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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a worksharing variation (EMA/VRA/0000184065) for Nobivac L4 (EMEA/V/C/002010) and Nobivac LoVo L4 (EMEA/V/C/005628)

Common name: Canine leptospirosis vaccine (inactivated)

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

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Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 65 of Regulation (EU) 2019/6, the marketing authorisation holder, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 20 September 2024 an application for a group of variations requiring assessment for Nobivac L4 and Nobivac LoVo L4, following a worksharing procedure.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Addition of a new therapeutic indication or modification of an approved one
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data

This group of variations is to implement the following changes:

G.I.7.a – Addition of a new therapeutic indication or modification of an approved one for 2 new Leptospira serovars and existing Leptospira serovars and addition of efficacy against serovar Australis. A consequential name update from L4 to L6 is also proposed.

G.I.4 – Addition of associated non-mixed use with Nobivac Rabies (Nationally registered).

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, Part 4

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

G.I.7.a Addition of a new therapeutic indication or modification of an approved one against serovar Icterohaemorrhagiae

OOI

A study was carried out to evaluate the efficacy and onset of immunity to *L. interrogans* serogroup Icterohaemorrhagiae, serovar Icterohaemorrhagiae after administration of the Nobivac L4 or Nobivac LoVo L4 primary vaccination course from 6 weeks of age.

Twenty-nine 5 week and 4 days to 6 week and 1 day-old pups were assigned to three vaccinated groups of seven puppies each and a control group of eight puppies; Group 1 and 2 were vaccinated with two single doses of Nobivac LoVo L4 (0.5 mL) administered four weeks apart at 6 and 10 weeks of age using a different vaccine batch per group, Group 3 was vaccinated with two single doses of Nobivac L4 (1 mL) administered four weeks apart at 6 and 10 weeks of age, and Group 4 remained

unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study. All dogs were challenged with strain Verdun (*L. interrogans* serogroup Icterohaemorrhagiae, serovar Icterohaemorrhagiae) via a combination of intraperitoneal, intranasal, and conjunctival routes 20 days after the last vaccination. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed but as the OOI is set at 3 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80 % of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls.

Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied to evaluate pathological changes including liver and renal lesions. Statistically significant differences in total clinical signs of leptospirosis, leptospiraemia, leptospiruria, and renal carriage, as well as a reduction of mortality (no vaccinated animals died), were observed between the vaccinated and control groups (3/8 died).

Only 3/8 dogs of the control group died and no statistics on mortality were done, but further justification to support the claim "to prevent mortality" was provided by the applicant.

In conclusion, it was shown that both Nobivac L4 and Nobivac LoVo L4 provided protection against challenge with serovar Icterohaemorrhagiae three weeks after completion of the primary vaccination schedule. This is in line with the SPC claim: "*to prevent mortality, to reduce clinical signs, infection, urinary excretion and renal carriage*".

DOI

A study was carried out to evaluate a 1-year duration of immunity to *L. interrogans* serogroup Icterohaemorrhagiae, serovar Icterohaemorrhagiae after administration of the Nobivac L4 or Eurican Lmulti primary vaccination course from 6 weeks of age. Efficacy one year after completion of the primary vaccination course was assessed by challenge with a virulent *L. interrogans* serogroup Icterohaemorrhagiae, serovar Icterohaemorrhagiae strain Verdun. Thirty 5- to 8-week-old pups were assigned to three groups of ten puppies each; Group 1 was vaccinated with two single doses of Nobivac L4 administered four weeks apart at 6 and 10 weeks of age, Group 2 was vaccinated with two single doses of Eurican Lmulti administered four weeks apart at 6 and 10 weeks of age, and Group 3 remained unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study.

