Paul-Ehrlich-Institut
Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines
Paul-Ehrlich-Str. 51-59
63225 Langen
Germany

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PRIMUN NEWCASTLE C30

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0273/001/DC
Name, strength and pharmaceutical form	PRIMUN NEWCASTLE C30 Lyophilisate for suspension for chickens
Applicant	LABORATORIOS CALIER, S.A. c/ Barcelonès, 26 Pla del Ramassar 08520 LES FRANQUESES DEL VALLES (Barcelona) SPAIN Tel.:+34 93 8495133 E-mail: laboratorios@calier.es
Active substance	Newcastle disease virus, live, strain CLS
ATC Vetcode	QI01AD06
Target species	chickens
Indication for use	For the active immunization of chickens against Newcastle disease (ND) to reduce clinical signs and mortality. Onset of immunity after a single administration: 3 weeks after 1st vaccination. Duration of immunity in future layers: up to 10 weeks of age (after 2 administrations at day 1 and day 21). Duration of immunity in broilers: up to 6 weeks of age (after 2 administrations at day 1 and day 21).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	02/05/2018
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	ES, IT, PL, PT

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.

The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 6.0 - 7.0 $\log_{10}$ EID_{50} (50% embryo-infective dose: the virus titre causing infection in 50% of the embryos inoculated with the virus) of the live Newcastle disease virus (NDV), more exactly the lentogenic strain NDV_CLS. The excipients of the vaccine are listed below:

- Disodium phosphate
- Potassium dihydrogen phosphate
- Lactose monohydrate
- Skimmed milk powder
- Water, highly purified

The container/closure system are type I glass vials of 10 ml, closed with bromobutyl rubber stoppers and sealed with aluminium caps with a bottle green lid. The particulars of the containers and controls performed are provided and conform to the regulation.
The choice of the vaccine strain and formulation are accepted. Neither adjuvant nor preservative are included in the vaccine which is justified.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.
The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is the live Newcastle disease virus (NDV), lentogenic strain NDV_CLS, an established active substance described in the European Veterinary Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.
The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.
Starting materials of non-biological origin used in production comply with pharmacopoeia monographs or in-house specifications.
Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. and EMA guidelines; any deviation was adequately justified.
The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Control tests during production

The tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided.

E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular appearance, pH, residual moisture, vacuum, freedom of extraneous agents and freedom of mycoplasmas, identification, viral titration, and sterility/microbiological examination.

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions for 2 years.
The in-use stability of 2 hours of the reconstituted vaccine according to directions for use is supported by the data provided.

G. Other Information

The manufacturing of this live vaccine is well described, and conditions of transport and handling are also clearly indicated.

III. SAFETY ASSESSMENT

To demonstrate the safety of all three routes of administration with a tenfold overdose and the repeated vaccination of one dose, the same vaccine batch was used for the laboratory safety studies. The batch has been produced according to registered production processes and contained the maximally approved virus titre. For the additional safety studies for ND vaccines as required by Ph. Eur. monograph 0450 (Newcastle disease) respective for live virus vaccines like “increase of virulence”, ”intracerebral pathogenicity”, “spread and dissemination in the body” and “demonstration that vaccine strain is admissible for the vaccination against ND disease” by amino-acid sequencing, experimental vaccine batches were used, which were produced in line with the outline of production for PRIMUN NEWCASTLE C30 with the deviation that the working seed virus was used directly for the propagation of the vaccine virus as seed material.
For the field trials a batch obtained from the standard production run has been chosen. The virus titre of this batch lies in the mid-range of the registered titre specification.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated by laboratory studies performed under GLP conditions. In different studies the safety was tested for all three routes of vaccine administration. The studies to demonstrate the safety of one dose and the repeated administration of one dose have been combined in one study for each route of administration, which is acceptable. The vaccine was applied in one-day-old SPF chicks (minimum vaccination age). The observation period was 14 days after administration of the vaccine. Each bird was marked individually. The groups were housed separately in brooders. The daily observation was protocolled and the observation results were scored by a scoring index from 0 = healthy - No clinical signs up to 3 = mortality tracheitis. In addition, all birds were weighed at the start, during and at the end of the study. During the whole 14 days observation period, in all laboratory studies for one dose and overdose performed in SPF chicken, no clinical signs related to the vaccination were observed.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended, the specific Ph. Eur. Monograph 0450 (attenuated live vaccines for Newcastle disease) and the relevant guidelines.

