages *in vivo*. The cleavage site of the vaccine virus and the ICPI comply with Ph. Eur. monograph 0450.

Biological properties of the vaccine strain

The NDV vaccine strain Clone is classified as a lentogenic, low pathogenic strain of avian paramyxovirus type 1 (APMV-1). The ICPI of this vaccine strain is low and the amino acid sequence of the F protein cleavage site is shown to be characteristic of non- or low-virulent NDV strains.

No dedicated study was provided to address the biological properties of the vaccine strain of Vaxxon ND Clone. However, in the safety studies provided by the applicant no indication was noted that the vaccine strain differs from the original LaSota strain.

Recombination or genomic reassortment of the strains

The risk for recombination or genomic re-assortment is considered as very low by the applicant. It is noted that a more detailed assessment of the applicant is included in the Environmental Risk Assessment. For more information see the Environmental Risk Assessment.

It is agreed that NDV LaSota has been extensively investigated over the last decades and has demonstrated its safe long-term use in many vaccines authorised in the EU.

It can be concluded that the occurrence of recombination or genomic reassortment is very unlikely. This assessment was made in compliance with the respective legal requirements.

User safety

The applicant has presented a user safety risk assessment, which has been conducted in accordance with the 'CVMP Guideline on user safety for immunological veterinary medicinal products' (EMEA/CVMP/IWP/54533/2006).

Newcastle disease virus is only mildly pathogenic for humans and a conjunctivitis upon contact for the user is possible. The excipients of the lyophilisate and the solvent are commonly used in other vaccines and can be considered as not posing a risk for the user.

Two of the main potential routes of accidental contact with the product have been considered and it was concluded that dermal and conjunctival exposure are most likely to occur. The use of needles for the transfer of the solvent when using the eye drop administration was evaluated as well. Only veterinarians or trained personnel under their supervision will mix the product. Gentamicin was used in the manufacture of the MSV and a worst-case calculation is provided, resulting in an amount present in one dose which is not regarded as being pharmacologically active.

Section 3.5 of the SPC 'Special precautions to be taken by the person administering the veterinary medicinal product to animals' provides adequate warnings for the user.

Based on the above user risk assessment, the CVMP concludes that the product does not pose an unacceptable risk to the user when used in accordance with the proposed SPC revisions.

Study of residues

MRLs

The active substance is of biological origin intended to produce active immunity and does not fall within the scope of Regulation (EC) No 470/2009.

The excipients listed in section 2 of the SPC are either allowed substances for which no MRLs are required according to Table 1 of the Annex to Commission Regulation (EU) No 37/2010 or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

The residual level of the gentamicin used in the manufacturing process of the MSV was calculated to a level does not constitute a risk to the consumer, as it is not regarded as being pharmacologically active and far below the numerical MRLs established for this substance.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and, therefore, proposed to include a statement in section 3.8 of the SPC that

"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."

Clinical studies

Two clinical studies were provided in the dossier of Vaxxon ND Clone to assess the properties of the vaccine in the field. Both studies were GCP-compliant, combined, randomised, blinded trials, one in commercial layers in Hungary (semi-field trial) and one in commercial broiler chickens in the Netherlands (standard field trial). The relevant 'Guideline on clinical trials with immunological veterinary medicinal products EMA/CVMP/IWP/260956/2021' was considered by the applicant. In both trials, the chickens were vaccinated with a commercial dose of approximately 7.1 $\log_{10}$ ELD_{50} by spray, one group at one day of age and one group at one day of age and again at 21 days of age. For the layer study, a negative unvaccinated control group was included, which is uncommon, and for the broiler study, a positive control group vaccinated with a comparator vaccine was included.

In the first clinical study, 1,542 one-day-old layer chicks were included, which were divided into three treatment groups of 514 chickens each. In order to mimic field conditions, a standard vaccination schedule was applied to all three groups. For evaluation of safety, the birds were observed for local and systemic reactions daily for 14 days after each NDV vaccination and in addition observed and weighed at several points in time up to day 70. The reproductive tracts of 30 birds per group were examined at day 70. The study was considered valid since it was neither affected by serious technological disturbance nor overlaid by intercurrent disease that might have

impaired the evaluation of the examined parameters.

No systemic reactions and no local reactions were observed in any treatment group at any defined point in time. No abnormality was detected in the reproductive tract of examined chickens in any group at day 70. Body weight distribution was homogenous over the treatment groups at day 0. Concerning the body weight development, both vaccinated groups performed significantly better than the control group indicating no negative influence of the vaccination on the development of the body weight. Mortality rates were low and showed no significant difference between groups. The mean body weights and mortality rates were in conformity with the chicken breed used. The vaccine is regarded as safe when used at a commercial dose in one-day-old commercial layer chicks.

In the second clinical, 49,000 broiler chickens were divided into three treatment groups. The first group of 15,000 animals was vaccinated at day 0 with a comparator vaccine of a different manufacturer, whereas the second and third group (17,000 chicks each) were vaccinated with the test item on the same day. At day 21, only the chickens of the third group were revaccinated with the test item. The safety of the vaccine was evaluated by survey of general health observations, mortality, average slaughter weight, feed conversion rate and rejections at slaughterhouse.

