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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Eurican L_{multi} in the MA dossier

MODULE 1**PRODUCT SUMMARY**

EU Procedure number	FR/V/0288/001/DC
Name, strength and pharmaceutical form	Eurican L _{multi} Suspension for injection
Applicant	MERIAL 29 AVENUE TONY GARNIER 69007 LYON FRANCE
Active substances	One dose of suspension contains: Inactivated <i>Leptospira interrogans</i> serogroup and serovar Canicola strain 16070 : Activity according to Ph. Eur.447* Inactivated <i>Leptospira interrogans</i> serogroup and serovar Icterohaemorrhagiae strain 16069 : Activity according to Ph. Eur.447* Inactivated <i>Leptospira interrogans</i> serogroup and serovar Grippotyphosa strain Grippo Mal 1540 : Activity according to Ph. Eur.447* *80% of protection in hamsters
ATC Vetcode	QI07AB01
Target species	Dogs
Indication for use	Active immunisation of dogs to: prevent mortality, clinical signs, infection, bacterial excretion, renal carriage and renal lesions caused by <i>Leptospira interrogans</i> serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae prevent mortality and clinical signs, reduce infection, bacterial excretion, renal carriage and renal lesions caused by <i>Leptospira interrogans</i> serogroup Canicola serovar Canicola. prevent mortality, and reduce clinical signs, infection, bacterial excretion renal carriage and renal lesions caused by <i>Leptospira kirschneri</i> serogroup Grippotyphosa serovar Grippotyphosa.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on
the website <http://www.ircp.anmv.anses.fr/>

MODULE 3**PUBLIC ASSESSMENT REPORT**

Legal basis of original application	Application in accordance with Article 32 (3) of Directive 2001/82/EC as amended.
Date of completion of the original procedure	22th July 2015
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxemburg, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom

I. SCIENTIFIC OVERVIEW

The vaccine is a multivalent inactivated bacterial vaccine which is indicated for the immunisation of healthy puppies from seven weeks of age and dogs against leptospirosis. The vial contains inactivated components (*Leptospira Canicola*, *Leptospira Grippotyphosa* and *Leptospira Icterohaemorrhagiae*) presented in liquid form.

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; the reactions observed are indicated in the SPC (Summary of Product Characteristics).

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 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. QUALITY ASPECTS

A. *Composition*

One dose of suspension contains:

Active substances:

Inactivated *Leptospira interrogans* serogroup and serovar Canicola
strain 16070 Activity acc. to Ph. Eur.447*
Inactivated *Leptospira interrogans* serogroup and serovar Icterohaemorrhagiae
strain16069 Activity acc. to Ph. Eur.447*
Inactivated *Leptospira interrogans* serogroup and serovar Grippotyphosa
strain Grippo Mal 1540 Activity acc. to Ph. Eur.447*
*80% of protection in hamsters

The vaccine is filled in glass type I containers, closed with a chlorobutyl stopper and sealed with an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains is justified.

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

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

B. *Method of Preparation of the Product*

The product is manufactured fully in accordance with the principles of good manufacturing practices in a licensed manufacturing site.

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

C. *Control of Starting Materials*

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs where these exist, or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the "Table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and

control of mammalian veterinary vaccines" (Note for Guidance III/3427/93, 7B1m10a).

Seed lots and cell banks have been produced as described in the relevant guideline.

D. *Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies*

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.

E. *Control tests during production*

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

F. *Control Tests on the Finished Product*

The tests performed on the final product are in line with to the relevant requirements; any deviation from these requirements is justified. The tests performed are as follows:

- appearance
- pH
- volume
- potency
- determination of thiomersal content
- sterility: according to Ph. Eur. 2.6.1

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier.

G. *Stability*

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 (24 months) when stored under the approved conditions (at 2-8° C).

The vaccine must be used immediately after broaching.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the subcutaneous administration of one dose, an overdose and the repeated administration of one dose in the target species (20 dogs) is demonstrated in one laboratory study. Safety was assessed clinically in Specific Pathogen Free (SPF) dogs, over an appropriate time course, through observation and physical examination. Unvaccinated animals were used as control group. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Overall, the vaccine proved to be well tolerated in the target species. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under "adverse reactions".

