Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

Versican Plus P

Zulassungsdatum:	24.03.2016
Zulassungsnummer:	PEI.V.11781.01.1
Datum der Erstellung des öffentlichen Beurteilungsberichts:	27 April 2017
Datum der Bekanntgabe beim Antragsteller der/des Zulassungsänderung/Widerrufs, Rücknahme, Anordnung des Ruhens der Zulassung:	-

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Versican Plus P

PRODUCT SUMMARY

EU Procedure number	DE/V/0265/001/DC
Name, strength and pharmaceutical form	Versican Plus P, lyophilisate and solvent for suspension for injection
Applicant	Zoetis Belgium s.a. Rue Laid Burnait, 1 1348 Louvain-la-Neuve Belgium
Active substance(s)	Each dose of 1 ml contains: Lyophilisate (live attenuated): Canine parvovirus Type 2b, strain CPV-2b Bio 12/B $10^{4.3}$ – $10^{6.6}$ $TCID_{50}$* Solvent: Water for injections (*Aqua ad iniectabilia*): 1 ml * Tissue culture infectious dose 50%
ATC Vetcode	QI07AD01
Target species	Dogs
Indication for use	Active immunisation of dogs from 6 weeks of age: - to prevent clinical signs, leucopoenia and viral excretion caused by canine parvovirus.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Versican Plus P lyophilisate and solvent for suspension for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose of 1ml contains:

Active substances:

Lyophilisate (live attenuated):	**Minimum**	**Maximum**
Canine parvovirus Type 2b, strain CPV-2b Bio 12/B	$10^{4.3}$ $TCID_{50}$*	$10^{6.6}$ $TCID_{50}$

Solvent:

Water for injections (*Aqua ad iniectabilia*)	1 ml

* Tissue culture infectious dose 50%

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate and solvent for suspension for injection.

The visual appearance is as follows:
Lyophilisate: spongy matter of white colour.
Solvent: clear colourless liquid.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Active immunisation of dogs from 6 weeks of age:

- to prevent clinical signs, leucopoenia and viral excretion caused by canine parvovirus.

Onset of immunity:

- 3 weeks after the first vaccination

Duration of immunity: At least three years following the primary vaccination course

4.3 Contraindications

None.

4.4 Special warnings for each target species

A good immune response is reliant on a fully competent immune system. Immunocompetence of the animal may be compromised by a variety of factors including poor health, nutritional status, genetic factors, concurrent drug therapy and stress.

Immunological responses to CPV may be delayed due to maternally derived antibody interference. However, the vaccine has been proven to be protective against virulent challenge in the presence of maternally derived antibodies to CPV at levels equal or higher to those likely to be encountered under field conditions. In situations where very high maternally derived antibody levels are expected, the vaccination protocol should be planned accordingly.

4.5 Special precautions for use

Special precautions for use in animals

Vaccinate healthy animals only.

The live attenuated virus vaccine strain CPV-2b may be shed by vaccinated dogs following vaccination, shedding of CPV has been shown for up to 10 days. However, due to the low pathogenicity of this strain, it is not necessary to keep vaccinated dogs separated from non-vaccinated dogs and domestic cats. The vaccine virus strain CPV-2b has not been tested in other carnivores (except dogs and domestic cats) that are known to be susceptible to canine parvoviruses and therefore vaccinated dogs should be separated from them after vaccination.

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

In case of accidental self-injection, 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 in dogs a transient swelling (up to 5 cm) may commonly be observed at the injection site. These can occasionally be painful, warm or reddened. Any such swelling will either have spontaneously resolved or be greatly diminished by 14 days after vaccination. In rare cases gastrointestinal signs such as diarrhoea and vomiting or anorexia and decreased activity are possible.

As with any vaccine, in rare cases hypersensitivity reactions (i.e. anaphylaxis, angioedema, dyspnoea, circulatory shock, collapse) may occur. If such a reaction occurs, appropriate treatment should be administered without delay.

