EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 May 2022
EMA/601045/2022
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Vectormune ND (EMEA/V/C/003829/VRA/0016)

Vaccine common name: Newcastle disease and Marek's disease vaccine (live 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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Ceva-Phylaxia Co. Ltd (the applicant), submitted to the European Medicines Agency (the Agency) on 28 February 2022 an application for a variation requiring assessment for Vectormune ND.

1.2. Scope of the variation

Variation(s) requested		**Type**
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	VRA_2

to add the compatibility claim on the simultaneous use of Vectormune ND with Cevac Rispens vaccine.

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 2, Part 3 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

2.1. Introduction

Vectormune ND is a live vector vaccine authorized in the European Union (EU) to reduce mortality and clinical signs caused by Newcastle Disease Virus (NDV) and Marek's Disease Virus (MDV). The active ingredient is a modified live turkey herpes virus (HVT) with an inserted Fusion (F) gene of NDV. The vaccine is intended to be administered *in ovo* to 18-day-old embryos or by subcutaneous vaccination of chickens at one day of age. The solvent approved to be used with this vaccine is Cevac Solvent poultry.

Cevac MD Rispens is a monovalent, cell associated, live MDV vaccine, which is authorized by decentralized procedure in 25 EU member states for the active immunization of chickens to reduce mortality, clinical signs and lesions caused by MDV of very virulent pathotype. Its active ingredient is

a live attenuated CVI-988 serotype 1 MDV. This vaccine is also cell associated and has to be resuspended in the Cevac Solvent poultry, as Vectormune ND. The vaccine is recommended for subcutaneous vaccination of one-day-old chickens.

The compatibility claim of the vaccines has already been approved for Cevac MD Rispens.

This variation intends to add the compatibility claim to modify the product information of Vectormune ND by adding the compatibility claim for the simultaneous use with Cevac Rispens vaccine. The proposed solvent for the simultaneous administration is the Cevac Solvent Poultry, which is the approved diluent of both vaccines. The proposed route and age for the associated use was selected according to the approved indication that the vaccines have in common. Based on Cevac Rispens vaccine indication this is the subcutaneous administration at one day of age.

To shore up the compatibility claim, the applicant has conducted 4 laboratory studies and 1 field trial to demonstrate the quality, safety and efficacy of the mixed use in accordance with the EMA guideline EMA/CVMP/IWP594618/2010.

2.2. Quality

To support the quality of the simultaneous application, in-use shelf life of the mixed vaccines was investigated in 2 studies where the titre loss of the 2 vaccines over 2 hours was within the range of the vaccines used separately.

2.3. Safety

Target animal safety

A pre-clinical study and a field trial are provided.

A Good Laboratory Practice (GLP) 10X overdose study was performed with both vaccines using the Master Virus Seed (MVS) and the MVS+1 seed material for Cevac MD Rispens and Vectormune ND respectively. The study design was in line with Ph Eur 0589 (Marek's disease Vaccine (Live)). Three groups of chickens (42 per group) were subcutaneously (sc.) administered at one-day of age (the most susceptible category for the mixed use) with either the mixing of the 2 vaccines, the diluent or the highly virulent MDV-1 strain RB1B (by intraperitoneal route). To assess the safety of the association, clinical signs were monitored over 120 days (70 days for RB1B group and 14 days for the placebo) as well as local reactions at the injection site and macro- and microscopical lesions. The study complied to Ph Eur 0589 criteria since no birds died in the mixed use group and RB1B strain caused death or MDV typical clinical sign or lesions in more than 70% of birds in the correspondent group. In the mixed use group, no histological lesions of the oviduct and testis were detected nor were alterations by inspection or palpation at the injection sites.

A Good Clinical Practice (GCP) compliant field trial, investigating both safety and efficacy was carried out in layer chickens. Birds were vaccinated either with Vectormune ND mixed with Cevac MD Rispens according to the proposed protocol or with Cevac MD Rispens by s.c. route and Cevac Vitapest L by the oronasal route (comparator group). No natural outbreaks were detected. Mortality, clinical signs, body weight gain and local reaction were monitored.
Over the 4 weeks following vaccination, the cumulated mortality ratio in the mixed vaccines group was not significantly different than in the comparator group 2.
No clinical signs were noticed over the course of the trial.
No local reactions, either visible, or palpable, were detected on 30 randomly selected chickens.
The body weight gain was similar over the course of all the trial.