From day 22, the day after the booster vaccination, sneezing and coughing were observed over two days in the group vaccinated twice with the test vaccine. The applicant considers the clinical signs as a reaction to the booster vaccination via spray with a smaller droplet size. However, revaccination is not claimed for this vaccine. No other clinical signs were detected in this group or in the other groups indicating an important role of maternally derived antibodies on the manifestation of adverse reactions in broiler chickens when administering this vaccine.

The rejection rates were higher in the test groups than in the positive control group; however, the numbers of rejections are still low. Reasons for rejections included polyserositis, skin infection and hepatitis. No relation between the causes for rejection and the treatment was recognised. The average slaughter weights were comparable and the feed conversion rates were comparable between groups 1 and 2 and slightly lower in group 3. With 1.2% in group T02 and 1.4% in T03, the mortality rates were significantly higher in the groups vaccinated with the vaccine than the mortality rate in the positive control group. The significant difference in mortality between groups was based on the higher mortality of both test groups in the first week p.v., but no significant difference regarding mortality was noted between weeks 2 and 7.

It can be summarised that the presented safety data show that Vaxxon ND Clone can be safely administered at a commercial dose via spray to one-day-old MDA-positive commercial layer and broiler chickens. A repeated dose was not claimed and as no preclinical study on a repeated maximum dose in SPF chickens is provided, the reference to a second dose in the SPC is not accepted and was deleted.

Environmental risk assessment

The environmental risk assessment (ERA) concludes that the overall risk of the vaccine for the target species and non-target species, the user and the environment is effectively zero. The applicant considered for his evaluation the EMA 'Note for guidance on environmental risk assessment for immunological veterinary medicinal products' (EMEA/CVMP/074/95).

Based on the data provided, the ERA can stop at Phase I. Vaxxon ND Clone is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The applicant has provided two pivotal pre-clinical studies to investigate the safety of a single dose and the safety of a 10x overdose in chickens of the broiler and of the layer type. The birds were vaccinated at the minimum recommended age using 7.5 $\log_{10}$ ELD_{50} via the oculonasal route per eye drops. Batches used in these studies were pilot batches.

Based on the results, it was concluded that the safety for broiler chickens is not acceptable when the product is administered according to the recommended schedule and via the recommended route. A new study with a reduced maximum virus titre was requested to give assurance that the product will be safe in broiler chickens. The safety of a maximum single dose in layer chickens was demonstrated.

The additional study on the safety of a maximum single dose and an overdose in SPF broiler chickens was provided evaluating two different single maximum doses and overdoses. The same vaccine batch was used in this study. The safety of the maximum single dose of 7.5 ELD_{50} and a tenfold overdose of 8.5 ELD_{50} for broiler chickens given via eye drop was demonstrated. The safety of spray vaccination in broilers was further justified. However, no reduction of the maximum single dose is considered necessary.

The vaccination scheme consists only of one dose of the vaccine; however, in the two clinical studies, each one group was vaccinated via coarse spray with a repeated dose at 21 days of age. In layers, no clinical signs were noted but in broiler chickens sneezing and coughing for 2 days were detected after administration of a repeated dose. As no preclinical study on a repeated maximum dose in SPF chickens is provided, the inclusion of a second dose in the SPC is not accepted and was deleted.

Reproduction safety was not specifically investigated. In one clinical study, layer chickens vaccinated at one day of age were followed up until 70 days p.v.. No clinical signs and no anomalies concerning the reproductive tract were noted. However, the standard warning is included in the SPC.

As this is a live vaccine the applicant also conducted studies to establish the potential for spread and dissemination of the vaccine strain. The vaccine strain is excreted via the cloacal route at least for 14 days and spreads to unvaccinated chickens without causing clinical signs but leading to seroconversion. Spread to non-target species was not tested and should be avoided, as recommended in the PI. Reversion to virulence, the intracerebral pathogenicity index and the sequence of the cleavage site of the NDV strain were also investigated. The results show that the potential risk is low and acceptable. The biological properties of the vaccine strain were described adequately, do not differ from the properties of other NDV strains and are found to be acceptable.

The product is not expected to adversely affect the immune response of the target animals or of their progeny, and therefore no relevant tests on the immunological functions were carried out.

A user safety assessment in line with the relevant guidance document has been presented. The worst-case scenario for user safety is the development of mild conjunctivitis after accidental contact. The use of needles for the transfer of the solvent when using the eye drop administration was evaluated as well. Only veterinarians or trained personnel under their supervision will mix the product. The proposed warnings are considered adequate to mitigate the risk for the user. Because of decades of experience with NDV vaccines, the potential health risk of the product for users could be considered low and acceptable when used in accordance with the SPC.

An acceptable environmental risk assessment was provided according to the requirements of the relevant guidance. Vaxxon ND Clone will not pose a risk to the environment when used according to the SPC and the environmental risk assessment stops at Phase I.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

Introduction and general requirements

Vaxxon ND Clone is presented as a lyophilisate and contains live attenuated Newcastle disease virus strain Clone: 6.0-7.5 $\log_{10}$ ELD_{50}* (*ELD_{50}: embryo lethal dose 50%).

The product is administered by coarse spray after reconstitution in drinking water or by eye drop route after reconstitution in the specific solvent.

