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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for worksharing type II variation (EMEA/V/C/WS1282)

Vaccine common name: feline calicivirosis vaccine, feline viral rhinotracheitis, feline infectious enteritis (feline panleucopenia) vaccine (live) and/or feline leukaemia vaccine (inactivated)

Product name	Application number and EU numbers
LEUCOFELIGEN FeLV/RCP	EMEA/V/C/000143/WS1282/0007 - EU/2/09/097/001-002
Nobivac LeuFel	EMEA/V/C/004778/WS1282/0001 - EU/2/17/217/001-002
LEUCOGEN	EMEA/V/C/000144/WS1282/0006 - EU/2/09/096/001-002

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, Virbac (the applicant), submitted to the European Medicines Agency (the Agency) on 20 December 2017 an application for a type II variation for the vaccines LEUCOFELIGEN FeLV/RCP, Nobivac LeuFel and LEUCOGEN.

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
Precise scope of the variation application:		
To modify the duration of immunity of the feline leukaemia component. The applicant takes the opportunity to align the product information of the vaccines LEUCOGEN, LEUCOFELIGEN FeLV/RCP and Nobivac LeuFel with the latest QRD template.		

To modify the duration of immunity of the feline leukaemia component.

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 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The applicant intends to introduce a longer duration of immunity for the feline leukaemia component of the three vaccines: LEUCOFELIGEN FeLV/RCP, LEUCOGEN and Nobivac LeuFel. Therefore, the applicant performed an additional study with the largest combination (LEUCOFELIGEN FeLV/RCP) in order to assess the long-term efficacy of the feline leukaemia virus (FeLV)-derived component. This study also supports the long-term efficacy of LEUCOGEN and Nobivac LeuFel in line with the CVMP Guideline Requirements for combined vaccines and associations of immunological veterinary medicinal products (CVMP/IWP/594618/2010) as the FeLV-derived component and adjuvants are identical in all three products and it is only the number of active ingredients which is different.

The new duration of immunity study (Study F-134.160000-58011) is described below:

Study design:

Thirty-three cats aged 9-10 weeks, seronegative against FeLV, were included in this study and divided into three groups:

(Group 1) LEUCOFELIGEN FeLV/RCP primary + boost group consisted of 17 cats which were vaccinated with LEUCOFELIGEN FeLV/RCP on Days 0 and 21, and then 13 months after the second vaccination on Day 21.

(Group 2) LEUCOFELIGEN FeLV/RCP primary group consisted of 5 cats which were vaccinated with LEUCOFELIGEN FeLV/RCP on Days 0 and 21.

(Group 3) Control group consisted of 11 cats which were vaccinated with Feligen CRP on Days 0 and 21, and then 13 months after the second vaccination on Day 21.

After the vaccinations the cats were observed daily for clinical signs. The rectal temperature was measured regularly and blood samples for serological tests were taken regularly.

Three years after the 2nd vaccination, 16 cats from the LEUCOFELIGEN FeLV/RCP primary + boost group (Group 1), 5 cats from the LEUCOFELIGEN FeLV/RCP primary group (Group 2) and 9 cats from the control group (Group 3) were challenged intraperitoneally (5 x 10^5 plaque-forming units (PFU)/cat) with a virulent FeLV-A strain. After the challenge the cats were observed daily for clinical signs and rectal temperature was measured regularly. Blood samples for the FeLV p27 antigenaemia testing were taken weekly from the 3rd week to the 15th week.

Results:

After vaccination no clinical signs attributable to vaccination could be determined. No increase of the rectal temperature above the upper limit (39.5 °C) could be detected. All vaccinated cats had developed antibodies against FeLV after the second vaccination. The titres decreased considerably during one year after primary vaccination. The titres obtained after the vaccination one year after the primary vaccination demonstrate the booster effect of this vaccination.

After the challenge all animals remained healthy and did not show clinical signs of disease. In all groups slight hyperthermia was sometimes observed, probably related to animal handling. All cats were free from FeLV p27 antigen before challenge. After challenge 1/16 cats (6.3%) were persistently infected in the LEUCOFELIGEN FeLV/RCP primary + boost group, none of the cats (0%) was persistently infected in the LEUCOFELIGEN FeLV/RCP primary group, and 4/9 cats (44.4%) were persistently infected in the control group.

With regards to the FeLV infection, an age-related resistance of adult cats exists. This phenomenon is well-known. Therefore, it is difficult to fulfil the requirements of European Pharmacopoeia (Ph. Eur.) monograph 1321 “Feline leukaemia vaccine (inactivated)” (infection of at least 80% of control cats is required) in duration of immunity studies. In the current study, the percentage of persistently infected control animals was only 44.4% instead of 80%. Hence, the preventable fraction (PF) was used to show that the challenge was still valid. This approach was considered acceptable by the CVMP. The PF compares the infection rates in controls and in vaccinated cats in order to adjust the severity of the challenge and the degree of the natural resistance in the controls. (PF (%) = (% of infection in controls - % of infection in vaccinates: % of infection in controls) x 100).

In this case the PFs obtained for the vaccinated animals were higher than the minimum PF required by the Ph. Eur. monograph 1321 (86% and 89% versus 75% required) relevant to this study. This demonstrated a duration of immunity of three years for the FeLV component of LEUCOFELIGEN FeLV/RCP that is compliant with the relevant Ph. Eur. monograph 1321.

Based on the results of the study described above, the proposed wording for SPCs and package leaflets of the three vaccines is as follows:

LEUCOFELIGEN FeLV/RCP

Section 4.2 of the SPC and section 4 of the package leaflet:

After the primary vaccination course, the duration of immunity lasts for one year for all components.