Environmental Risk Assessment
The recombination or genomic reassortment of the strains when administered together has been addressed by the applicant. While the recombination is theoretically possible, its occurrence is very rare thanks especially to superinfection inhibition at the cellular level and if it would occur, it would be in the context of vaccinated flocks in which its spread is very unlikely. This frequency of occurrence is shored up by the epidemiology of the concurrent use of these vaccine strains throughout Europe and United States.

User & consumer safety
The amount of the excipients is doubled when the 2 vaccines are combined in the same solvent and they remain without any pharmacological activity.
With regard to trace amounts of antibiotics carried over from the manufacturing process, the calculation provided for the mixed administration taking into account the worst-case scenarios has shown that they are still below the maximum residue limit (MRL) values. Therefore, the mixing of Vectormune ND and Cevac MD Rispens vaccines has no further impact on the user safety.

In conclusion the mixed use of Vectormune ND and Cevac MD Rispens has been shown safe for the target birds as well as for the user, the consumer and the environment.

2.4. Efficacy

To demonstrate the efficacy of the mixed use, 3+1 preclinical studies and 1 field trial were conducted. In the preclinical studies, the vaccine batches were used at their maximum passage level and Vectormune ND was at the minimum dose (2500 PFU) while Cevac Rispens was at its maximum dose (5000 PFU).

The efficacy towards NDV was assessed in commercial layer pullets at the onset, 30 days after vaccination and the duration of immunity in line with Ph Eur 0450 while the one towards MDV was at onset in line with Ph Eur 0589.

In one study, the onset of ND immunity was investigated in one-day-old layer chickens following vaccination with Vectormune ND and Cevac MD Rispens vaccines by the subcutaneous route (Group 1). As controls, 12 non-vaccinated layer chickens and 12 SPF chickens were included.
Twenty-one days after vaccination, birds were challenged with the virulent strain Herts 33/56.
Birds had maternally derived antibodies at hatching (NDV ELISA titre: 10583 & MDV ELISA titre: 56297) except for the SPF controls.
PCR results from the organs sampled prior to vaccination were negative excluding an accidental NDV infection.
The test was valid as, four days after challenge, 100% of the SPF control chickens were dead and during the observation period before challenge no vaccinated or control chickens showed abnormal clinical signs or died from causes not attributable to the vaccine.
The vaccinated groups had a significantly higher clinical protection (100%) than the non-vaccinated MDA+ controls (66.7%).

The duration of immunity of Vectormune ND was investigated in another study. Day-old layer chickens (24) were vaccinated with Vectormune ND and Cevac MD Rispens vaccines by the subcutaneous route according to the proposed protocol. As controls, non-vaccinated layer chickens (12) and SPF chickens (12) were included.
Birds had maternally derived antibodies at hatching (NDV ELISA titre: 10583 ELISA units & MDV ELISA titre: 56297 ELISA units) except for the SPF controls.
PCR results from the organs sampled prior to vaccination were negative excluding an accidental NDV infection.

Birds were challenged 18 weeks after vaccination by Herts 33/56 NDV strain. All controls died, whereas all vaccinated birds survived without showing notable clinical signs of Newcastle disease.

The onset of protection against MDV after mixed vaccination was challenged 9 days after vaccination in another study.
One-day-old layer chickens were vaccinated on D0 by the subcutaneous route (Group 1) with a mixture of 2500 PFU Vectormune ND and 5000 PFU Cevac MD Rispens. Non-vaccinated layer and SPF chickens were also used as controls.
Birds had maternally derived antibodies at hatching (MDV ELISA titre: 105834 ELISA units) except SPF controls.
No clinical signs or mortality were observed in any of the groups during the period between the day of hatching and the challenge (D0-09).
All chickens were challenged on D9 by the intraperitoneal route with the MD70/13-4 MDV strain.
The percentage of birds which were infected by MDV was 94.3% in control groups and 0% in the vaccinated one.