The relevant SPC claims with regard to efficacy are:

Target species: chickens

Vaccination scheme: one single administration

Minimum dose: min. 6.0 ELD_{50}* (*ELD_{50}: embryo lethal dose 50%)

Indication:

"For the active immunisation of chickens (broilers, future layers and breeders) from one day of age to reduce mortality and clinical signs of disease caused by infection with Newcastle disease virus."
Onset of immunity: 3 weeks after vaccination
Duration of immunity: 8 weeks (broilers) and 10 weeks (future layers and breeders)

The purpose of the trials described in this part of the dossier is to demonstrate the efficacy of the immunological veterinary medicinal product. All claims made by the applicant with regard to the properties, effects and use of the product shall be fully supported by the results of the specific studies provided in this application for a marketing authorisation.

Relevant guidelines and monographs

Any documentation in relation to efficacy is presented according to the requirements of Regulation (EU) 2019/6, Annex II, Section IIIb.

More detailed guidance is provided by various Ph. Eur. monographs and CVMP and VICH guidelines:

- Ph. Eur. 0062: Vaccines for veterinary use
- Ph. Eur. 5.2.7: Evaluation of efficacy of veterinary vaccines and immunosera
- Ph. Eur. 0450: Newcastle disease vaccine (Live)
- VICH GL9: Guideline on Good Clinical Practice
- EMEA/CVMP/682/99: Note for guidance: Duration of protection achieved by veterinary vaccines
- EMA/CVMP/IWP/439467/2007: Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals
- EMA/CVMP/IWP/260956/2021: Guideline on clinical trials with immunological veterinary medicinal products
- EMA/CVMP/IWP/594618/2010: Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs).

Challenge model

No separate study on a development of a challenge model was performed. However, the challenge was validated within the frame of the efficacy studies.

NDV challenge studies were performed in accordance with Ph. Eur. 0450. They were conducted by two contract laboratories.

The challenge strains used in the laboratory efficacy trials were strain NDV Herts Weybridge 33/56, which was manufactured at the national food chain safety office, or strain NDV Herts, manufactured at Royal GD.

Herts 33/56 is widely used as ND reference strain in different animal experiments and is the reference strain of the Ph. Eur. monograph 0450. Batch protocols of the NDV challenge strains used at the two above mentioned laboratories are provided.

The chickens in the studies were infected with the challenge virus by intramuscular (i.m.) route at a dose of 5 $\log_{10}$ ELD_{50} as required according to Ph. Eur. monograph 0450, 2-3-5 Immunogenicity.

Efficacy parameters and tests

Clinical observation

After challenge, as per Ph. Eur. 0450, the chickens were monitored for 14 days for the occurrence of clinical signs related to NDV infection (morbidity) or death (mortality) according to a defined scoring system:

0: No occurrence of clinical evidence of Newcastle disease
1: Occurrence of clinical evidence of Newcastle disease
2: Mortality caused by NDV

Validation of techniques to assess efficacy variables

Serology

In the laboratory studies and field trials, the haemagglutination (HA) inhibition test (HI) test was used for serology testing. The SOP of this HI test is provided.

The HI titre is the highest dilution of antiserum causing complete inhibition of 4 or 8 units of virus. Both contract laboratories performed the HA inhibition test for NDV with 4 HA units. HI titres may be regarded as being positive if there is inhibition at a serum dilution of 1/16 (4 $\log_2$) or more against 4 HA units of antigen as described in Article 6(1) of Commission Delegated Regulation (EU) 2020/689 supplementing Commission Regulation (EU) 2016/429) referring to the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals and the guidance described by the European Union Reference.

Efficacy documentation

In total, five laboratory studies were performed to demonstrate the efficacy of the product.
Both routes of application, coarse spray and eye drop route, have been used for vaccination of day-old chickens in these studies.
In the laboratory studies, the chicks were given a minimum dose of 6.0 ELD_{50} of the vaccine strain at the most attenuated passage level that will be present in the vaccine. In all laboratory studies but one, Vaxxon H120-Clone was used, which contains the same NDV strain Clone and excipients as Vaxxon ND Clone and in addition the live attenuated infectious bronchitis virus strain Massachusetts H120. The approach to use a vaccine with more components for efficacy studies is in line with section 4.1.3 of EMA/CVMP/IWP/594618/2010 and therefore considered acceptable.

All batches used for the efficacy and field trials were representative batches of the production

method described in the quality part of the corresponding dossier. Batch release certificates of the mentioned batches are provided. The passage level of these batches is MSV+5.

The laboratory efficacy tests were performed using SPF chickens as requested in the relevant Ph. Eur. monographs. Additional laboratory studies were conducted in MDA-positive commercial broiler or layer type chickens to evaluate the efficacy of Vaxxon ND Clone in the presence of maternally derived antibodies (MDA).

To confirm the efficacy of the vaccine under field conditions, two combined safety and efficacy field trials were performed, one in MDA-positive commercial broiler chicks and one in layer type chickens, where the chicks were vaccinated with commercial doses of vaccine.

The laboratory efficacy tests were conducted according to previously defined protocols. The combined field safety and efficacy trials were compliant with the requirements of GCP.