All dogs were challenged 391 days after the last vaccination with *L. interrogans* serogroup Icterohaemorrhagiae, serovar Icterohaemorrhagiae strain Verdun via a combination of intraperitoneal, intranasal, and conjunctival routes 13 months after the second vaccination, at an age of 15 months. Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied to evaluate pathological changes including renal lesions. Statistically significant differences in the clinical signs of leptospirosis and renal lesions were not observed between the vaccinated and control groups. Mortality and renal carriage were not observed in any of the dogs. Leptospiraemia was significantly reduced in both Nobivac L4 and Eurican Lmulti vaccinated dogs, and leptospiruria was clearly more present in the control group, although not at a high enough prevalence to result in a significant difference. In conclusion, it was shown that Nobivac L4 reduced infection following challenge with serovar Icterohaemorrhagiae one year after completion of the primary vaccination schedule. However, the DOI for prevention of mortality and reduction of clinical signs, urinary excretion and renal carriage could not be demonstrated and this is reflected in the SPC.

Addition of a new therapeutic indication or modification of an approved one against serovar Grippotyphosa

OOI

A study was carried out to evaluate the onset of immunity to *L. kirschneri* serogroup Grippotyphosa, serovar Grippotyphosa after administration of a Nobivac L4 or Nobivac LoVo L4 primary vaccination course from 6 weeks of age.

Twenty-six 6-week-old pups were assigned to three vaccinated groups of six puppies each and a control group of eight puppies; Groups 1 and 2 were vaccinated with two single doses of Nobivac LoVo L4 (0.5 mL) administered four weeks apart at 6 and 10 weeks of age using a different vaccine batch per group. Group 3 was vaccinated with two single doses of Nobivac L4 (1 mL) administered four weeks apart at 6 and 10 weeks of age, and Group 4 remained unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study. Dogs were challenged with strain Duyster P2574 (*L. kirschneri* serogroup Grippotyphosa, serovar Grippotyphosa) via a combination of intraperitoneal, intranasal, and conjunctival routes 20 days after the second vaccination, at an age of 3 months. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed, but as the OOI is set at 3 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80 % of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls.

Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied to evaluate pathological changes including liver and renal lesions. Statistically significant differences in the total clinical signs of leptospirosis, leptospiraemia, leptospiruria, renal carriage, and renal lesions were observed between the vaccinated and control groups.

Regarding the body temperature, the total clinical scores differed significantly between all three vaccinated groups and the control group ($p=0.0414$, $p=0.0407$, and $p=0.0279$ for Group 1, Group 2, and Group 3, respectively. However, no statistically significant differences were observed between groups for clinical scores for signs of leptospirosis. While there was a statistically significant difference claimed for total clinical score, this can be mainly attributable to a difference in rectal temperature and therefore does not adequately support a distinct reduction in clinical signs associated with severe leptospirosis. In addition, two of the vaccinated dogs could be identified with a temperature above 39.4 °C (one dog 40.3 °C and another dog 39.5 °C).

In conclusion, it was shown that both Nobivac L4 and Nobivac LoVo L4 provided protection against challenge with serovar Grippotyphosa three weeks after completion of the primary vaccination schedule for a prevention of renal carriage and urinary excretion and a reduction of infection, clinical signs and renal lesions.

However, as in relation to the clinical signs, the difference is attributable to difference in the elevated rectal temperature (no other clinical signs of disease), this was reflected in the SPC.

DOI

A study was carried out to evaluate a 1-year duration of immunity to *L. kischneri* serogroup Grippotyphosa, serovar Grippotyphosa after administration of the Nobivac LoVo L4 primary vaccination course from 6 weeks of age.

Twenty 5 week and 1 day to 6 week and 6 days-old pups were assigned to two groups of ten puppies each; Group 1 was vaccinated with two single doses of Nobivac LoVo L4 administered four weeks apart at 6 and 10 weeks of age, Group 2 remained unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study. Dogs were challenged with *L. kischneri* serogroup Grippotyphosa, serovar Grippotyphosa strain Duyster via a combination of intraperitoneal, intranasal, and conjunctival routes 13 months (384 days) after the second vaccination, at an age of 15 months. Post challenge, the dogs were observed for clinical signs of leptospirosis (including body

temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied to evaluate pathological changes including renal lesions. Statistically significant differences in the clinical signs of leptospirosis and renal lesions were not observed between the vaccinated and control groups. Mortality and renal carriage were not observed in any of the dogs. Leptospiraemia was significantly reduced in vaccinated dogs, and leptospiruria was clearly more present in the control group, although statistics only indicated a trend (0.063). However, it should be noted that the group size was small, since 3 dogs were excluded from the study.

