United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Eurican L4 Suspension for Injection for Dogs

Date Created: August 2023

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Eurican L4 Suspension for Injection for Dogs
Applicant	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim Rhein Germany
Active substance(s)	Inactivated *Leptospira interrogans* serogroup and serovar Canicola, strain 16070 Inactivated *Leptospira interrogans* serogroup and serovar Icterohaemorrhagiae, strain 16069 Inactivated *Leptospira interrogans* serogroup and serovar Grippotyphosa, strain Grippo Mal 1540 Inactivated *Leptospira interrogans* serogroup Australis and serovar Bratislava, strain 16785
ATC Vetcode	QI07AB01
Target species	Dogs
Indication for use	Active immunisation of dogs from 7 weeks of age to prevent or reduce mortality, clinical signs, infection, bacterial excretion, renal carriage and renal lesions caused by: • *Leptospira interrogans* serogroup Canicola serovar Canicola, • *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae, • *Leptospira kirschneri* serogroup Grippotyphosa serovar Grippotyphosa, and • *Leptospira interrogans* serogroup Australis serovar Bratislava. See table below

Serogroup / Serovar	Indication					
	Mortality	**Clinical signs**	**Infection**	**Bacterial excretion**	**Renal carriage**	**Renal lesions**
Canicola / Canicola	Prevention*	Prevention*	Reduction	Reduction	Reduction	Reduction
Icterohaemorrhagiae / Icterohaemorrhagiae	Prevention	Prevention	Reduction	Reduction	Reduction	Reduction
Icterohaemorrhagiae / Copenhageni	Prevention**	Prevention**	Prevention**	Prevention**	Prevention**	Prevention**
Grippotyphosa / Grippotyphosa	Prevention***	Prevention	Reduction	Reduction	Reduction	Reduction
Australis / Bratislava	Prevention	Prevention	Prevention	Prevention	Prevention	Prevention

* For *Leptospira interrogans* serovar Canicola, no mortality and clinical signs occurred during challenge experiment for duration of immunity.
** For Leptospira *interrogans serovar* Copenhageni the duration of immunity was not established.
*** For *Leptospira kirschneri serovar* Grippotyphosa, no mortality occurred during challenge experiment for duration of immunity.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	2/6/2023

I. SCIENTIFIC OVERVIEW

This is a full application for a centralised procedure in accordance with Article 3(2) of Regulation (EC) No 776/2004.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains: inactivated *Leptospira interrogans* serogroup and serovar Canicola, strain 16070; inactivated *Leptospira interrogans* serogroup and serovar Icterohaemorrhagiae, strain 16069; inactivated *Leptospira interrogans* serogroup and serovar Grippotyphosa, strain Grippo Mal 1540; inactivated *Leptospira interrogans* serogroup Australis and serovar Bratislava, strain 16785 and the excipients potassium chloride, sodium chloride, potassium dihydrogen phosphate, disodium phosphate dihydrate, water for injections.

The container/closure system consists of type 1 glass bottles closed with chlorobutyl type 1 stoppers. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains, inactivating agent, and the absence of preservative are justified.

The inactivation process and the detection limit of the control of inactivation are correctly validated.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of: thawing the seed lot, adding, stirring and inactivating.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are: inactivated *Leptospira interrogans* serogroup and serovar Canicola, strain 16070; inactivated *Leptospira interrogans* serogroup and serovar Icterohaemorrhagiae, strain 16069; inactivated *Leptospira interrogans* serogroup and serovar Grippotyphosa, strain Grippo Mal 1540; and inactivated *Leptospira interrogans* serogroup Australis and serovar Bratislava, strain 16785 They are established active substances. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Starting materials of non-biological origin used in production comply with the European Pharmacopoeia or in house specifications.

Biological starting materials used are in compliance with in house monographs and are appropriately screened for the absence of extraneous agents according to the Guidelines; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

The packaging also complies.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

II.E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests are appearance, pH, volume, potency, thiomersal detection, and sterility.

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

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 15 months.
Shelf life after first opening the immediate packaging: use immediately.
Store and transport refrigerated (2°C to 8°C).
Do not freeze.
Protect from light.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in a single, new GLP study. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Effects on reproductive performance were examined: the safety of the veterinary medicinal product has not been established during pregnancy.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The interactions of the vaccine with Eurican DAPPI, Eurican DAP, and Rabisin were studied. Safety and efficacy data are available which demonstrate that this vaccine can be mixed with Boehringer Ingelheim live attenuated vaccines against distemper, adenovirus, parvovius and parainfluenza type 2 respiratory infections. Safety and efficacy data are available which demonstrate that this vaccine can be administered on the same day as, but not mixed with, Boehringer Ingelheim's rabies vaccine in dogs from 12 weeks of age. Efficacy of the vaccine for for protection against the Copenhageni serovar has not been investigated after use with Boehringer Ingelheim's rabies vaccine on the same day. No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product except the products mentioned above. A

decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

Field studies

A single new field safety and efficacy study was carried out, after a primary course of two injections at a four-week interval, or a booster injection in previously vaccinated dogs. The safety evaluation was based on the monitoring of immediate and delayed, local and general adverse reactions. The overall percentage of dogs that experienced at least one adverse effect during the study, regardless of the type of vaccine etc. was 14.2%. In general, the adverse reactions reported were mild and transient. The safety of the vaccine was demonstrated.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the overall risk of the product to the environment is effectively zero as the product is inactivated. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements.