Table 1: Overview of efficacy studies

Study title	**Type of study**	**Product**	**Target titre/ ELD_{50}**	**Challenge day p. vacc./ strain/dose**
Laboratory studies				
Study to assess a 21-day onset of immunity of Vaxxon H120 Clone against NDV challenge in one-day-old SPF layer chickens	Onset of immunity	Vaxxon H120-Clone	6.0	21 days/NDV Herts 5.0 log_{10} EID_{50}
Study to assess a 10-week duration of immunity of Vaxxon ND Clone against NDV challenge in one-day-old SPF layer chickens	Duration of immunity	Vaxxon ND Clone	6.0	10 weeks/NDV Herts 5.0 log_{10} EID_{50}
Study to assess an 8-week duration of immunity of Vaxxon H120-Clone against NDV challenge in one-day-old SPF broiler chickens	Duration of immunity	Vaxxon H120-Clone	6.0	8 weeks/NDV Herts 5.0 log_{10} EID_{50}
Study to assess a 21-day onset of immunity of Vaxxon H120-Clone against NDV challenge in one-day-old MDA+ broiler chickens	MDA+	Vaxxon H120-Clone	6.0	21 days/NDV Herts 5.0 log_{10} EID_{50}
Study to assess a 21-day onset of immunity of Vaxxon H120-Clone against NDV challenge in one-day-old MDA+ layer chickens	MDA+	Vaxxon H120-Clone	6.0	21 days/NDV Herts 5.0 log_{10} EID_{50}
Field studies				
Study to assess the safety and efficacy of Vaxxon ND Clone vaccine in one-day-old commercial layer chickens under field conditions in Hungary	Clinical study	Vaxxon ND Clone	7.1	-
Study to assess the safety and efficacy of Vaxxon ND Clone in one-day-old commercial broiler chickens under field conditions in The Netherlands.	Clinical study	Vaxxon ND Clone	7.1	-

Pre-clinical studies

Dose determination

No separate study on dose determination was performed. However, all onset of immunity (OoI) studies were performed with the minimum infectious titre and confirm the efficacy of the vaccine.

Onset of immunity

The applicant has performed one challenge study to evaluate the onset of immunity for Vaxxon ND Clone (same ND component and excipients as contained in Vaxxon H120- Clone, which is used for the study) in SPF chickens in accordance with the immunogenicity study prescribed in Ph. Eur. monograph 0450.

One group of day-old SPF chickens was vaccinated by eye-drop, a second group by coarse spray, and both groups with a minimum titre of the NDV strain Clone contained in Vaxxon H120-Clone. A third group of unvaccinated animals was kept as controls. NDV-specific serum antibody titres were determined by HI test in 5 chickens of each group at day 20, prior to challenge.

Three weeks after vaccination, 20 birds from each vaccinated group and 10 birds from the control group were challenged intramuscularly with NDV strain Herts. All birds were observed daily for clinical signs until 14 days after challenge.

The setup of the challenge model fulfils the requirements of Ph. Eur. monograph 0450.

The challenge with Herts 33/56 virulent strain is valid (100% of controls dead by 6 days after challenge). The protection level at challenge of 95% for chickens vaccinated by eye-drop and 100% for chickens vaccinated by coarse spray administration is in line with Ph. Eur. pass criteria for ND live vaccines.

In addition, all vaccinated animals were positive for ND-specific antibodies at the time of challenge in contrast to the controls, which all remained seronegative. Whereas no claim is proposed on serological data, these data are generated in order to link the serological response to the protection in challenge.

The claimed OoI of 21 days corresponds to the time of challenge foreseen for the immunogenicity test of Ph. Eur. 0450. Accordingly, the study supports the claimed OoI and fulfils the requirements of the Ph. Eur. monograph for the immunogenicity test.

The claims on reduction of mortality and clinical signs of disease caused by infection with Newcastle disease virus after 21 days from vaccination are supported by the study.

Duration of immunity

To evaluate the duration of immunity (DoI) of Vaxxon ND Clone (same ND component as contained in Vaxxon H120-Clone), one study in SPF layers with Vaxxon ND Clone and one study in SPF broiler chickens with Vaxxon H120-Clone were performed in accordance with the immunogenicity study prescribed in Ph. Eur. monograph 0450.

In both studies, one group of day-old SPF chickens was vaccinated by eye-drop, a second group by coarse spray, and both groups with a minimum titre of Vaxxon-H120-Clone. A third group of unvaccinated animals was kept as controls. NDV-specific serum antibody titres were determined by HI test in all chickens of each group prior to challenge.

At 10 weeks after vaccination for the layer chickens and 8 weeks for the broiler chickens, 20 birds from each vaccinated group and 10 birds from the control group were challenged intramuscularly with NDV strain Herts. All birds were observed daily for clinical signs until 14 days after challenge.

Study in layers

The setup of the challenge model fulfils the requirements of Ph. Eur. monograph 0450.

The challenge with Herts 33/56 virulent strain is valid (100% of controls dead by 6 days after challenge). The protection level in challenge of 100% for chickens vaccinated by eye-drop or by coarse spray administration is in line with Ph. Eur. pass criteria for ND live vaccines. In the group of the animals vaccinated by eye-drop, 22 out of 23 (96%) and 100% of the animals vaccinated by coarse spray were positive for NDV-specific antibodies at the time of challenge in contrast to the controls, which all stayed seronegative.