Effects on reproductive performance were examined in one laboratory study on 10 vaccinated bitches and 10 controls. As the vaccine proved to be safe in pregnant bitches, the vaccine can be used during pregnancy. A corresponding note is included in the SPC and package leaflet.

The assessment of the interaction of this product with the Merial's canine vaccines was made. Suitable warnings are included in the SPC and package leaflet.

Details are given in the Summary of Product Characteristics (SPC) as follows:

4.6 Adverse reactions (frequency and seriousness)

Immediately after injection, a slight swelling (≤ 2 cm) at the injection site may commonly be observed, usually regressing within 1-6 days. This can, on some occasions, be accompanied by slight pruritus, heat and pain at the injection site. Transient lethargy and emesis may also be observed.

Uncommon reactions such as anorexia, polydipsia, hyperthermia, diarrhoea, muscle tremor, muscle weakness and injection site cutaneous lesions may be observed.

As with any vaccine, rare hypersensitivity reactions may occur. In such cases, appropriate symptomatic treatment should be provided.

The frequency of adverse reactions is defined using the following convention:

- *very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)*
- *common (more than 1 but less than 10 animals in 100 animals)*
- *uncommon (more than 1 but less than 10 animals in 1,000 animals)*

- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Can be used during pregnancy

4.8 Interaction with other medicinal products and other forms of interaction

The product can be mixed with Merial live attenuated vaccines against distemper, adenovirosis, parvovirosis and parainfluenza type 2 respiratory infections.

*Safety and efficacy data are available which demonstrate that this vaccine can be administered on the same day but not mixed with Merial's rabies vaccine in dogs from 12 weeks of age. In that case, the efficacy against *Leptospira Icterohaemorrhagiae* was demonstrated only for the reduction of renal lesions and bacterial excretion, and the efficacy against *Leptospira Grippotyphosa* was demonstrated only for the reduction of renal carriage, renal lesions and bacterial excretion.*

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

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No other adverse reactions other than those mentioned in section 4.6 were observed after administration of a 2-fold overdose of the suspension.

Field studies

Six field studies were performed to assess the safety of the vaccine. Dogs of different breeds, genders and ages (297 puppies and 366 adults) were vaccinated either with the product under test or with a commercial vaccine according to the vaccination scheme. All animals were observed for local or systemic reactions during the studies.

Overall, the vaccine proved to be well tolerated in the target species. The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under "adverse reactions".

Ecotoxicity

The applicant provided an environmental risk assessment which showed that the risk for the environment and other animals and species posed by this vaccine can be considered as very low.

Warnings and precautions as listed in the product literature for its disposal are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the Monograph 447 of Ph. Eur.:

Nine studies were performed in laboratory conditions. The efficacy in the dog was demonstrated by means of challenge trials.

- Efficacy of the *Leptospira canicola* component:

The onset of immunity was established based on the results of a randomised blinded trial in which 7 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of seven dogs was included. All the dogs were challenged at 14 days after the second vaccination. Mild to severe signs were observed in unvaccinated control dogs (leading to euthanasia of 2 animals with severe signs). All the vaccinated dogs remained in good general condition without any clinical signs.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical scores; number of days that the organisms are detected in the blood; number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

The duration of immunity was established based on the results of a randomised blinded trial in which 11 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of eleven dogs was included. All the dogs were challenged at 12 months after the second vaccination. Mild to moderate clinical signs were observed for 7 control animals (dehydration, apathy or digestive disorders) for 1 to 10 days. All vaccinated dogs remained in good general condition with no clinical signs except one dog that had hyperthermia.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical

scores; number of days that the organisms are detected in the blood; number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

Study	Group	Number of dogs with				
		Clinical signs	Infection Leptospiremia	Leptospiuria	Re-isolation from kidney	Lesions in kidney
Onset immunity Lc	Vaccinated (7)	0	0	0	0	0
	Control (7) 80% : ≥ 6	5 2 dogs euthanised	7	7	6	6
	p-value	p=0.021	p < 0.001 (duration)	p < 0.001 (duration)	p = 0.005	p = 0.005
Duration immunity Lc	Vaccinated (11)	0	9	4	2	1
	Control (10) 80% : ≥ 8	7	10	8	8	8
	p-value	p= 0.001	p=0.010 (duration)	p=0.004 (duration)	p=0.007	p<0.001
Final claim		Prevent clinical signs	Reduction of infection	Reduction of bacterial excretion	Reduction of renal carriage	Reduction of renal lesions