A GCP compliant field trial, investigating both safety and efficacy, was carried out in layer chickens. Day-old chickens were vaccinated either with Vectormune ND mixed with Cevac MD Rispens (6000 birds) according to the proposed protocol or with Cevac MD Rispens by s.c. route and Cevac Vitapest L by the oronasal route (14000 birds of the comparator group).

The birds had very high anti-NDV maternally derived antibody level at hatching (average titre = 18,323 ELISA units) and 35% of them had anti-MDV antibodies.
No natural outbreaks were detected by PCR in organs sampled over the 104 monitoring days (D24, D54, D81 and D109).
The anti-NDV antibody titre plateaued from 54 days after vaccination onwards around 11000 mean ELISA unit.
Supportive efficacy data were obtained from complementary laboratory MD and ND challenges in line with Ph. Eur. respective monographs.
One of the studies is not included in this variation but was assessed within the Cevac MD Rispens authorisation procedure. In a nutshell, 94.3% of the vaccinated birds were protected from the challenge of the vvMDV-1 strain RB1B, while 2.9% of the non-vaccinated birds and none of the SPF were.

In the other study, birds from those included in the field trial were transferred just further vaccination to a laboratory (25 vaccinated and 20 control pullets) and challenged 30 days after with the Herts 33/56 NDV strain.
On the day of challenge infection (D30) 12 non-vaccinated layers and the 10 non-vaccinated SPF chickens were taken out for challenge by at-random selection from 20 birds of each group and challenged together with the 25 vaccinated birds. The control pullets had remaining anti-NDV maternally derived antibodies (mean ELISA titre = 3176 ELISA units) while the mean titre of the vaccinates was 5.576 and the titre of the SPF was below the positive threshold.
Non-vaccinates birds died or showed notable clinical signs of ND (100% protection) while all the SPF birds died. The non-vaccinated pullets had a significantly lower protection (72.7%) than the vaccinated ones ($p = 0.023$).

In conclusion, the associated use of Vectormune ND and Cevac MD Rispens vaccines has been shown efficacious in laboratory studies and as efficacious as a comparative association of vaccines in a field trial.

3. Benefit-risk assessment of the proposed change

Vectormune ND is a suspension and solvent for suspension for injection containing cell-associated live recombinant turkey herpes virus (rHVT/ND) expressing the fusion protein of Newcastle disease virus D-26 lentogenic strain (2,500 – 8,000 PFU/dose).

The vaccine is intended to be administered to 1-day old chickens and 18-days old embryonated chicken eggs to reduce the mortality and clinical signs caused by Newcastle disease virus and to reduce mortality, clinical signs and lesions caused by virulent Marek's disease virus.

The proposed variation is to add the compatibility claim on the simultaneous use of Vectormune ND with Cevac Rispens vaccine which has already been granted within the Cevac Rispens authorization. From the evidence provided by the MAH, the subsequent benefit/risk balance of the variation can be drawn.

3.1. Benefit assessment

Direct therapeutic benefit

The concurrent use with Cevac Rispens provides Vectormune ND with a protection extended to very virulent strains of MDV which increases its benefit.

3.2. Risk assessment

Quality:

The in-use shelf-life after mixing has been adequately addressed and is recommended within a period not exceeding 2 hours, as already stated in the product information.

Safety:

Risks for the target animal:

The risks toward the target animal associated with the mixing of the vaccines have been addressed in 2 studies in line with the current Ph. Eur. monographs and no conspicuous adverse events have been reported.
The risk of recombination has been assessed to be negligible.

Risk for the environment:

The risk that the strains or a recombinant strain spread in the environment has been assessed and considered as negligible.

Risk for the user and consumer:

The risks for the consumer and the user have been assessed and remain unchanged and negligible.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

3.4. Evaluation of the benefit-risk balance

The concurrent use with Cevac Rispens provides Vectormune ND with a protection extended to very virulent strains of MDV which increases its benefit.
The associated risks are negligible.
Therefore, based on the data presented, the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for a 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 (Regulation (EU). 2019/6), as follows:

This vaccine can be mixed and administered with Cevac MD Rispens by subcutaneous application.

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.

Changes are required in the following Annexes to the Union marketing authorisation.

I, IIIA and IIIB.

As a consequence of this variation, sections 4.8 and 6.2 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.