Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

Versican L3R

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<tr>
<td>Zulassungsnummer:</td>
<td>PEI.V.11603.01.1</td>
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<tr>
<td>Datum der Bekanntgabe beim Antragsteller der/des Zulassungsänderung/Widerrufs, Rücknahme, Anordnung des Ruhens der Zulassung:</td>
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PAUL-EHRLICH-INSTITUT
PAUL-EHRLICH-STRASSE 51-59
63225 LANGEN
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Versican L3R
### PRODUCT SUMMARY

<table>
<thead>
<tr>
<th><strong>EU Procedure number</strong></th>
<th>DE/V/0257/001/MR</th>
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<tr>
<td><strong>Name, strength and pharmaceutical form</strong></td>
<td>Versican L3R, suspension for injection</td>
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</table>
| **Applicant** | Pfizer Ltd  
Ramsgate road  
Sandwich  
Kent CT13 9NJ  
UK |
| **Active substance(s)** | **Active substances (inactivated)**  
*Leptospira interrogans* serovar Icterohaemorrhagiae, strain MSLB 1008,  
ARL* titre $\geq$ 1:32  
*Leptospira interrogans* serovar Canicola, strain MSLB 1010  
ARL* titre $\geq$ 1:32  
*Leptospira kirschneri* serovar Grippotyphosa, strain MSLB 1009  
ARL* titre $\geq$ 1:64  
Rabies virus, strain SAD Vnukovo-32  
$\geq$ 2.0 IU** |
| **ATC Vetcode** | QI07AL01 |
| **Target species** | Dogs |
| **Indication for use** | Active immunization of dogs to reduce clinical signs and infection caused by *Leptospira interrogans* serovars Canicola, Icterohaemorrhagiae and *Leptospira kirschneri* serovar Grippotyphosa and to prevent mortality and infection caused by rabies virus. |

*Antibody micro agglutination -lytic reaction  
**International units  
Adjuvant: Aluminium hydroxide gel, 1.8 - 2.2 mg
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT
Versican L3R, suspension for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Composition per 1 ml dose:

Active substances (inactivated):

*Leptospira interrogans* serovar Icterohaemorrhagiae, strain MSLB 1008
ARL\(^*\) titre ≥ 1:32

*Leptospira interrogans* serovar Canicola, strain MSLB 1010
ARL\(^*\) titre ≥ 1:32

*Leptospira kirschneri* serovar Grippotyphosa, strain MSLB 1009
ARL\(^*\) titre ≥ 1:64

Rabies virus, strain SAD Vnuoko-32
≥ 2.0 IU\(^**\)

* Antibody micro agglutination -lytic reaction
\(^**\) International units

Adjuvant:

Aluminium hydroxide gel 1.8 - 2.2 mg

Excipient:

For a full list of excipients, see section 6.1.
3. PHARMACEUTICAL FORM

Suspension for injection
Pink colour with fine sediment

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Active immunization of dogs to reduce clinical signs and infection caused by *Leptospira interrogans* serovars Canicola, Icterohaemorrhagiae and *Leptospira kirschneri* serovar Grippotyphosa, and to prevent mortality and infection caused by rabies virus.

**Onset of immunity:** Immunity has been demonstrated from 3 weeks after completion of the primary course for Rabies and from 4 weeks after the primary course for *Leptospira* components.

**Duration of immunity:** At least one year following the primary vaccination course.
Reduction of urinary excretion of *Leptospira* has not been shown.

4.3 Contraindications

None.

4.4 Special warnings for each target species

None
4.5 Special precautions for use

*Special precautions for use in animals*

Only healthy animals should be vaccinated.

Do not use in animals that are showing signs of rabies or that are suspected of being infected with rabies virus.

*Special precautions to be taken by the person administering the veterinary medicinal product to animals*

In case of accidental self-injection, wash the area with water. If symptoms develop, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

Following subcutaneous administration to dogs, swelling may occur at the injection site and reach a maximum diameter of up to 10 mm. These reactions generally disappear after 10 days and may on rare occasions be sensitive to palpation for up to 3 days after vaccination.

As with any vaccine rare, occasional hypersensitivity reactions may occur. If such a reaction occurs, appropriate treatment should be administered without delay.

4.7 Use during pregnancy or lactation

Laboratory studies have shown the vaccine can be used during pregnancy

4.8 Interaction with other medicinal products and other forms of interaction

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product other than other vaccines in the Versican range. 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**

**Dosage and route of administration:**
Inject the entire content of the vial (1 ml) subcutaneously. Do not use chemically sterilised syringes or needles, as these may interfere with the effectiveness of the vaccine.

**Primary vaccination course:**
Two doses of Versican L3R between 2 and 4 weeks apart. The first dose can be given as young as 8 weeks of age. The second dose should be given not younger than 12 weeks of age.