Altogether, it was shown that Nobivac LoVo L4 reduced infection following challenge with serovar Grippotyphosa one year after completion of the primary vaccination course and this is reflected in the SPC.

Addition of a new therapeutic indication or modification of an approved one against existing serovars

***L. interrogans* serogroup Canicola, serovar Canicola**

A study was carried out to evaluate the efficacy against *L. interrogans* serogroup Canicola, serovar Canicola after administration of the Nobivac L4 primary vaccination course from 6 weeks of age. Twenty-four 5 to 7 weeks old pups, all but 3 serologically negative for Leptospira, were assigned to two vaccinated groups and a control group of eight puppies each; Group 1 was vaccinated with two single doses of Nobivac L4 (1 mL), and Group 2 was vaccinated with two single doses of a competitor's leptospira vaccine (1 mL), both administered four weeks apart at 6 and 10 weeks of age, while Group 3 remained unvaccinated. The 3 seropositive puppies had very low titres and were vaccinated with the competitor vaccine and it was therefore accepted that the inclusion of these study animals did not impact on the validity of the study results. The groups were obtained from eight litters, and the pups were weaned at 8 weeks or 8 weeks and 2 days of age. After 10 days of acclimatisation, the first sampling was performed. All dogs participated in the challenge phase and were challenged with strain Moulton (*L. interrogans* serogroup Canicola, serovar Canicola) via a combination of intraperitoneal, intranasal, and conjunctival routes 20 days after the last vaccination. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed, but as the OOI is set at 3 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80 per cent of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls.

Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied on day 76 to evaluate pathological changes including liver and renal lesions. Statistically significant differences ($p<0.0001$ – $p< 0.0023$) in the clinical signs, total clinical signs of leptospirosis, leptospiraemia, leptospiruria, renal carriage, and renal lesions and protection from mortality were observed between both the Nobivac L4 vaccinated and the Versican Plus L4 vaccinated groups and the control group.

In conclusion, it was shown that Nobivac L4 provided reduction in clinical signs, infection, prevention of urinary excretion, renal carriage, renal lesions, and mortality against challenge with serovar Canicola three weeks after completion of the primary vaccination schedule.

Since for serovars Canicola, Copenhageni and Bananal/Liangguang, at DOI a reduction of infection and urinary excretion were demonstrated, a footnote was added to delineate the serovars for which only a reduction of infection and reduction of urinary excretion was supported.

***L. interrogans* serogroup Icterohaemorrhagiae, serovar Copenhageni**

A study was carried out to evaluate the efficacy against *L. interrogans* serogroup Icterohaemorrhagiae, serovar Copenhageni after administration of the Nobivac L4 primary vaccination

course from 6 weeks of age.

Forty-eight 5 to 6 weeks old pups were assigned to five vaccinated groups and a control group of eight puppies each. Group 1 and Group 4 were vaccinated with different Nobivac L4 batches, Group 2 was vaccinated with a competitor's leptospira vaccine, and Group 3 and Group 5 were vaccinated with different Nobivac L4 batches with 25% antigen concentrations. All vaccines were administered as two single doses four weeks apart at 6 and 10 weeks of age, and Group 6 remained unvaccinated. All pups were negative for Leptospira by serology or had low titres prior to the start of the study.

Dogs were challenged with strain CF1 (*L. interrogans* serogroup Icterohaemorrhagiae, serovar Copenhageni) via a combination of intraperitoneal, intranasal, and conjunctival routes 3 weeks after the second vaccination, 20 days after the last vaccination. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed, but as the OOI is set at 3 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80 per cent of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls.

Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 29-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied on day 77 or 78 to evaluate pathological changes including liver and renal lesions. Statistically significant differences in the total clinical signs of leptospirosis, leptospiraemia, leptospiruria, renal carriage, and renal lesions, as well as protection from mortality, were observed between both the Nobivac L4 (full antigen content) vaccinated groups and the control group. The competitor's leptospira product vaccinated group only showed significant reduction of total clinical signs and leptospiruria.

In conclusion, it was shown that Nobivac L4 provided reduction of clinical signs, infection, urinary excretion, renal carriage, and renal lesions and prevention of mortality against challenge with serovar Copenhageni three weeks after completion of the primary vaccination schedule.

L. kirschneri serogroup Grippotyphosa, serovar Bananal/Liangguang

A study was carried out to evaluate the efficacy against *L. kirschneri* serogroup Grippotyphosa, serovar Bananal/Liangguang after administration of the Nobivac L4 primary vaccination course from 6 weeks of age.

Twenty-four 5 to 6 weeks old pups were assigned to two vaccinated groups and a control group of eight puppies each; Group 1 was vaccinated with two single doses of Nobivac L4 (1 mL), and Group 2 was vaccinated with two single doses of a competitor's leptospira vaccine (1 mL), both were administered four weeks apart at 6 (day 0) and 10 (day 28) weeks of age, while Group 3 remained unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study. The groups were obtained from four litters, and the pups were weaned at 8 weeks of age.

Dogs were challenged with strain 11808 (*L. kirschneri* serogroup Grippotyphosa, serovar Bananal/Liangguang) via a combination of intraperitoneal, intranasal, and conjunctival routes 20 days after the last vaccination. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed, but as the OOI is set at 3 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80 per cent of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls. Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied on day 77 to evaluate pathological changes including liver and renal lesions. Statistically significant differences in the clinical signs, total clinical signs (i.e. clinical signs and body temperature after challenge) of leptospirosis, leptospiraemia, leptospiruria, renal carriage, and renal lesions were observed between the Nobivac L4 vaccinated group and the control group. The competitor's vaccinated group showed significant differences in leptospiraemia,

leptospiruria, renal carriage, and renal lesions.

In conclusion, it was shown that Nobivac L4 provided a reduction of total clinical signs and infection, and prevention of urinary excretion, renal carriage and renal lesions against challenge with serovar Bananal/Liangguang three weeks after completion of the primary vaccination schedule.

L. interrogans serogroup Australis, serovar Bratislava

A study was carried out to evaluate the efficacy against *L. interrogans* serogroup Australis, serovar Bratislava after administration of a Nobivac L4 primary vaccination course from 6 weeks of age.

Thirty-two 5-6 weeks-old pups were assigned to three vaccinated groups and a control group of eight puppies each; Group 1 was vaccinated with two single doses of Nobivac L4 batch 172714 (1 mL), Group 2 was vaccinated with two single doses of a competitor's leptospira vaccine (1 mL), Group 3 was vaccinated with two single doses of Nobivac L4 batch 183072 (1 mL), all administered four weeks apart at 6 and 10 weeks of age, while Group 4 remained unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study.

Dogs were challenged with strain Belfast (*L. interrogans* serogroup Australis, serovar Bratislava) via a combination of intraperitoneal, intranasal, and conjunctival routes 6 weeks after the second vaccination (day 69). However, in the study protocol is written that challenge took place at day 48. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed, but as the OOI is set at 6 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80% of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls.

Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 29-day observation period with re-isolation from blood, urine, kidney and liver. At the end of the study, the dogs were necropsied on day 97 or 98 to evaluate pathological changes including liver and renal lesions. Statistically significant differences in the clinical signs, total clinical signs of leptospirosis, leptospiraemia, and leptospiruria and protection from mortality were observed between both the Nobivac L4 vaccinated and the Versican Plus L4 vaccinated groups and the control group.

In conclusion, it was shown that Nobivac L4 provided reduction of clinical signs, prevention of infection and urinary excretion against challenge with serovar Bratislava six weeks after completion of the primary vaccination schedule. The reduction of infection has been demonstrated and granted at the initial MA.