No investigation of effect on reproductive performance was conducted; therefore the use of the vaccine is not intended for breeders and laying birds within 4 weeks before the start of lay.

From the studies performed to demonstrate the efficacy and safety of PRIMUN NEWCASTLE C30 no data were found suggesting that this product might adversely affect the immune system of the vaccinated animal. Therefore, a specific study was not carried out.

For the attenuated live virus strain included in the vaccine, specific studies were carried out to describe the spread, dissemination, reversion to virulence and the testing of the intracerebral pathogenicity index of the vaccine strain.

It was demonstrated that no reversion to virulence is to be expected during multiple passages in the target host animals, as in the third passage group of the study no more virus could be detected and the study group of the additional safety study, which received a virus inoculum from the harvest of the second passage group, stayed healthy during the 14 day observation period after the inoculation of the “passage 2” virus harvest.

In another study the spread and dissemination in the body was investigated. The dissemination in the body was demonstrated by positive PCR-testing of different organ samples, cloacal and oropharynx swabs, obtained from the vaccinated chickens. The respiratory tract must be considered the main virus excretion route although virus excretion via faeces cannot be excluded. Spread of the vaccine strain from vaccinates into the environment and to unvaccinated chickens and susceptible birds of other species, if they are in direct or indirect contact with the vaccinated flock, is possible at least for 10 days after the vaccination.

A respective warning and instructions to minimise the risk of spread to unvaccinated birds are included in the SPC.

The requirement for the intracerebral pathogenicity test is that the pathogenicity index per group may not be higher than 0.5. The results in this test performed with this product are 0.2 and 0.1 for the test groups. Thus, the product passed the requirement for pathogenicity testing.

No specific assessment of the interaction of this product with any other medicinal product was made. The SPC section 4.8 wording is chosen respectively.

Field studies

Three studies, carried out according to the principles of Good Clinical Practice (GCP), have been performed to demonstrate the safety of the vaccine under field conditions. The first and second trial was performed in one day old broiler chicken. The first was performed with a single vaccination by spray. The second trial was performed with a second vaccination via drinking water three weeks later. The third trial was performed in one day old pullets. In the three trials the vaccination was performed with a commercial standard vaccine batch (batch virus titre 6.5 log10 EID_{50}/dose) at the first day of life via spray administration. The revaccination of the pullets three weeks later was performed via drinking water. In both trials the birds additionally underwent the ordinary vaccination program used on the farm.
Observation was performed daily from day 2 to day 28 in the first broiler study and up to day 42 in the second broiler study. In the study with pullets the daily observation was performed up to day 70.
The compiled parameters refer to clinical signs after vaccination, mortality and feed conversion ratio.

In all three field trials some chickens developed slight respiratory signs 7-10 days after the vaccination. All animals went into complete remission in about five days.

The production parameters of the flock, like mortality rate, body weight increase and feed conversion rate showed no particularities in comparison to the expected mean parameter results from the broiler and pullet rearing production.

The slight respiratory signs which were observed a few days after vaccination in the pullet trial are incorporated adequately in the wording of SPC section 6.

Environmental Risk Assessment

The vaccine strain is not considered to be significantly pathogenic for humans but it can be transmitted to humans as well. NDV manifestations in humans are limited to conjunctivitis and the recovery is usually rapid. It is known from literature that lentogenic NDV is not able to replicate in mammalian hosts. No risks to human safety associated with the widespread use of the vaccine have been identified. In addition, the product literature contains adequate instructions for self-protection for the person(s) who vaccinate(s) the flocks.
The spread and dissemination of the vaccine was studied. An excretion of vaccine virus has been demonstrated. High virus concentrations could be detected in the respiratory tract of animals and virus was also detectable in small concentrations from cloacal swabs.
The vaccine strain is lentogenic and the virus concentration detected from cloacal swabs was low.

