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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Vectormune ND (EMEA/V/C/003829/II/0007)

Common name: Marek's disease (live) & Newcastle disease vaccine (inactivated recombinant)

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, CEVA-Phylaxia Veterinary Biologicals Co. Ltd. (the applicant), submitted to the European Medicines Agency (the Agency) on 23 June 2017 an application for a type II variation for Vectormune ND.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

to add a new category of target species -layer chickens and to precise the current indication. This application relates to the following sections of the current dossier held by the Agency:

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 3 and Part 4

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific overview

Vectormune ND is a bivalent, cell associated, live vector vaccine developed for the active immunization of chickens to reduce mortality and clinical signs caused by Newcastle disease (ND) and to reduce mortality, clinical signs and lesions caused by virulent Marek's disease.

The vaccine contains one active ingredient: the modified live turkey herpes virus (rHVT/ND) which is a recombinant serotype 3 Marek's disease virus (MDV) (also called Meleagrid Herpesvirus 1). It was constructed using the FC-126 HVT vaccine strain as a vector, genetically modified to express the immunogenic Fusion (F) gene of Newcastle disease virus (NDV). The parent MDV strain (FC-126) is naturally avirulent and has already been used to prepare vector vaccines for chickens.

The vaccine is cell-associated and is presented as frozen suspension for injection in sealed ampoules which has to be resuspended/diluted in a sterile solvent before in-ovo vaccination to 18 day old embryos or by subcutaneous vaccination of chickens from one day of age.

MDV is a contagious lymphoproliferative disorder of chickens and has been identified as a major cause of poultry mortality and production losses in many countries since its first description as polyneuritis by Josef Marek in 1907. It is present in all major poultry producing areas of the world.

The causative agent of MDV is a cell-associated Alphaherpesvirus called Gallid herpesvirus type 2 (GaHV-2), commonly called Marek's disease virus type 1 (MDV-1). Various live vaccines have been used throughout the world to control MDV. Vaccines are either cell-associated or cell free preparations. Cell-associated vaccines are known to be more efficacious in the presence of maternally derived antibodies against MDV.

NDV causes highly contagious disease in chickens that leads to substantial economic losses in the poultry industry worldwide. In Europe between 2005 and 2009, 230 ND outbreaks have been reported in 13 countries. Besides general biosecurity measures in commercial poultry facilities, the major tool in the prevention of ND, is vaccination. Several live and attenuated vaccines are available. In live vaccines, lentogenic strains (for example Hitchner Bl) are used. According to the current practice it is considered that to protect chickens against ND live vaccines offer the best protection when administered to chicks on the day of hatching.

In Vectormune ND the insertion of the immunogenic F gene of NDV the rHVT/ND strain is capable to induce an immune response against NDV, while the original biological and immunological properties of the parent Fc-126 strain were attained.

The vaccine is already registered in the European Union for the vaccination of broiler type chickens (License number: EU/2/00/000/001-003) and in several other countries all around the world.

In the frame of the present variation the applicant wishes to introduce the use of Vectormune ND on layer type chickens by subcutaneous vaccination.

Justification of the variation

ND is an economically important disease of poultry for which vaccination is applied as a preventive measure in many countries. According to the routine broiler and layer vaccination practice in countries where vNDV is endemic live lentogenic vaccines, chiefly B1 and LaSota strains, are used and typically administered to poultry by mass application via drinking water in the farm or by spray vaccination in the hatchery. The vaccination may be repeated between 14-28 days of age. The frequency of revaccination to protect chickens throughout life largely depends on the risk of exposure and virulence of the field virus challenge. Large layer flocks are also have to be vaccinated with inactivated NDV vaccines usually at 16-18 weeks of age but latest 3 weeks before start of the laying period.

Taking this common practice into consideration the applicant intends to extend the use of the Vectormune ND vaccine on layers. A single shot of vaccine in layers at one-day of age can provide immunity against ND up to 18 weeks of age. Further immunity may be maintained by vaccinating the birds with inactivated ND vaccines. Vectormune ND vaccine applied at the hatchery can also provide protection against virulent pathotypes of Marek's disease in the most susceptible age of chickens.