With respect to the proposed prevention of mortality claim (at 6 weeks post-vaccination), since only 1/8 control dogs died post-challenge, the claim 'prevention of mortality' is not supported as the incidence of mortality is too low in the control group to conclude that a prevention claim would be appropriate in vaccinated dogs.

Addition of efficacy against serovar Australis

A study was carried out to evaluate the onset of immunity to *L. interrogans* serogroup Australis, serovar Australis after administration of a Nobivac L4 or Nobivac LoVo L4 primary vaccination course from 6 weeks of age.

Twenty-nine 6-week-old pups were assigned to three vaccinated groups of seven puppies each and a control group of eight puppies; Groups 1 and 2 were vaccinated with two single doses of Nobivac LoVo L4 (0.5 mL) administered four weeks apart at 6 and 10 weeks of age using a different vaccine batch per group, Group 3 was vaccinated with two single doses of Nobivac L4 (1 mL) administered four weeks apart at 6 and 10 weeks of age, and Group 4 remained unvaccinated. All pups were negative for Leptospira by serology prior to the start of the study. All dogs were challenged with strain Dohhilo (*L. interrogans* serogroup Australis, serovar Australis) via a combination of intraperitoneal, intranasal, and conjunctival routes 3 weeks after the second vaccination, at an age of

3 months. This is not in line of the Eur. Ph. 01/2017:0447, where challenge at 25 to 28 days after last vaccination is prescribed, but as the OOI is set at 3 weeks, this is acceptable. Moreover, according to the Eur. Ph., the test can be considered as valid since at least 80 per cent of the vaccinates show no more than mild signs of disease and urinary excretion and infection in the vaccinates was significantly lower compared to the controls.

Post challenge, the dogs were observed for clinical signs of leptospirosis (including body temperature and body weight) and sampled for leptospiraemia, agglutinating serum antibodies, leptospiruria, and urinalysis at varying timepoints over a 28-day observation period. At the end of the study, the dogs were necropsied to evaluate pathological changes including liver and renal lesions. Statistically significant differences in the clinical signs of leptospirosis, leptospiraemia, leptospiruria, and renal lesions were observed between the vaccinated and control groups with re-isolation from blood, urine, kidney and liver. No mortality in the vaccinated groups was noted whereas 5 of the 8 control dogs died.

In conclusion, it was shown that both Nobivac L4 and Nobivac LoVo L4 provided protection against challenge with serovar Australis three weeks after completion of the primary vaccination schedule. This is in line with the information in the SPC in section 4.1: *"It was demonstrated that the vaccine provides cross-protection against L. interrogans serogroup Australis serovar Australis at three weeks after vaccination."*

However, according to the Guideline on the acceptability of names for veterinary medicinal products processed through the centralised procedure '*For vaccines composed of several serotypes when adding a new serotype the original invented name may be kept; the name is then followed by the number of serotypes present…*' and '*The invented name of a medicinal product should not be misleading with respect to the composition of the product*.'

The proposed suffix "L6" suggests the presence of six different serogroups of Leptospira, but the vaccines contain serovars of Leptospira belonging to four serogroups.

Based on the above, the inclusion of the proposed suffix "L6" in the invented names of the products may lead to a risk of confusion among veterinarians and animal healthcare providers, who may incorrectly interpret the name as indicating six distinct serogroups.

Therefore, the consequential name update from L4 to L6 proposed by the MAH is not accepted.

G.I.4 Associated non-mixed use with Nobivac Rabies

The applicant proposes to include a statement in section 3.8 of the SPC to state: "Safety and efficacy data are available which demonstrate that this vaccine can be administered at the same time but at different administration sites with vaccine in the Nobivac range against rabies." A GCP-compliant field study was carried out to assess the compatibility of associated non-mixed use of Nobivac L4 and Nobivac Rabies at revaccination. Dogs that were vaccinated with Nobivac Rabies approximately three years before (maximum 4 years) and with Nobivac L4 approximately one year previously and were due for revaccination were included. A total of 229 dogs from 60 different breeds, including large and miniature breeds were included in the study with 76 dogs included in a group vaccinated with Nobivac Rabies + Nobivac L4 at the same time at different administration sites, 78 dogs included in a group vaccinated with Nobivac L4 only and 75 dogs included in a group vaccinated with Nobivac Rabies only at revaccination. To assess the safety of the associated use of Nobivac Rabies and Nobivac L4, dogs were clinically examined at admission and three weeks after vaccination. Concomitant treatments and adverse events were recorded throughout the study.