The main risk for the environment was identified as the spreading of dung and slurry in the fields. This risk can be excluded by pre-storage of these waste materials for two months in summer and 3 months during winter. Therefore, the product is not expected to have any significant adverse effects on the environment.

The risk for spread of the vaccine strain into the food chain is negligible.
In the increase of virulence study it was demonstrated that virus seed material for PRIMUN NEWCASTLE C30 could not be detected in both, brain tissue or in tracheal mucosa tissues of the third passage. These data suggest that the vaccine strain does not revert to virulence when passaged in a host animal.
The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the safety of the product for humans and the environment is acceptable.

IV. EFFICACY

IV.B Clinical Studies

Laboratory trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements, which show that the vaccine can be used for active immunisation of one day old chickens against Newcastle Disease (ND) and to reduce clinical signs and mortality caused by the disease.

Onset of immunity is 3 weeks after vaccination. The duration of immunity in broilers is 6 weeks and in future layers 10 weeks. The vaccination scheme is the same for both production types: first vaccination on day 1 and revaccination on day 21 of life.

To determine the onset of immunity SPF chickens were vaccinated with the proposed minimum dose of PRIMUN NEWCASTLE C30 via spray, oculonasal instillation or in drinking water in different groups. An unvaccinated control group was included.
Efficacy of vaccination was demonstrated by intramuscular infection with a virulent ND Herts (Weybridge 33/56) strain as required by Ph. Eur. Monograph 0450. After challenge 21 days after vaccination 90% of vaccinated chickens survived and showed no clinical signs of Newcastle disease. All control chickens died. Therefore, the studies fulfil the requirements of Ph. Eur. Monograph 0450. Onset of immunity was determined with 3 weeks after vaccination.

An additional laboratory study was performed to examine the influence of maternal derived antibodies (MDA) on the efficacy of the vaccine. Several MDA-positive animals were vaccinated with different doses of the vaccine on day 1 and day 21 via oral application. Unvaccinated control groups with or without MDAs were included. Antibody titre development was monitored throughout the trial. An influence on the development of protective antibodies after vaccination due to MDAs was noted. An appropriate warning was included in the SPC.

Field trials

The applicant has performed three combined safety and efficacy field studies; two in broilers and one in future layers. All field trials were performed in Italy. The animals were vaccinated under field conditions and monitored for general health and zootechnical parameters (mortality, body weight, feed conversion ratio, serology).

In the first field trial broiler chicks were vaccinated on their first day of life. The birds were challenged with a virulent NDV Herts strain (Weybridge 33/56) in a laboratory facility to assess the duration of immunity. Unvaccinated controls were included. Unfortunately, a higher dose than required was chosen and the trial failed to prove duration of immunity after a single vaccination.

For the second field trial in broilers were vaccinated with PRIMUN NEWCASTLE C30 via coarse spray. The vaccination was repeated 22 days after the first administration of the vaccines via drinking water.
On day 40 of the study blood sampling for serology was performed and a commercial ELISA kit used for evaluation. On day 43 of the study randomly chosen animals were brought to a laboratory facility and challenged with a virulent NDV Herts strain (Weybridge 33/56) to assess the duration of immunity. Unvaccinated controls were included. 90% of the birds vaccinated in the field were protected against challenge. All control chickens died. A detailed statistical analysis was provided. Duration of immunity for broilers of 6 weeks after two vaccinations on day 1 and day 21 was confirmed.

The field trial with future layer chickens followed the same study scheme as the second field trial: birds were vaccinated with PRIMUN NEWCASTLE C30 on day 1 via coarse spray and a second time on day 21 via drinking water. General health and zootechnical parameters were monitored (mortality, body weight, feed conversion ratio, serology). On day 70 of the study randomly chosen birds were challenged intramuscularly with a virulent NDV Herts strain (Weybridge 33/56) in a laboratory facility. Unvaccinated controls were included. 95% of the animals vaccinated in the field were protected from challenge. All control chickens died. Duration of immunity for future layers of 10 weeks after two vaccinations on day 1 and day 21 was confirmed.

No field infections with Newcastle Disease were noted during the trials.

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit-risk profile for the target species is favourable and the quality, safety and efficacy of the product for the target species chickens, humans and the environment is acceptable.