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

- very common (more than 1 in 10 animals displaying adverse reactions 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

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Therefore the use is not recommended during pregnancy and lactation.

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 Versiguard Rabies and Versican Plus L4. 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 by the veterinarian.

4.9 Amounts to be administered and administration route

Subcutaneous use.

Dosage and route of administration:
Aseptically reconstitute the lyophilisate with the solvent. Shake well and administer immediately the entire contents (1 ml) of the reconstituted product.

Reconstituted vaccine: Whitish to yellowish colour with light opalescence.

Primary vaccination scheme:
Two doses of Versican Plus P 3–4 weeks apart from 6 weeks of age.

Leptospira:
If protection against *Leptospira* is required, dogs can be vaccinated with two doses of Versican Plus P mixed with Versican Plus L4 3–4 weeks apart from 6 weeks of age: The contents of a single vial of Versican Plus P should be reconstituted with the contents of a single vial of Versican Plus L4 (instead of the solvent). Once mixed, the contents of the vial should appear a whitish to yellowish colour with a slight opalescence. The mixed vaccines should be injected immediately via the subcutaneous route.

Rabies:
If protection against rabies is required:
First dose: Versican Plus P from 8–9 weeks of age.
Second dose: Versican Plus P mixed with Versiguard Rabies 3–4 weeks later, but not before 12 weeks of age.
The contents of a single vial of Versican Plus P should be reconstituted with the contents of a single vial of Versiguard Rabies (instead of the solvent). Once mixed, the contents of the vial should appear a pink/red or yellowish colour with a slight

opalescence. The mixed vaccines should be injected immediately via the subcutaneous route.

The efficacy of the rabies fraction is proven after a single dose from 12 weeks of age in laboratory studies. However, in field studies 10% of seronegative dogs did not show seroconversion (>0.1 IU/ml) 3–4 weeks after single primary vaccination against rabies. Some animals may also not show titres > 0.5 IU/mL after the primary vaccination. Antibody titres drop over the course of the 3-year duration of immunity, although dogs are protected when challenged. In case of travelling to risk areas or outside the EU, veterinary surgeons may wish to give additional rabies vaccinations after 12 weeks of age to ensure that the vaccinated dogs have an antibody titre of ≥ 0.5 IU/mL, which is generally regarded as sufficiently protective and that they meet the travel test requirements (antibody titres ≥ 0.5 IU/mL).

Although the efficacy of the rabies fraction has been demonstrated following administration at 12 weeks, at the discretion of the veterinary surgeon, in case of need, dogs younger than 8 weeks can be vaccinated with Versican Plus P mixed with Versiguard Rabies as the safety of this association has been demonstrated in 6 week old dogs.

Revaccination scheme:
A single dose of Versican Plus P should be given every 3 years.

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 10-fold overdose of the vaccine. However in a minority of animals pain was observed at the injection site immediately after administration of a 10-fold overdose of the vaccine. The pain was transient and subsided without requiring any therapy.

4.11 Withdrawal period(s)

Not applicable.

5. IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Immunologicals for canidae, live viral vaccines. ATCvet code: QI07AD01.

The vaccine is intended for the active immunisation of healthy puppies and dogs against disease caused by canine parvovirus

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilisate:
Tris/Trometamol
Edetic acid (Chelaton II)

Sucrose
Dextran 70

Solvent:
Water for injections

6.2 Incompatibilities

Do not mix with any veterinary medicinal products except those mentioned in section 4.8.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years. Shelf life after reconstitution according to directions: use immediately.

6.4. Special precautions for storage

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

6.5 Nature and composition of immediate packaging

Type I glass vial containing 1 dose of lyophilisate closed with a bromobutyl rubber stopper and aluminium cap.
Type 1 glass vial containing 1 ml of solvent closed with a chlorobutyl rubber stopper and aluminium cap.