- Efficacy of the *Leptospira icterohaemorrhagiae* component:

The onset of immunity was established based on the results of a randomised blinded trial in which 7 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of seven dogs was included. All the dogs were challenged at 14 days after the second vaccination. Six out of the seven controls (86%) presented mild to severe clinical signs (icterus, dehydration, diarrhoea, loss of weight) leading to euthanasia of 2 animals on day 5 post-challenge. All the vaccinated dogs remained in good general condition without any clinical signs or hyperthermia.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical scores; number of days that the organisms are detected in the blood; number

of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

The duration of immunity was established based on the results of a randomised blinded trial in which 10 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of eleven dogs was included. These dogs were previously used for the demonstration of the Pi2 duration of immunity. All the dogs were challenged at 12 months after the second vaccination. Clinical signs were observed for all control animals: 3 dogs were euthanised, the 7 remaining controls exhibited clinical signs (dehydration, digestive disorders, icterus) for 1 to 10 days. All vaccines remained in good general condition with no clinical signs.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical scores; number of days that the organisms are detected in the blood; number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

Study	Group	Number of dogs with				
		Clinical signs	Infection Leptospiremia	Leptospiruria	Re-isolation from kidney	Lesions in kidney
Onset immunity Li	Vaccinated (7)	0	0	0	0	0
	Control (7) 80% : ≥ 6	6 2 dogs euthanised	7	7	6	6
	p-value	p=0.005	p < 0.001 (duration)	p < 0.001 (duration)	p = 0.005	p = 0.005
Duration immunity Li	Vaccinated (11)	0	2	0	0	0
	Control (11) 80% : ≥ 8	11 3 dogs euthanised	11	11	10	10
	p-value	p < 0.001	p < 0.001 (duration)	p < 0.001 (duration)	p < 0.001	p < 0.001
Final claim		Prevent clinical signs	Prevent infection	Prevent bacterial excretion	Prevent renal carriage	Prevent renal lesions

- Efficacy of the *Leptospira grippotyphosa* component:

The onset of immunity was established based on the results of a randomised blinded trial in which 14 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of seven dogs was included. All the dogs were challenged at 14 days after the second vaccination. Six out of the seven controls (86%) presented mild to severe clinical signs (apathy, icterus, dehydration, diarrhoea, loss of weight) leading to euthanasia of 3 animals on day 7-11 post-challenge. All the vaccinated dogs remained in good general condition without any clinical signs or hyperthermia.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical scores; number of days that the organisms are detected in the blood; number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

The duration of immunity was established based on the results of a randomised blinded trial in which 12 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of ten dogs was included. These dogs were previously used for the demonstration of the CAV-2 duration of immunity. All the dogs were challenged at 12 months after the second vaccination. Among the 10 control dogs, only one animal had slight clinical signs associated with a severe loss of weight during the first week post-challenge. All vaccines remained in good general condition with no clinical signs.

A significant reduction was seen between the vaccines and the controls for the number of kidney samples in which the organisms are detected.

Study	Group	Number of dogs with				
		Clinical signs	Infection Leptospiremia	Leptospiruria	Re-isolation from kidney	Lesions in kidney
Onset immunity Lg	Vaccinated (7)	0	0	0	0	0
	Control (7) 80% : ≥ 6 euthanised	6 3	7	5	7	6
	p-value	p=0.047	p < 0.001 (duration)	p < 0.021 (duration)	p < 0.001	p = 0.005
Duration immunity	Vaccinated (12)	0	5	2	2	1

Lg	Control (10) 80% : ≥ 8	1	8	7	6	5
	p-value	p=0.455*	p=0.059 (duration)	p=0.005 (duration)	p= 0.048	p= 0.043
Final claim		Reduction of clinical signs	Reduction of infection	Reduction of bacterial excretion	Reduction of renal carriage	Reduction of renal lesions