General requirements

During the preparation of the laboratory and field study protocols the following regulatory references were considered:

- Directive 2001/82 EC as amended
- Vaccines for Veterinary Use – Ph. Eur.0062

- Evaluation of safety of veterinary vaccines and immunosera – Ph. Eur. 5.2.6
- Evaluation of Efficacy of Veterinary Vaccines and Immunosera – Ph. Eur. 5.2.7
- Marek's disease Vaccine (Live) – Ph. Eur. 0589
- Newcastle disease Vaccine (Live) – Ph. Eur. 0450
- CVMP Guideline on Live Recombinant Vector vaccines for veterinary use (EMEA/CVMP/004/04-Final)
- Directive 2010/63/EU, Hungarian Act XXVIII/1998 and the Hungarian Governmental Decree No. 40/2013. (II.14.)
- EMA Guideline on statistical principles for veterinary clinical trials (EMEA/CVMP/816/00-FINAL)
- EMA Guideline on field trials with veterinary vaccines (EMEA/CVMP/852/99-FINAL)

To support these new category of target species, one safety study (an overdose study to investigate the safety towards the reproductive tract five efficacy laboratory studies and one field study were carried out.

Studies were conducted in male and female birds although the vaccine will be given to day-old pullets for ethical reasons. No differences between the males and females are expected with regards to safety or efficacy results and therefore, the use of males in this variation is acceptable.

This is not a Minor Use or Minor Market (MUMS) product neither the proposed new type of target species qualifies it for a MUMS status.

No scientific advice was received for this variation.

2.1. Safety

Overdose study to investigate the safety towards the reproductive tract

To complement the original safety data package, a 10x overdose safety study was conducted to investigate whether the subcutaneous vaccination of day-old pullets could impact their reproductive physiology. The design of study was in accordance with the requirements laid out in the 589 monograph of the European Pharmacopeia (Ph. Eur. 589) for MDV vaccine (live). The study was also Good Laboratory Practise (GLP) compliant.

Forty two specific pathogen free (SPF) Babcock chickens (n=42) (Group 1) were administered with 0.2 ml of Vectormune ND with the highest titre of the least attenuated passage of the vaccine strain to be included in the final product, in compliance with the Ph. Eur. 526 monograph for evaluation of safety of veterinary vaccines and immunosera.

The birds were monitored over 120 days and compared to a positive control group (Group 2) to demonstrate the susceptibility of the flock to MDV and also to a negative control group administered with the sterile diluent (Group 3).

The safety parameters investigated were clinical signs over the course of the monitoring time and pathological and histological lesions of the oviduct and testis at the completion of the study.

Results:

In the positive control group (Group 2), 95% of the birds died and were MDV positive.

In chickens of Group 1 (vaccinated ones) there were no clinical signs of disease or disability in any birds except one which died due to trauma in the cervical region during vaccination. There were no injection site reactions. No lesions were found in the 10 oviduct and 10 testis sampled.

In conclusion, the vaccine was found safe after subcutaneous use in day old lay chickens at a tenfold dose and complied with Ph. Eur. 589 safety criteria.

Safety field trial

A field trial was performed with 10470 commercial day old birds vaccinated with Vectormune ND. Results from the observed zootechnical parameters as well as clinical observations confirmed that there was no negative impact from the vaccination in relation to safety (see summary below).

2.2. Efficacy

Altogether, five laboratory efficacy studies (including 2 complementary laboratory studies in accordance with EMA's guideline on field trial with veterinary vaccines) and one field study were carried out in chickens intended to be used as layers in the future). Conventional birds with maternal derived antibodies (MDA+) at the youngest recommended age (Day 0) were vaccinated by the subcutaneous route at the minimum protective dose authorized for the final product (2500 PFU/dose). The batches used in the efficacy were made with the virus at Master Seed Virus which is the maximum passage authorized, in compliance with Ph. Eur. 526.