Following a first booster vaccination one year after the primary vaccination course, a **duration of immunity of 3 years** has been demonstrated for the leukaemia component.

Section 4.9 of the SPC and section 8 of the package leaflet:

Primary vaccination:

- first injection in kittens from 8 weeks of age
- second injection 3 or 4 weeks later.

Maternally derived antibodies can negatively influence the immune response to vaccination. In such cases where maternally derived antibodies are expected, a third injection may be appropriate from 15 weeks of age.

Revaccinations:

Following a first booster vaccination one year after the primary vaccination course, subsequent vaccinations can be performed **at intervals of three years** for the leukaemia component.

In this case, since annual revaccination is required for calicivirus, rhinotracheitis virus and panleucopenia virus components, a single dose of FELIGEN RCP can be used annually.

The vaccine can be used as a booster for kittens or cats previously vaccinated with FELIGEN RCP and LEUCOGEN separately

LEUCOGEN and Nobivac LeuFel

Section 4.2 of the SPC and section 4 of the package leaflet:

After the primary vaccination course, the duration of immunity lasts for one year.

Following a first booster vaccination one year after the primary vaccination course, **a duration of immunity of 3 years** has been demonstrated.

Section 4.9 of the SPC and section 8 of the package leaflet:

Primary vaccination:

- first injection in kittens from eight weeks of age
- second injection 3 or 4 weeks later.

Maternally derived antibodies can negatively influence the immune response to vaccination. In such cases where maternally derived antibodies are expected, a third injection may be appropriate from 15 weeks of age.

Revaccinations: Following a first booster vaccination one year after the primary vaccination course, subsequent vaccinations can be performed at **intervals of three** years.

3. Conclusions

The CVMP agrees with the proposed vaccination scheme for the FeLV component of the three vaccines LEUCOFELIGEN FeLV/RCP, LEUCOGEN and Nobivac LeuFel.

From an immunological point of view, the first booster vaccination one year after the primary vaccination course is reasonable. The titres of the vaccinated group show a drastic decrease during the first year after the second vaccination. At the day of the booster vaccination, 4/16 cats (25%) did not have a FeLV titre. The titres obtained after the booster vaccination demonstrate the booster effect of this vaccination. Therefore, the booster vaccination one year after the primary vaccination course is important as the animals are still young and susceptible to FeLV infection. When they are older, revaccination periods of three years are sufficient due to the age-related resistance. Thus, it is necessary to avoid yearly vaccinations in older cats, especially when the duration of immunity for the FeLV component actually is 3 years. Therefore, the revaccination schedule for the FeLV component was revised to "…subsequent vaccinations can be performed at intervals of three years". Practitioners would be able to make judgment whether a shorter revaccination period is necessary for a cat or not.

4. Benefit-risk assessment of the proposed change

LEUCOFELIGEN FeLV/RCP is authorised as a lyophilisate and suspension for injection for the active immunisation of cats from eight weeks of age against feline calicivirosis to reduce clinical signs, feline viral rhinotracheitis to reduce clinical signs and viral excretion, feline panleucopenia to prevent leucopenia and to reduce clinical signs, and feline leukaemia to prevent persistent viraemia and clinical signs of the related disease.

LEUCOGEN is authorised as a suspension for injection for the active immunisation of cats from eight weeks of age against feline leukaemia for the prevention of persistent viraemia and clinical signs of the related disease.

Nobivac LeuFel is authorised as a suspension for injection for the active immunisation of cats from eight weeks of age against feline leukaemia for the prevention of persistent viraemia and clinical signs of the related disease.

The proposed variation is to modify the duration of immunity of the feline leukaemia component of these three products.

4.1. Benefit assessment

Direct therapeutic benefit

The direct benefits of these products remain unaffected by this variation.

Additional benefits

A longer duration of immunity for LEUCOFELIGEN FeLV/RCP, LEUCOGEN and Nobivac LeuFel has some advantages for the animal and the pet owner. The number of veterinary appointments necessary for vaccination is reduced.

4.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety remains unaffected by this variation. The vaccine LEUCOFELIGEN FeLV/RCP is still well tolerated by the target species.

In the PSUR covering the period 01.07.2014-30.06.2017 it was recommended to add the following sentence to section 4.6 of the SPC and section 6 of the package leaflet: "*Febrile limping syndrome reactions may occur very rarely in kittens, as reported in the literature after the use of any vaccine containing a feline calicivirus componen*t". The SPC and package leaflet were amended accordingly.

Efficacy:

Efficacy remains unaffected by this variation.

4.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information of all the three vaccines 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.

4.4. Evaluation of the benefit-risk balance

No change to the impact of the products is envisaged on the following aspects: quality, safety, user safety, environmental safety and consumer safety.

The direct benefits of the products remain unchanged. The benefit of this variation is an additional one and relates to the longer duration of immunity of the three vaccines affected LEUCOFELIGEN FeLV/RCP, LEUCOGEN and Nobivac LeuFel that has some advantages for the animal and the pet owner e.g. stress for the animal is decreased as the number of veterinary appointments necessary for vaccination are reduced.

Based on the data presented, the overall benefit-risk is deemed positive for all three products.

5. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for LEUCOFELIGEN FeLV/RCP, LEUCOGEN and Nobivac LeuFel can be approved, since data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No 1234/2008), as follows:

To modify the duration of immunity of the feline leukaemia component of the vaccines LEUCOGEN, LEUCOFELIGEN FeLV/RCP and Nobivac LeuFel. (The applicant has also taken the opportunity to align the product information with the latest QRD template).

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

Changes are required in the Annexes to the Community marketing authorisation.

- I, IIIA and IIIB.