Accordingly, the claimed DoI of 10 weeks can be considered supported.

Study in broilers

The setup of the challenge model fulfils the requirements of Ph. Eur. monograph 0450.

The challenge infection is performed with NDV Herts Weybridge 33/56 strain.

Several unfavourable events were mentioned with regard to this study, such as some clinical findings, before and after challenge, of different origin and various severity. Parts of the findings after challenge are considered related to aggression matters of male towards female chickens, which were however adequately handled. Nevertheless, the study can be considered to fulfil the validity criteria of Ph. Eur. The challenge is valid since 100% of the control animals were dead by 6 days after challenge. The protection level in challenge of 100% for chickens vaccinated by eye-drop or by coarse spray administration is in line with Ph. Eur. pass criteria for ND live vaccines. In addition, 100% of the animals vaccinated either by eye-drop or by coarse spray were positive for NDV-specific antibodies at the time of challenge in contrast to the controls, which all stayed seronegative.

The claims on reduction of mortality and clinical signs of disease caused by infection with Newcastle disease virus are supported by the study. The DoI of 8 weeks for broilers can be considered supported. Clinical signs were observed in 4 animals after vaccination (signs of bronchitis in two animals and neurological signs in two further animals). The neurological signs (torticollis) were finally concluded not to be related to vaccination. However, it could not be excluded that the other clinical signs (stunting and ruffled feathers) were not related to the vaccine and they are therefore reflected as adverse events in the SPC.

Maternally derived antibodies (MDA)

The applicant has performed two challenge studies to evaluate the OoI for Vaxxon ND Clone (same ND component as contained in Vaxxon H120-Clone), one in commercial broiler chickens and one in commercial layer chickens to evaluate the efficacy of the vaccination in the presence of MDA. The studies were conducted in accordance with the immunogenicity test prescribed in Ph. Eur. monograph 0450.

In both studies, one group of day-old chickens was vaccinated by eye-drop, a second group by coarse spray, and both groups with a minimum titre of the NDV strain Clone contained in Vaxxon H120-Clone. A third group of unvaccinated broilers was kept as controls (and a fourth group of SPF layers, only in study RD-REP-2022-0014). NDV-specific serum antibody titres were determined by HI test in all chickens prior to challenge at day 20.

Three weeks after vaccination, 20 birds from each vaccinated group and 10 birds from the control group were challenged intramuscularly with NDV strain Herts. All birds were observed daily for clinical signs until 14 days after challenge.

Study in broilers

The setup of the challenge model fulfils the requirements of Ph. Eur. monograph 0450, even if this is not mandatory for studies with commercial chickens.

From the SPF control animals, 10/10 (100%) died before they were euthanised because of reaching the humane end-point criteria. They can be considered to validate the challenge with Herts 33/56 virulent strain for this study and to confirm validity for the other studies, where the SPF control animals were euthanised after reaching the humane endpoint.

The protection level in challenge of 80% for chickens vaccinated by eye-drop and 90% for chickens vaccinated by coarse spray is considered adequate in commercial animals. Part of the vaccinated animals (5/20 after coarse spray vaccination, 8/23 after eye-drop vaccination) were positive for NDV-specific antibodies at the time of challenge in contrast to the controls, which were all seronegative except for one MDA+ control broiler of group 3.

According to reflection paper EMA/CVMP/IWP/439467/2007, the challenge infection to demonstrate efficacy of a vaccine in the presence of MDA is supposed to be performed at the time when MDA in controls before challenge are sufficiently low. This is considered for the timing of the study according to the defined test criteria of the HI test.

However, most of the vaccinated chickens were protected in challenge despite being seronegative for NDV-specific antibodies at the time of challenge according to the defined test criteria. This is also applicable for the MDA+ control animals, 70% of which were protected in challenge even if 10/11 were seronegative at the time of challenge. Accordingly, protection does not seem to be correlated to the defined HI titre values of ≥ 4 $\log_2$ but may be present at lower titre levels (or to depend on other/additional factors). Retrospectively, the challenge infection is considered to have been performed at a time where the controls were still (partly) protected (by MDA).

Nevertheless, it can be concluded that vaccinated animals are protected at the claimed OoI of 21 days to an acceptable level, and that the level of protection is higher than in the control animals.

The claims on reduction of mortality and clinical signs of disease caused by infection with Newcastle disease virus are supported by the study.

Study in layers

The setup of the challenge model fulfils the requirements of Ph. Eur. monograph 0450. No group of SPF chickens is included to validate the challenge. In study RD-REP-2022-0014, the challenge with exactly the same challenge material was validated by an included SPF control group. Considering the results in this group (100% of controls dead by 4 days after challenge), the challenge in the present study may be regarded as validated as such.

Full protection in challenge (100%) both for chickens vaccinated by eye-drop or by coarse spray is achieved in the study. However, the protection rate of the control animals (8/10) is very high in this study as well.

All vaccinated animals of both groups were positive for NDV-specific antibodies at the time of challenge. In the control group 3, 6 of 11 layer chickens were still seropositive at the time of challenge.