The effect of Nobivac Rabies (n=73) on the serological response to Nobivac L4 and –vice versa- the effect of Nobivac L4 on the serological response to Nobivac Rabies were investigated at 3 weeks after revaccination (primary parameters to assess the compatibility). All groups showed the expected serological response to the vaccines administered. As the lower limits of the one-sided 95% confidence intervals of the difference in all four Leptospira antibody titres between the Rabies+L4 group (n=75) and L4 group (n=77) were between -0.32 and 0.13 log2 and did not exceed the pre-set margin of -2.40 log2, the Leptospira antibody responses after non-mixed use of Nobivac L4 and

Nobivac Rabies is non-inferior to single use of Nobivac L4 and with this the applicant considers that compatibility for Nobivac L4 with Nobivac Rabies is demonstrated.

Vice versa, the compatibility was further demonstrated for Nobivac Rabies as the lower limit of the one-sided 95% confidence interval of the difference in Rabies antibody titres between the Rabies+L4 group and Rabies group was -1.73 IU/ml log2 and also did not exceed the pre-set margin of -2.00 log2, which means the Rabies antibody response after non-mixed use of Nobivac L4 and Nobivac Rabies is also non-inferior to single use of Nobivac Rabies under the conditions of this study.

Concerning efficacy, it can be accepted that the data presented support an absence of serious interference or negative impact on efficacy of either vaccine, using serology as a surrogate marker of efficacy**.**

Regarding safety, one serious adverse event was reported in the Rabies group, but this was classified as unlikely related to the vaccine. Non-serious adverse events (n=11) were, as the number of cases which required concomitant treatments, homogenously distributed among the different groups. Furthermore, immediate reactions during or just after vaccination were not observed. However, the study was not conducted under worst case scenario conditions for evaluation of safety (not conducted in minimum age puppies). In accordance with the Guideline on Requirements for combined vaccines and associations of IVMPs, it is expected that at least one study performed in laboratory conditions or in a field trial is necessary to demonstrate the safety of the association of the IVMPs, investigating the administration of one dose of each IVMP to the most sensitive category of each target species by one of the recommended routes. If different minimum ages are approved for the individual IVMPs, the safety of the association should be established for the oldest of the minimum recommended ages for the individual IVMPs. A study investigated the safety of Nobivac DHPPi reconstituted in Nobivac L4 and administered at the same time but at a different site with Nobivac Respira Bb. Eight 6 weeks old SPF Beagle dogs were vaccinated subcutaneously with Nobivac Respira Bb, Nobivac DHPPI reconstituted in Nobivac L4 and Nobivac Rabies. The control group (n=6) was vaccinated with Nobivac DHPPI reconstituted in Nobivac L4 and Nobivac Rabies.
Two additional vaccinations were given at 8 weeks of age and 10 weeks of age, but without administration of Nobivac Rabies.
The vaccinations did not induce an increase in temperature or any clinical signs. Local reactions were observed at injection site of Nobivac DHPPi+L4 in several dogs in both groups and at the Nobivac Respira Bb vaccination site in a few dogs of the test group. All these were non-painful reactions and of acceptable size and duration. The reactions to the Nobivac DHPPi+L4 vaccination were not exacerbated by the Nobivac Respira Bb administered at the same time.
As dogs were also vaccinated with Nobivac Rabies at the first vaccination of 6 weeks, the description of these clinical signs would also apply for the vaccination including Nobivac Rabies. These reactions were in line with the reactions described in the SPC.

Considering the above, the associated non-mixed use with Nobivac Rabies is supported.