- Efficacy against a challenge with *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Copenhageni

The onset of immunity was established based on the results of a randomised blinded trial in which 7 seronegative puppies 8-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of seven dogs was included. All the dogs were challenged at 13 days after the second vaccination. Five out of the seven controls presented mild to severe clinical signs (apathy, icterus, dehydration, vomiting) leading to euthanasia of 4 animals on day 7-11 post-challenge. All the vaccinated dogs remained in good general condition without any clinical signs or hyperthermia.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical scores; number of days that the organisms are detected in the blood; number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

Study	Group	Number of dogs with				
		Clinical signs	Infection Leptospiremia	Leptospiruria	Re- isolation from kidney	Lesions in kidney
Onset immunity L.copenhageni	Vaccinated (7)	0	0	0	0	0
	Control (7) 80% : ≥ 6	5 4 dogs euthanised	7	7	7	7
	p-value	p=0.011	p < 0.001 (duration)	p < 0.001 (duration)	p < 0.001	p < 0.001
Final claim		Prevent clinical signs	Prevent infection	Prevent bacterial excretion	Prevent renal carriage	Prevent renal lesions

No study was provided to establish the duration of immunity.

- Association of the vaccine with a Merial rabies vaccine

A serological monitoring of one year was performed on 42 seronegative puppies 7-9 weeks old randomized into 3 groups: 14 dogs were vaccinated twice (at 4 weeks interval), first with Eurican DAPPi₂-L_{multi} and then with Eurican DAPPi₂-L_{multi} associated (but not mixed) with Rabisin; 14 dogs were vaccinated twice (at 4 weeks interval) with Eurican DAPPi₂-L3; 14 dogs were vaccinated once with Rabisin.

Serological responses against the viral components of the vaccine (CDV, CAV, CPV and CPiV) and Rabisin (rabies virus) was significantly non inferior in dogs vaccinated with Eurican DAPPi₂-L_{multi} and Rabisin when compared to that in dogs vaccinated with only one of the 2 vaccines. The applicant has shown that the titers obtained are above serological protective threshold for the CDV, CAV and CPV components and therefore the challenge for these components can be omitted.

With regard to the *Leptospira canicola* component, the demonstration of the compatibility is based on the results of a trial in which 6 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval), first with Eurican DAPPi₂-L_{multi} and then with Eurican DAPPi₂-L_{multi} associated (but not mixed) with Rabisin. A control group of six dogs was included. All the dogs were challenged at 14 days after the second vaccination. Mild to severe signs were observed in unvaccinated control dogs (leading to euthanasia of 1 animal with severe signs). All the vaccinated dogs remained in good general condition without any clinical signs.

A significant reduction was seen between the vaccines and the controls for the following parameters: clinical scores and haematological and biochemical scores; number of days that the organisms are detected in the blood; number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

With regard to the *Leptospira icterohaemorrhagiae* component, the demonstration of the compatibility is based on the results of a trial using puppies issued from the serological monitoring in which 7 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval), first with DAPPi₂-L_{multi} and then with Eurican DAPPi₂-L_{multi} associated (but not mixed) with Rabisin. A control group of six dogs vaccinated with Rabisin was included. All the dogs were challenged one year after the second vaccination. All dogs remained in good general condition without any clinical signs except 2 controls with ocular sign (conjunctivitis or purulent discharge) one day.

A significant reduction was seen between the vaccines and the controls for the following parameters: number of days with leptospiruria per dog and kidney histopathological scores.

With regard to the *Leptospira grippotyphosa* component, the demonstration of the compatibility is based on the results of a trial using puppies issued from the serological monitoring in which 7 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval), first with Eurican DAPPi₂-L_{multi} and then with Eurican DAPPi₂-L_{multi} associated (but not mixed) with Rabisin. A control group of six dogs vaccinated with Rabisin was included. All the dogs were challenged one year after the second vaccination. All dogs remained in good general condition without any clinical signs except one vaccinated dog which presented icterus from days 4 to 19 post-challenge and one control which presented icterus for 2 days.

A significant reduction was seen between the vaccines and the controls for the following parameters: number of days that the organisms are detected in the urine and the number of kidney samples in which the organisms are detected.