Five trials were carried out to demonstrate efficacy of the product.
The first trial was to test efficacy in *Leptospira* Australis. The results of this study concluded that the vaccine induces seroconversion. Prevention of mortality was demonstrated in the vaccinated group compared to the control group ($p=0.003$). Prevention of clinical signs was demonstrated in the vaccinated group compared to the control group ($p=0.003$). Reduction of biological parameters disorders was not demonstrated in the vaccinated group compared to the control group ($p=0.107$). Prevention of infection was demonstrated ($p<0.001$). Prevention of bacterial excretion was demonstrated in the vaccinated group compared to the control group ($p=0.011$). prevention of renal carriage and prevention of renal lesions were demonstrated in the vaccinated group compared to the control group ($p=0.003$ and $p<0.001$ respectively).

The second trial was to test efficacy in a dilution of *Leptospira* Australis at ¼ and 1/10. The results for the serological data are as follows. All control dogs remained seronegative until challenge and then seroconverted after the challenge. All animals vaccinated with ¼ dose seroconverted during the vaccine phase and all animals had an increase of titre after the challenge. In the group vaccinated with 1/10 dose, only two animals seroconverted during the vaccine

phase and had an increase of titre after the challenge. Two vaccinates seroconverted after the challenge and two other vaccinates had no antibodies detected after the challenge. The data for mortality and clinical signs shows that all vaccinates except one animal vaccinated with ¼ dose remained in good health with no clinical signs. Prevention of mortality and clinical signs were demonstrated in vaccinated groups compared to control group (p=0.003 and p=0.003 respectively. It was concluded that administration of diluted doses is efficacious.

The third study was to determine efficacy in *Leptospira* Canicola. It was shown that all vaccinates seroconverted during the vaccine phase, and all remained in good health with no clinical signs. Prevention of mortality was demonstrated (p=0.030) and prevention of clinical signs was demonstrated (p=0.011). prevention of biological parameters disorders was not clearly demonstrated, as only a trend was observed (p=0.099). Prevention of infection was demonstrated (p<0.001). Vaccinates had no positive signs in urine samples, no positive signs in kidney samples and no renal lesions, except for one that had a single positive urine sample but no other positives. Prevention of bacterial excretion was not demonstrated in the vaccinated group (p=0.073) but a trend was observed. Prevention of renal carriage and renal lesions were demonstrated (p=0.011). It was determined that this dosage is efficacious.

Leptospira Icterohaemorrhagiae
All vaccinates seroconverted during the vaccine challenge and all remained in good health with no clinical signs. Prevention of mortality was demonstrated in vaccinated group (p<0.001) and prevention of clinical signs was demonstrated (p=0.003). Prevention of biological parameters disorders was demonstrated (p<0.001). Prevention of infection was demonstrated (p=0.003). Prevention of bacterial excretion was demonstrated (p=0.003). Prevention of renal carriage and renal lesions were demonstrated (p<0.001).

Leptospira Grippotyphosa
All vaccinates seroconverted during the vaccine challenge and all remained in good health with no clinical signs except for one with a slight increase in temperature. Prevention of mortality was demonstrated in vaccinated group (p=0.034) and prevention of clinical signs was demonstrated (p=0.011). Prevention of biological parameters disorders was demonstrated (p=0.003). Prevention of infection was demonstrated (p<0.001). Prevention of bacterial excretion was demonstrated (p=0.004). Prevention of renal carriage and renal lesions were demonstrated (p=0.003 and p<0.001 respectively).

Onset of Immunity

Studies were conducted to determine the onset and duration of immunity. The studies indicated that the onset of immunity is accepted at two weeks after the second vaccination course for all strains. A duration of immunity was accepted to be at least one year after the second injection of the primary vaccination course for all strains.

Field Trials

The applicant has presented a single new field and safety study carried out using this product mixed with Eurican DAPPI as a worst case, after a primary course of two injections at four weeks interval, or a booster injection in previously vaccinated dogs. Statistical analysis classified the animals into categories according to size (weight/kg). In both the primo vaccination and the booster trials, the vaccine conferred a strong and rapid immune response against all eight components to most animals. Seroconversion in animals presenting significant levels of antibodies prior to the first injection of primo vaccination support the efficacy of this vaccine in the face of maternally derived antibodies at a level found in the general population. It was concluded that there is a good correlation between antibody titres and protection as high titres were reached in close to 100% of the vaccinated dogs.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product is favourable.

MODULE 4

POST- AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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