3. Benefit-risk assessment of the proposed change

These products are authorised for the active immunisation of dogs against:

- *Leptospira interrogans* serogroup Canicola serovar Canicola to reduce infection and urinary excretion

- *L. interrogans* serogroup Icterohaemorrhagiae serovar Copenhageni to reduce infection and urinary excretion

- *L. interrogans* serogroup Australis serovar Bratislava to reduce infection

- *L. kirschneri* serogroup Grippotyphosa serovar Bananal/Liangguang to reduce infection and urinary excretion.

The proposed variation is to add a new therapeutic indication or modification of an approved one for 2 new Leptospira serovars and existing Leptospira serovars, addition of efficacy against serovar Australis and associated non-mixed use with Nobivac Rabies (Nationally registered). A consequential name update from L4 to L6 is also proposed, however, it is not accepted.

3.1. Benefit assessment

Direct therapeutic benefit

Besides the already authorised claims, the product is safe and efficacious against *Leptospira interrogans* serovar Icterohaemorrhagiae, *Leptospira kirschneri* serovar Grippotyphosa, *Leptospira interrogans* serovar Canicola, *Leptospira interrogans* serovar Copenhageni, *Leptospira kirschneri* serovar Bananal/Liangguang, and *Leptospira interrogans* serovar Bratislava. Cross-protection is demonstrated against *Leptospira interrogans* serovar Australis.

Serovar (Serogroup)	**Additional indications not yet authorized**
Canicola (Canicola)	to prevent mortality, renal carriage and renal lesions and reduce clinical signs.
Icterohaemorrhagiae (Icterohaemorrhagiae)	to prevent mortality and reduce infection, urinary excretion, clinical signs and renal carriage.
Copenhageni (Icterohaemorrhagiae)	to prevent mortality and reduce clinical signs, renal carriage, and renal lesions.
Bratislava (Australis)	to prevent urinary excretion and reduce clinical signs
Grippotyphosa (Grippotyphosa)	to prevent urinary excretion and renal carriage and reduce infection, clinical signs (based on reduction of pyrexia) and renal lesions.
Bananal/Liangguang (Grippotyphosa)	to prevent renal carriage and renal lesions and reduce clinical signs.

Additional benefits

Cross-protection is also demonstrated against *Leptospira interrogans* serovar Australis.

Additional reduction of urinary excretion decreases the amount of Leptospira shed and, as such, reduce the zoonotic risk.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation

Safety:

Safety for the target animal, user and the environment remain unaffected by this variation.

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

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

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

4. Conclusion

Based on the original and complementary data presented on efficacy (and efficacy and safety for the associated-use claim), the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Nobivac L4 and Nobivac LoVo L4 can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU). 2019/6), as follows:

- Addition of a new therapeutic indication or modification of an approved one for 2 new Leptospira serovars, and existing Leptospira serovars:

Serovar (Serogroup)	**New therapeutic indication or modification**
Canicola (Canicola)	to prevent mortality, renal carriage and renal lesions and reduce clinical signs.
Icterohaemorrhagiae (Icterohaemorrhagiae)	to prevent mortality and reduce infection, urinary excretion, clinical signs and renal carriage.
Copenhageni (Icterohaemorrhagiae)	to prevent mortality and reduce clinical signs, renal carriage, and renal lesions.
Bratislava (Australis)	to prevent urinary excretion and reduce clinical signs.
Grippotyphosa (Grippotyphosa)	to prevent urinary excretion and renal carriage and reduce infection, clinical signs (based on reduction of pyrexia) and renal lesions.
Bananal/Liangguang (Grippotyphosa)	to prevent renal carriage and renal lesions and reduce clinical signs.

- Addition of associated non-mixed use with Nobivac Rabies (Nationally registered)
- Addition of efficacy against serovar Australis

However, the following proposed change has not been accepted:

- The change of the name from Nobivac L4 and Nobivac LoVo L4 to Nobivac L6 and Nobivac LoVo L6.

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 Community marketing authorisation.

I, IIIA and IIIB

Please refer to the separate product information showing the tracked changes.

As a consequence of these variations, sections 3.2, 3.8 and 4.1 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.