- Efficacy of the booster vaccination

Fourteen SPF puppies were primovaccinated with Eurican DAPPi₂-L_{multi} vaccine at the age of 8 and 12 weeks. A booster vaccination was carried out between 12 and 15 months after the second injection of primovaccination.

The results of the serological follow up showed that the vaccination could boost the immune response in dogs.

Field Trials

Two field studies were carried out to demonstrate the safety and the efficacy of the vaccine under field conditions.

The first study was performed in 10 veterinary practices in France. 93 puppies of various breeds never vaccinated before (7 to 24 weeks old, average 10.7 weeks) were vaccinated twice with Eurican DAPPi₂-L_{multi} vaccine at 4 weeks interval.

The results of the serological follow up showed that primovaccination with the vaccine induced a good immune response in puppies.

The second study was performed in 10 veterinary practices in France. 108 dogs of various breeds (more than 12 months old, average 5.7 years) previously vaccinated were vaccinated once with Eurican DAPPi₂-L_{multi} vaccine. The results of the serological follow up showed that the vaccination could boost the immune response in dogs previously vaccinated with a commercial vaccine.

The following conclusions can be drawn from the results of the studies concerning onset and duration of immunity, indications for use and immunisation scheme:

Active immunisation of dogs to:

- prevent mortality, clinical signs, infection, bacterial excretion, renal carriage and renal lesions caused by *Leptospira interrogans* serogroup *Icterohaemorrhagiae* serovar *Icterohaemorrhagiae*
- prevent mortality* and clinical signs, reduce infection, bacterial excretion, renal carriage and renal lesions caused by *Leptospira interrogans* serogroup *Canicola* serovar *Canicola*.
- prevent mortality*, and reduce clinical signs, infection, bacterial excretion, renal carriage and renal lesions caused by *Leptospira kirschneri* serogroup *Grippotyphosa* serovar *Grippotyphosa*.
- prevent mortality, clinical signs, renal infection, bacterial excretion, renal carriage and renal lesions caused by *Leptospira interrogans* serogroup *Icterohaemorrhagiae* serovar *Copenhageni*.**

Onset of immunity: 2 weeks for all strains

Duration of immunity: at least one year after the second injection of the primary vaccination course for all strains.

* For *Leptospira Canicola* and *Grippotyphosa*, no mortality occurred during the duration of immunity challenge.

** For *Leptospira Copenhageni* the duration of immunity was not established.

4.8 Interaction with other medicinal products and other forms of interaction

The product can be mixed with Boehringer Ingelheim live attenuated vaccines against distemper, adenovirosis, parvovirosis and parainfluenza type 2 respiratory infections.

*Safety and efficacy data are available which demonstrate that this vaccine can be administered on the same day but not mixed with Boehringer Ingelheim's rabies vaccine in dogs from 12 weeks of age. In that case, the efficacy against *Leptospira Icterohaemorrhagiae* was demonstrated only for the reduction of renal lesions and bacterial excretion, and the efficacy against *Leptospira Grippotyphosa* was demonstrated only for the reduction of renal carriage, renal lesions and bacterial excretion. Efficacy of the vaccine 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

4.9 Amounts to be administered and administration route

When Lmulti is used alone, inject a 1-ml dose subcutaneously

When Lmulti is used as a diluent of a Merial freeze-dried vaccine, aseptically reconstitute the contents of the lyophilisate with the suspension for injection. Shake well before use. The entire contents of the reconstituted vial should be administered as a single dose.

The following schedule should be followed:

Primary vaccination: Two injections separated by an interval of 4 weeks from 7 weeks of age.

Revaccination: Administer one dose 12 months after completion of the primary vaccination course. Dogs should be revaccinated with a single booster dose on an annual basis.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION

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 veterinary Heads of Agencies website (<http://www.hma.eu/vmrproductindex.html>).

This section 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.

Quality changes

Summary of change	Approval date
Extension of the approved shelf-life from 18 to 24 months	2016
Addition of an alternative manufacturing site for the Leptospira active ingredients.	2016

Safety/efficacy changes

Summary of change	Approval date
Addition of an indication for use (SPC section 4.2- Leptospira Copenhageni) related to the active immunization provided by Leptospira antigens	2017