No new efficacy studies were performed on SPF birds as these studies had already been conducted and presented in the original dossier and results were considered applicable also for the present variation. Moreover, the studies in MDA+ birds represent the worst case scenario for investigating efficacy. Therefore the use of conventional birds was considered acceptable.

2.2.1. Efficacy in layers against Newcastle disease

ND efficacy (3 weeks onset of immunity (OOI)) test of Vectormune ND vaccine on layer chickens after subcutaneous vaccination

The objective of the study was to investigate the efficacy of the Vectormune ND vaccine against a NDV challenge in layer chickens 3 weeks after subcutaneous vaccination. The design of this study was in accordance with the Ph. Eur. 450 monograph requirements on live ND vaccines with the exception that conventional birds were enrolled.

Conventional Hy-Line one day-old chickens (n=24) were vaccinated by the subcutaneous route and challenged on day 21 with 5x 10^5 EID_{50} of the virulent ND strain Hert 33/56. Negative control conventional chickens (n=12) were left unvaccinated (Group 2) as well as anon vaccinated control SPF chickens (n=12) (Group 3).

Results:

No local or general adverse reactions were noticed following vaccination.

Conventional birds had high MDA titres (ELISA) against both NDV and MDV on Day 0, with respectively 10583 and 56297 mean ELISA titres (Group 1 and 2).

The challenge was severe enough given that all the SPF birds of the Group 3 control group died within 4 days following the challenge.

In the non-vaccinated layer control group 66.7% (Group 2) of the birds were unaffected by the challenge while 96% of the vaccinates were protected (no clinical signs) for up to 2 weeks post challenge.

On the basis of the above results it was considered that the protection afforded by the vaccine met the indication of reduction of mortality and clinical signs at the onset of immunity as proposed in the SPC and that vaccination increased the 67% protection afforded by MDA up to almost a full protection.

ND efficacy (18 weeks duration of immunity) test of Vectormune ND vaccine on layer chickens after subcutaneous vaccination

The objective of the study was to investigate the efficacy of Vectormune ND vaccine against NDV challenge in layer chickens for the proposed duration of immunity, 18 weeks after subcutaneous vaccination. The design of study was in accordance with the Ph. Eur. 450 monograph on live ND vaccines with the exception of the use of conventional birds in the study.

Twenty four conventional Hy-Line day-old chickens (n=24) were vaccinated by the subcutaneous route and challenged on day 126 with 5x 10^5 EID_{50} of the virulent ND strain Hert 33/56. A negative control group with conventional chickens (n=12) was left unvaccinated (Group 2), as well as a non-vaccinated control group with SPF chickens (n=12) (Group 3).

Results:

No local or general adverse reactions were noticed following vaccination.

Conventional birds had high MDA titres (ELISA) against both NDV and MDV on day 0, (10583 and 56297 ELISA titres for Groups 1 and 2 respectively).

Vaccinated birds already seroconverted to NDV at day 39 by comparison to the non-vaccinated conventional control group and reached a mean titre of 10722 on day 126.

All birds from both control group died after challenge whereas all the vaccinates were protected (no clinical signs) for up to 2 weeks post challenge.

As a result of the above, duration of immunity of 18 weeks was regarded demonstrated for the vaccine in compliance to the Ph. Eur. 450 monograph efficacy criteria.

2.2.2. Efficacy in layers against Marek's disease

One OOI study was conducted to determine the immunogenic effect of the Vectormune ND vaccine against Marek's disease in layer chickens.

Marek's disease efficacy test of Vectormune ND vaccine on layer chickens with MD70 challenge after subcutaneous vaccination

The objective of the study was to investigate whether Vectormune ND met the indication for a NDV protection following challenge in layer chickens at the OOI. It should be noted that the proposed OOI by the applicant for NDV was 1week but vaccination by subcutaneous route in this study was 9 days. The design of study was in accordance with the Ph. Eur. 589 monograph regarding MDV vaccine with the exception that conventional birds were enrolled in the study.