The efficacy of the Rabies fraction is proven after a single dose from 12 weeks of age, therefore the first dose may be given with compatible product Versican DHPPi/L3 or Versican L3 if only a single Rabies dose is desired (please refer to SPC for Versican DHPPi/L3 and Versican L3).

**Revaccination scheme:**
A single dose of Versican L3R to be given annually thereafter.

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

No adverse effects other than those mentioned under section 4.6 (Adverse reactions) have been observed after administration of an overdose of the vaccine.

4.11 **Withdrawal period(s)**

Not applicable.

5. **IMMUNOLOGICAL PROPERTIES**

Pharmacotherapeutic group: Inactivated viral and inactivated bacterial vaccines
ATCvet code: QI07AL01

The vaccine is intended for the active immunisation of healthy puppies and dogs against diseases caused by *Leptospira interrogans* serovars Canicola,
Icterohaemorrhagiae and *Leptospira kirschneri* serovar Grippotyphosa, and rabies virus.

The rabies strain is of canine origin and is produced in a BHK cell culture system

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection

6.2 Incompatibilities

Do not mix with any other veterinary medicinal product.

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: administer the vaccine immediately

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C). Do not freeze.

6.5 Nature and composition of immediate packaging

The vaccine is supplied in Type I glass vials complying with Ph Eur. Vials are closed with a chlorobutyl rubber stopper and aluminium cap.

The vaccine is supplied in quantities of 1, 5, 10, 20, 25, 50 or 100 x 1 ml in plastic boxes
Not all pack sizes may be marketed.
6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer
(Address to be defined for each country where the licence would be granted)

8. MARKETING AUTHORISATION NUMBER(S)

TBC

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<TD/MM/YYYY> <DD month YYYY>…
To be defined

10 DATE OF REVISION OF THE TEXT

24/09/2012

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.
PUBLIC ASSESSMENT REPORT

| Legal basis of mutual recognition application | Mutual recognition application in accordance with Article 31 of Directive 2001/82/EC as amended. |
| Date of completion of the mutual recognition procedure | 24.09.2012 |
| Date product first authorised in the Reference Member State | 21.02.2012 |
| Concerned Member States for mutual recognition procedure | AT, BE, FR, LU, PT |

I. SCIENTIFIC OVERVIEW

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 slight 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. 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

Composition per 1 ml dose:

Active substances (inactivated):

* Leptospira interrogans serovar Icterohaemorrhagiae, strain MSLB 1008
  ARL* titre ≥ 1:32
* Leptospira interrogans serovar Canicola, strain MSLB 1010
  ARL* titre ≥ 1:32
* Leptospira kirschneri serovar Grippotyphosa, strain MSLB 1009
  ARL* titre ≥ 1:64

Rabies virus, strain SAD Vnukovo-32, ≥ 2.0 IU**

* Antibody micro agglutination -lytic reaction
** International units

Adjuvant:

Aluminium hydroxide gel 1.8 - 2.2 mg

Container/closure system:

The vaccine is filled in 3 ml glass type I containers:
The vials are closed with a chlorobutyl rubber stopper and an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulations of Monograph 3.2.1 of the European Pharmacopoeia (Ph.Eur.).

The choice of the adjuvant (aluminium hydroxide) and the vaccine strains (*Leptospira* Icterohaemorrhagiae, strain MSLB 1008, *Leptospira* Canicola, strain MSLB 1010, *Leptospira* Grippotyphosa, strain MSLB 1009, and rabies virus, strain SAD Vnukovo-32) are justified.

The inactivation process and the detection limit of the control of inactivation 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 Practice (GMP) from a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided. Process validation data on the product have been presented in accordance with the relevant European guidelines. The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with the pharmacopoeia monograph 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, 7Blm10a). 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 in detail. These tests are as follows:

Leptospira:
- growth and purity
- bacterial count
- demonstration of inactivation
- sterility
- demonstration that rabbit serum is no longer contained
Rabies virus:
- determination of titre before inactivation
- pH determination
- demonstration of inactivation
- sterility
- glycoprotein test

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements.

- appearance
- sterility: according to Ph.Eur. 2.6.1
- test for air tightness
- determination of aluminium content
- volume
- pH determination
- identity of Leptospira and rabies virus
- demonstration of inactivation
- potency
- safety

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.

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

The vaccine must be used immediately after broaching.
III. SAFETY ASSESSMENT

Versican L3R is a multivalent vaccine for dogs containing inactivated *Leptospira interrogans*, serovars *Icterohaemorrhagiae* and *Canicola*, and *Leptospira kirschneri*, serovar *Grippotyphosa*, and inactivated rabies virus. It is intended for stimulation of an active immunity against infections with *Leptospira* and rabies virus. This vaccine contains aluminium hydroxide as adjuvant. The suspension for injection is administered subcutaneously. Dogs from an age of 8 weeks can be vaccinated.