According to reflection paper EMA/CVMP/IWP/439467/2007, the challenge infection to demonstrate efficacy of a vaccine in the presence of MDA is supposed to be performed at the time when MDA in controls before challenge are sufficiently low, which is not fully considered for the timing of the study. However, there is an obvious difference in protection rates between vaccinated groups (100% protection) and the control group (80% protection). Differences are also observed in the number of seropositive chickens and in the level of measured titres between each of the vaccinated groups and the control group, which is stated to be significant.

In this study, a correlation is observed between antibody reaction and protection (100% seroconversion in connection with 100% protection in challenge) in vaccinated animals, which is also, but less applicable to the control animals, where 6/11 (54.5%) were seropositive, but 8/10 (80%) protected in challenge.

These results in the control animals support the earlier assumption that the cut-off value for the HI-test (≥ 4 $\log_2$) may be too high to clearly distinguish between protection and non-protection.

The claims on reduction of mortality and clinical signs of disease caused by infection with Newcastle disease virus are supported by the study.

Interactions

No studies on interactions were performed. Accordingly, the following sentence is included in section 3.8 of the SPC:

"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."

Clinical trials

Two clinical studies were performed to support the efficacy of the vaccine, one in layers in Hungary and one in broilers in The Netherlands.

Study in layers

The objective of the study in layers was to assess the safety and efficacy of Vaxxon ND Clone after being administered via coarse spray to female Tetra SL-LL commercial layer hybrid chickens. The study was performed at closed farm facilities, which mimicked the field conditions of pullets growing on littered floor houses and allowed keeping non-vaccinated controls and two treatment groups in fully separated circumstances. This approach is rather uncommon for a field study, where a group vaccinated with a different, but comparable product (positive control group) is commonly included in order to evaluate the superiority/inferiority of the test product.

In total, 1,632-day-old chicks were included in the study and divided into three treatment groups of 544 chicks each.

At day 0 of the study, thirty chicks per treatment group were bled to excess in order to determine the homogeneity of maternally derived antibodies (MDA) over the treatment groups. The same day, one test group was vaccinated with one dose of Vaxxon ND Clone, a second test group was vaccinated with one dose of Vaxxon ND Clone at one day of age and revaccinated at 21 days of age and the chicks of the third group were kept as unvaccinated controls. As common under field conditions, a standard vaccination schedule was applied equally to the three groups.

The study was categorised as randomised, masked, negative controlled semi-field clinical study, performed according to GCP standard. The study was considered valid since it was neither affected by

serious technological disturbance nor overlaid by intercurrent disease, which might have negatively impacted the evaluation of the parameters examined.

According to the measured NDV HI antibody titres, the vaccine virus did not spread between the treatment groups.

The efficacy was evaluated by measurement of the NDV-specific serum antibodies via HI test at different times during the study (day 14, 21, 56, 70). The same cut-off value in the HI test of 4.0 $\log_2$ was applied as in the laboratory studies.

At the start of the study, high and homogenous levels of NDV HI antibody titres were detected in day-old chicks (mean titres 5.0 – 6.0 $\log_2$). The HI titres gradually decreased in all groups until day 21 to different degrees. The decrease was highest in the control group (0.6 $\log_2$ GMT). In both vaccinated groups, the mean titres were significantly higher than in the control group with 3.0 $\log_2$ in group 1 and 2.2 $\log_2$ in group 2 at day 21.

After the second vaccination of group 2, the mean HI titre in this group reached a peak of 3.5 $\log_2$ at day 56 (whereas it was down to negligible levels in group 1), with a following decrease to 2.8 $\log_2$ until day 70. The mean titres in group 2 (vaccinated twice with Vaxxon ND Clone) were significantly higher at days 56 and 70 than for the two other groups.

However, the number of animals reaching the cut-off titre of 4.0 $\log_2$ is considered clinically more relevant than the significant difference in titre levels between groups in general. Whereas in the vaccinated groups 1 and 2, 74.3% and 60%, respectively, were seropositive at day 14 (51% of the controls), less than half of the animals per group were seropositive at day 21 in the once vaccinated group (42.9%) and only 20% in the group where a second vaccination with the vaccine was envisaged (2.9% of unvaccinated animals in the control group). The differences between groups 1 and 2 seem to reflect the variability of the seroconversion, as both groups had received one dose of vaccine at that time. After revaccination of group 2, the percentage of protected animals reached 71.4% at day 56 and decreased to a level of 54.3% at day 70, whereas it goes down to 0% from day 56 on in group 1. Since no serology data are available between day 21 and day 56, the development of the immune response after one vaccination cannot be sufficiently concluded. Therefore, the possible lack of efficacy in MDA+ chickens has been reflected in the SPC (section 3.4):

"Maternally derived antibodies (MDA) can significantly interfere with the development of active immunity."

Despite a clearly better seroconversion after repeated use of Vaxxon ND Clone is observed and acknowledged by the applicant, the repeated use is not claimed. The applicant further suggested to recommend a re-vaccination for animals with MDA at three weeks of age. However, in the absence of any safety data on re-vaccination in SPF animals, this recommendation cannot be accepted and will not be included in the SPC.

Altogether, the results of the field trial relativise the efficacy of the vaccine in layers in the field in the presence of (high levels) of MDA and this is addressed by a relevant warning in section 3.4 of the SPC.