Thirty five conventional Hy-Line day-old chickens (n=35) were vaccinated by the subcutaneous route and challenged on day 8 by peritoneal injection of 20 PFU of an MDV strain (MD70). A negative control group of conventional chickens (n=35) was left unvaccinated and another control group with SPF

chickens (n=35) was also left unvaccinated (Groups 2 and 3 respectively).

Results:

No local or general adverse reaction was noticed following vaccination.

Conventional birds had high MDA titres (ELISA) against Marek's disease on day 0 (mean ELISA titre = 105,834).

Over the 70 days of observation, 4 vaccinates and 33 birds from each control group were diagnosed as MDV positive (based on clinical signs and/or lesions).

The Ph. Eur. 589 efficacy criteria regarding the achievement of a relative protection percentage of 87.9%.was met. As a result the claimed OOI of seven days can be accepted despite that challenge was performed at day 9 post vaccination. This is because results of another OOI study in SPF chicks, with a challenge at day 7, which was part of the original registration file for Vectormune ND are also supportive.

2.2.3. Efficacy field trial

Field safety and efficacy trial of Vectormune ND vaccine in layer pullets

The field trial was carried out in a Hungarian farm in compliance with Good Clinical Practise (GCP) requirements. Hy-Line commercial layer chickens were vaccinated at one day of age, at hatchery, either with Vectormune ND (n= 10470) Group 1 or Nobilis ND C2 (n=10200) Group 2. Then the birds were moved to the pullet farm in 2 separate hen houses corresponding to the 2 types of vaccinates. Some birds from those groups enrolled in two complementary laboratory challenge studies that will be described later in the report.

A supplementary MDV vaccination with Nobilis Rismavac + CA126 was administered to both groups to protect them against very virulent Marek's disease strains. This supplementary vaccination prevented the investigation of the protection of Vectormune ND against any Marek's disease field outbreaks. A normal vaccination schedule was applied afterwards.

Results:

No MDV or NDV outbreaks were detected by PCR from samples taken from both groups during the observation period (days35, 66, 102) and upon completion (day 118).

The safety following Vectormune ND vaccination was corroborated by a mortality rate within the normal range (~ 0.8%) the week after vaccination. No differences were reported between the two vaccinated groups for body weight. Finally, no local reactions were reported following vaccination with Vectormune ND.

Serology results indicated that NDV antibodies remained high throughout the trial.

ND efficacy test of Vectormune ND vaccine in layer chickens after subcutaneous vaccination complementary to field trial

The objective of this complementary study was to investigate the efficacy of Vectormune ND vaccine against a NDV challenge in layer chickens 3 weeks after the OOI in laboratory conditions. This investigation was performed as a complementary efficacy test to the field trial described above. The design of this study was in accordance with the Ph. Eur. 450 monograph on live Newcastle disease vaccines with the exception of the fact that commercial birds were enrolled in the study.

Twenty two day - old chickens from the hatchery (n=22) were moved to the laboratory and challenged on day 21 with 5 10^5 EID_{50} of the virulent NDV strain Hert 33/56 (Group 1). An MDA positive control group of chickens from the same hatchery (n=12) that were left unvaccinated was used (Group 2) as well as a control SPF chicken group (n=12) (Group 3).

Results:

No local or general adverse reaction was observed following vaccination.

Birds had high MDA titres (ELISA) against NDV (mean ELISA titre = 14511).

The challenge was severe enough given that all the SPF birds of the control group died within 4 days further challenge.

In the conventional unvaccinated control group all birds died whereas all the vaccinates were protected (no clinical sign) for up to 2 weeks post challenge.

In conclusion, the vaccine was shown to be efficacious in commercial chickens with MDAs against NDV, under laboratory conditions and in compliance with the efficacy requirements of the Ph. Eur. 450 monograph.