*Laboratory trials*

The vaccine was developed as part of a larger combination (Versican DHPPi/L3R) consisting of live virus components (canine distemper virus [CDV], canine adenovirus Type 2 [CAV2], canine parvovirus [CPV], canine parainfluenzavirus [CPi]) presented in freeze-dried form in a vial to be reconstituted with a vial of inactivated components (rabies virus, *Leptospira Canicola*, *Leptospira Icterohaemorrhagiae*, and *Leptospira Grippotyphosa*) presented in liquid form. The liquid fraction also contains aluminium hydroxide as adjuvant.

Therefore many of the safety studies presented in the dossier were undertaken using Versican DHPPi/L3R, which is consistent with the requirements of the guideline on combination products (CVMP/IWP/52/97).

The trials have been performed in the target species (dogs). All animals used were seronegative to the individual antigens.

The safety of the administration of one dose, an overdose (double dose) and the repeated administration of one dose in the target animal (dog) was demonstrated in laboratory trials.

The animals were allocated to different groups and were administered either a single dose, an overdose or repeat single doses with an interval of several weeks. Unvaccinated animals were used as control group. All animals were monitored for local and systemic reactions during the study.

Overall, the vaccine Versican L3R proved to be well tolerated in the target species dog. The local and systemic reactions observed are described in the SPC (Summary of Product Characteristics) and package leaflet under “adverse reactions”.

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. As the vaccine Versican L3R 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.

Versican L3R is an inactivated vaccine. There is no reason to suppose that it might adversely affect immunological functions of the recipient. Therefore, no specific studies to examine the effect on immunological functions have been carried out.

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

After vaccination, hypersensitivity reactions may occur. This is also described in the SPC and package leaflet.

No information is available on the safety of this vaccine when used with any other veterinary medicinal product other than other vaccines in the Versican range (Versican DHPPi/L3 and Versican L3). 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**

Field studies were performed to assess the safety of the vaccine Versican L3R. Dogs of different breeds, genders and ages were vaccinated with Versican L3R according to the vaccination scheme. All animals were observed for local or systemic reactions during the studies. Overall, the vaccine Versican L3R proved to be well tolerated in the target species dog. 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. No warnings are therefore required in the SPC and package leaflet.
IV. EFFICACY

IV.B Laboratory Trials

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

- Leptospirosis: Monograph 447
- Rabies Monograph 451

The vaccine was developed as part of a larger combination (Versican DHPPi/L3R) consisting of live virus components (canine distemper virus [CDV], canine adenovirus Type 2 [CAV2], canine parvovirus [CPV], canine parainfluenzavirus [CPi]) presented in freeze-dried form in a vial to be reconstituted with a vial of inactivated components (rabies virus, Leptospira Canicola, Leptospira Icterohaemorrhagiae, and Leptospira Grippotyphosa) presented in liquid form. The liquid fraction also contains aluminium hydroxide as adjuvant.

Therefore many of the efficacy studies presented in the dossier were undertaken using Versican DHPPi/L3R, which is consistent with the requirements of the guideline on combination products (CVMP/IWP/52/97).

The efficacy in the target species dog was demonstrated by means of challenge trials. In these trials, seronegative animals at the minimum vaccination age of 8 weeks were vaccinated with Versican L3R and subsequently challenged with Leptospira or rabies virus. Unvaccinated animals served as controls. The results clearly demonstrate the efficacy of Versican L3R.

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

Active immunization of dogs
✓ to reduce clinical signs and infection caused by Leptospira interrogans serovars Canicola, Icterohaemorrhagiae and Leptospira kirschneri serovar Grippotyphosa
✓ and to prevent mortality and infection caused by rabies virus.

Reduction of urinary excretion of Leptospira has not been shown.
Onset of immunity: Immunity has been demonstrated from 3 weeks after completion of the primary course for Rabies and from 4 weeks after the primary course for Leptospira components.

Duration of immunity: At least one year following the primary vaccination course.

Vaccination scheme:

Two doses of Versican L3R between 2 and 4 weeks apart. The first dose can be given as young as 8 weeks of age. The second dose should be given not younger than 12 weeks of age.

The efficacy of the Rabies fraction is proven after a single dose from 12 weeks of age, therefore the first dose may be given with compatible product Versican DHPPi/L3 or Versican L3 if only a single Rabies dose is desired (please refer to SPC for Versican DHPPi/L3 and Versican L3).

Revaccination scheme:
A single dose of Versican L3R to be given annually thereafter.

Field Trials

The applicant has conducted field studies on the efficacy of Versican L3R. Dogs of different breeds, genders and ages were vaccinated with Versican L3R according to the vaccination scheme. All animals were regularly bled during the study to determine antibodies to Leptospira, and rabies virus. The results confirm the observations made in the laboratory studies. The vaccine Versican L3R proved to be efficacious in the target species dog.

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.