Study in broilers

The field trial in boilers was performed to evaluate the safety and efficacy of Vaxxon ND Clone after administration via coarse spray to Hubbard broilers kept under commercial conditions. A total number of 60,000 animals was divided into three treatment groups. The first group of 15,000 animals was vaccinated at day 0 with a comparable vaccine of a different manufacturer, whereas the second and third group of 17,000 chicks each were vaccinated with the test item the same day. At day 21, the

chickens of the third group were re-vaccinated with the test item, whereas the other two groups were left unvaccinated at that time.

The study was categorised as a randomised, controlled field study conducted in accordance with VICH GL 9 Good Clinical Practice (GCP), EMEA/CVMP/VICH/359665/2005 Guideline on target animal safety for veterinary live and inactivated vaccines and applicable local and/or regional regulatory requirements. The study was considered valid since it was neither affected by serious technological disturbance nor overlaid by intercurrent disease, which might have negatively impacted the evaluation of examined parameters.

No concomitant treatment was applied within the frame of the study.

The efficacy was evaluated by measurement of the NDV-specific serum antibodies via HI test at different times during the study. High and homogenous levels of NDV HI antibody titres were detected in day-old chicks (mean titre 7.3 $\log_2$). The HI titres gradually decreased in all groups until day 21. In both IVMP vaccinated groups, however, the percentage of seropositive animals in the group vaccinated with Vaxxon ND clone was 53.3% (with a cut off value of HI 4.0 $\log_2$). The percentage of seropositive animals decreases in this group to 36.6 % at day 42 and 16.7% at day 54. As revaccination at day 21 cannot be recommended in the absence of any safety data in SPF animals, the results of the group vaccinated twice with the vaccine is not further considered. The relatively low percentage of seropositive broiler chickens (even if higher, according to the available field data, compared to the layers results) is addressed by a corresponding warning under section 3.4 of the SPC as mentioned above.

Overall conclusion on efficacy

The onset of immunity is demonstrated at 21 days post vaccination according to laboratory studies performed with SPF animals. The laboratory studies performed in MDA+ layer and broiler chickens in principle confirmed the defined onset of immunity. However, they were conducted at a time when the control animals were still protected by MDA to a high level at challenge as the protectivity of the measured levels of MDA at challenge was underestimated. This underestimation is considered to be based on the biological variability of serology related protection.

The duration of immunity could be considered demonstrated in a laboratory study with layer SPF chickens for 10 weeks after vaccination for layers and in a study with broiler SPF chickens for 8 weeks for broilers. Some adverse events (stunting, ruffled feathers) observed in one duration of immunity study after vaccination are reported in the SPC.

Field data (serological response after vaccination measured by HI test, cut off value 4 $\log_2$) suggest some negative influence of MDA on the development of immunity after one vaccination in broilers.

The same is applicable also to layers where the field trial results show an interference of the MDA with the development of an active immunity.

The recommendation for re-vaccination in MDA positive chickens, as proposed by the applicant, cannot be accepted in the absence of any safety data in SPF animals on re-vaccination. Section 3.4 of the SPC was therefore modified as follows in order to reflect the possible reduced efficacy of Vaxxon ND Clone in commercial animals:

"Maternally derived antibodies (MDA) can significantly interfere with the development of active immunity."

Part 5 – Benefit-risk assessment

Introduction

Vaxxon ND Clone is an immunological veterinary medicinal product formulated as a lyophilisate and solvent for oculonasal suspension and intended for eye-drops application after reconstitution in the specific solvent or coarse-spray application (if diluted with water). The target species is chicken. The active substance is Newcastle disease virus (NDV), strain Clone, live. Vaxxon ND Clone is a refinement of the vaccine Izovac Clone that was licensed through a national procedure in Italy and in some countries outside the EU. Both vaccines contain the same active substance – Newcastle disease virus (NDV) strain Clone – but a different stabiliser. Following its registration in the EU through the centralised procedure, the national market authorisation for the predecessor of Vaxxon ND Clone will be withdrawn.

It is intended for the active immunisation of chickens from day one of age, by one administration to reduce mortality and clinical signs of disease caused by infection with NDV. The withdrawal period is zero days.

Vaxxon ND Clone is presented in packs containing 10 glass vials (type I) of 1,000 doses of the lyophilisate and 10 bottles (polyethylene) of 30 ml of solvent or 10 glass vials of 1,000, 2,000 or 2,500 doses of lyophilisate and contains the following concentration of the active substance per dose: 6.0-7.5 $\log_{10}$ ELD_{50} (ELD_{50}: embryo lethal dose 50%).

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 (full application).

Benefit assessment

Direct benefit

The benefit of the product is the reduction of mortality and clinical signs of disease caused by infection with Newcastle disease virus, a highly contagious disease that causes devastating losses in unvaccinated animals. The onset of immunity is demonstrated at 21 days post vaccination according to laboratory studies performed with SPF animals. The laboratory studies performed in MDA+ layer and broiler chickens confirm the defined OoI in principle. However, these were conducted at a time when the control animals were still protected by MDA to a high level at challenge and therefore the protection rates may partly be due to remaining MDA. In the context that the serological status of the chickens was examined prior to challenge and the control chickens protected at lower MDA levels than expected, it can be considered as difficult to draw a borderline at which HI titre level protection can be concluded for ND vaccination.