Marek's disease efficacy test of Vectormune ND vaccine in layer chickens after subcutaneous vaccination complementary to field trial

The objective of the second complementary study was to investigate the efficacy of Vectormune ND vaccine against a MDV challenge in layer chickens two days after the OOI when the susceptibility to the disease is maximal under laboratory conditions. This trial was performed as a complementary to the field trial described earlier in the report.

Thirty three day-old chickens from the hatchery (n=33) were moved to the laboratory and challenged on day on day 9 by peritoneal injection of 20 PFU of an MDV strain (MD70) (Group 1). A negative control group of chickens from the same hatchery (n=33) was left unvaccinated (Group 2) as well as another control group that remained unvaccinated with SPF chickens (n=33) (Group 3).

Results:

No local or general adverse reactions were observed following vaccination.

Conventional birds had high MDA titres (ELISA) against Marek's disease on day 0.

Over the 70 days of observation, two vaccinates and 31 birds from the MDA positive control group 2 and 27 from the SPF control group 3 were diagnosed MDV positive (either had clinical signs and/or lesions recorded).

In conclusion, the vaccine was shown to be efficacious in commercial chickens with MDAs against MDV under laboratory conditions and in compliance with the Ph. Eur. 589 efficacy criteria achieving a relative protection of 93.5% with an OOI of 7 days. Although challenge was performed at day 9 after vaccination; the 7 day OOI was originally supported by another OOI study in the original dossier.

Overall conclusion on the variation

Vectormune ND met the criteria of the Ph. Eur. monograph regarding safety for veterinary vaccines, when injected to pullets at the lowest age of administration with a vaccine at its maximum of potency.

Results from efficacy laboratory studies with Vectormune ND, as well as results from two laboratory

studies that were complementary to the efficacy field trial, met the efficacy criteria of both Ph. Eur. 450 (NDV OOI and duration of immunity) and Ph. Eur. 589 (MDV OOI) monographs respectively. Thus these results corroborate those obtained with broilers and justified to extend the duration of NDV immunity.

3. Benefit-risk assessment of the proposed change

This product is authorised for the active immunisation of 18 day-old embryonated chicken eggs or one-day-old chicks to reduce mortality and clinical signs caused by NDV and to reduce mortality, clinical signs and lesions caused by MDV.

The OOI against ND is 3 weeks of age and the duration of immunity against NDV was satisfactorily shown to be18 weeks of age. The OOI against MDV was claimed at 1 week of age although challenge in both MDV studies was performed at 9 days post vaccination. The claimed OOI of 1 week is however supported by the results of the OOI study in SPF chicks, with a challenge at day 7, which was part of the original registration file for Vectormune ND. Duration of immunity against MDV is a single vaccination that is sufficient to provide protection during the risk period of infection.

The vaccine is for in-ovo and subcutaneous use and is presented in Type I glass ampoule containing 1,000, 2,000 or 4,000 doses of the vaccine with solvent.

The proposed variation is to add a new category of target species -layer chickens and to precise the current indication. The variation also includes a slight rewording of the current indication against Marek disease specifying that it the vaccine works against a virulent MDV.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of this variation is the extension of the use of the product to a new category of the target species, that is laying hens and to subsequently extend the duration of immunity against NDV up to 18 weeks.

The benefit was established in well-designed laboratory and field studies conducted to an acceptable standard.

Additional benefits

None.

3.2. Risk assessment

No change to the impact of the product is envisaged on the following aspects: quality, safety and efficacy.

3.3. Risk management or mitigation measures

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 animals, user, environment and consumer and to

provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety and consumer safety. The benefit of this variation relates to efficacy and the extension of the use of the product to a new subgroup of the target species, that is laying hens and extend the duration of NDV up to 18 weeks.

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

4. Conclusion

Based on the original and complementary data presented on safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Vectormune ND can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follow:

The proposed variation is to add a new category of target species -layer chickens and to precise the current indication. The variation also includes a slight rewording of the current indication against Marek disease specifying that it the vaccine works against a virulent MDV.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.