The DoI was demonstrated in a laboratory study with layer SPF chickens for 10 weeks after vaccination for layers and in a study with broiler SPF chickens for 8 weeks for broilers.

Field data (serological response after vaccination measured by HI test) on efficacy suggest that MDA may interfere with the development of active immunity and this is reflected in section 3.4. of the SPC.

Additional benefits

Vaxxon ND Clone is easy to apply to chickens from the first day of life via the oculonasal route by eye drop or coarse spray application.

Vaxxon ND Clone can be administered at an early age of the birds (1-day-old) at the hatchery to provide protection against early replication of virulent NDV. Accordingly, the high prevalence of clinical signs and mortality in case of infection can be reduced.

Vaxxon ND Clone increases the range of available treatment possibilities for the active immunisation of chickens against infections with NDV.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Therefore, the quality of Vaxxon ND Clone is considered adequately demonstrated.

Safety

Risks for the target animal

Administration of Vaxxon ND Clone in accordance with SPC recommendations is tolerated in broilers (study on safety for broiler chickens) and in layer chicken (evidence was provided in the study on spread and the comparative study of the MSV and the MSV+5). However, for broiler chickens the main reported adverse reactions after administration of a single maximum dose include 1 to 4 days of coughing (7 out of 10 broilers were concerned) and buccopharyngeal flutter for 1 to 2 days (2 out of 10 broilers were concerned). The potential for transient adverse effects such as described cannot be excluded after administration of a single maximum dose. Additionally, spraying seems to be a more critical route and the applicant justified further the safety of this route in broiler chickens.

The administration of a tenfold overdose in layers resulted in coughing and buccopharyngeal flutter for 1 to 3 days (in 4 out of 10 layers) and in coughing, buccopharyngeal flutter, nasal discharge or dyspnoea for 1 to 7 days (in 18 out of 20 broilers and 3 of them had to be euthanised for animal welfare reasons).

In the field studies, only limited adverse reactions after administration of a repeated commercial dose were noted in broiler chickens (repeated dose is not claimed and no corresponding preclinical study was provided, therefore no reference to a second dose was accepted in the SPC).

There are some safety matters observed in one duration of immunity study in 4 chickens (2 deaths in animals with signs of respiratory disease, neurological signs in 2 animals with a fatal outcome in one). These reactions were reflected in section 3.6 of the SPC because they cannot be excluded to be based on vaccination and especially as they were observed after administration of a minimum dose of vaccine.

Risk for the user

NDV strain Clone can cause a mild conjunctivitis in humans when contact to the eyes occurs. The excipients used in this product (lyophilisate and solvent) can be regarded as posing no risk for the user. A worst-case calculation for antibiotics used in the manufacture of the MSV is provided.

The lyophilisate is delivered in glass vials. Skin or eye contact may occur due to spillage during reconstitution or administration. A risk assessment concerning the use of needles for the transfer of solvent to the lyophilisate has been added as well. This transfer will only be performed by professionals; therefore, the risk is very low.

The user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment

The vaccine virus is shed with excretions and can remain infectious in the environment at least for 14 days. Spread to chickens was observed. No study is provided to assess the spread of the vaccine strain to non-target species. This is not obligatory but was considered for the warnings included in the SPC.

Vaxxon ND Clone is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

A residue study is not required. The withdrawal period is set at zero days.

Risk management or mitigation measures

The following measures are included in the SPC to minimise the above-mentioned risks:

- The vaccine strain is excreted by chickens for at least 14 days following vaccination.
- The vaccine strain can spread to unvaccinated chickens, but the spread does not induce clinical signs of disease and may lead to seroconversion. Special precautions should be taken to avoid spreading of the vaccine strain to other susceptible bird species.
- The personal protective equipment is specified (gloves and goggles / face shield).
- The vaccine strain can be found in the environment for at least 14 days. Adequate hygiene measures are recommended in the SPC.
- Possible adverse events are depicted in the SPC under section 3.6: Coughing, ruffled feathers, buccopharyngeal flutter and additionally head shaking and decreased activity may be noted after administration of a (maximum) single dose for 1 to 2 days. A reduced growth rate may be also noticed.
- Possible adverse events are depicted in the SPC under section 3.10: Coughing, buccopharyngeal flutter, nasal discharge, head shaking or dyspnoea may be observed following administration of a 10-fold overdose between day 3 and 10 p.v.

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, the environment, and consumer and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: *"For the active immunisation of chickens from one day of age to reduce mortality and clinical signs of disease caused by infection with Newcastle disease virus."* Whereas the product has been proven efficacious under laboratory conditions, the results of the field trials are reflected by including a warning (MDA interference) under section 3.4 of the SPC.

Information on development, manufacture and control of the active substance and finished product has been presented and leads to the conclusion that the product is expected to have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate

precautionary measures have been included in the SPC and other product information. The product has been shown to be efficacious and the claimed indications as proposed by the applicant can be supported.

Based on the data presented, the overall benefit-risk balance is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Vaxxon ND Clone is approvable, since the data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.