Pack sizes:
Plastic box containing 25 vials of lyophilisate and 25 vials of solvent. Plastic box containing 50 vials of lyophilisate and 50 vials of solvent.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TBC nationally

8. MARKETING AUTHORISATION NUMBER(S)

TBC nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10. DATE OF REVISION OF THE TEXT

TBC

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

PUBLIC ASSESSMENT REPORT

Legal basis of decentralised procedure application	Decentralised procedure application in accordance with Article 31 of Directive 2001/82/EC as amended.
Date of completion of the decentralised procedure	27 January 2016
Concerned Member States for mutual recognition procedure	BE, BG, DK, FR, HR, HU, IE, IT, LU, NO, SE, SI, UK
Date of completion of repeat use procedure	21 April 2017
New concerned Member States for mutual recognition procedure after repeat use procedure	CY, EL

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:

Each 1 ml dose of Versican Plus P contains the following:

Active substance:

Lyophilisate (live attenuated):	**Minimum**	**Maximum**
Canine parvovirus Type 2b, strain CPV-2b Bio 12/B	$10^{4.3}$ $TCID_{50}$*	$10^{6.6}$ $TCID_{50}$

Solvent:

Water for injections (*Aqua ad iniectabilia*)	1 ml

* Tissue culture infectious dose 50%

Container/closure system:
The vaccine is filled in 3 ml glass type I containers.
The vials of the lyophilisate are closed with a bromobutyl rubber stopper and an aluminium cap. The vials of the solvent 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 vaccine strain (canine parvovirus Type 2b, strain CPV-2b Bio 12/B) is justified.

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 certificate 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.

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.

D. Control tests during production

The tests performed during production are described in detail.

These tests are as follows:

Lyophilisate

- sterility
- test for mycoplasma
- determination of virus titre

- cell count
- virus identity
- pH determination (on the vaccine bulk after blending)
- sterility (on the vaccine bulk after blending)

Solvent
There are no in-process controls for the liquid fraction (water for injection).

E. Control Tests on the Finished Product

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

The following tests are performed:

Lyophilisate
- appearance
- test for absence of extraneous agents
- sterility: according to Ph. Eur. 2.6.1
- test for mycoplasma
- virus identity
- determination of virus titre
- determination of residual humidity
- vacuum test

Solvent
- appearance
- sterility: according to Ph. Eur. 2.6.1
- test for air tightness
- volume
- test for acidity or alkalinity
- test for conductivity
- test for oxidisable substances
- test for chlorides, nitrates, sulfates, ammonium, calcium, magnesium
- determination of the residue after evaporation
- test for bacterial endotoxins (Ph. Eur. 2.6.14)

Reconstituted vaccine
- appearance
- pH determination

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.

F. 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 Plus P is a monovalent vaccine for dogs containing live attenuated canine parvovirus type 2b. It is intended for stimulation of an active immunity against infections with canine parvovirus. The lyophilisate is solved with a solvent (water for injection) and subsequently administered subcutaneously. Dogs from an age of 6 weeks can be vaccinated.

Laboratory trials

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 (tenfold 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 groups. All animals were monitored for local and systemic reactions during the studies.
Overall, the vaccine Versican Plus P 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.

The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Therefore the use is not recommended during pregnancy and lactation. A corresponding note is included in the SPC and package leaflet.

As the canine parvovirus may have immunosuppressive properties, a study was performed to investigate the immunological properties of the canine parvovirus. It could be shown that the canine parvovirus has no negative impact on the immune system of the vaccinated dogs.

For the live attenuated canine parvovirus type 2b strain included in the vaccine specific studies were carried out to describe the spread, dissemination in the vaccinated animal, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain. No reversion to virulence of the vaccine antigen was observed in these studies. The live attenuated virus vaccine strain CPV2b may be shed by vaccinated animals following vaccination. However, due to the low pathogenicity of this strain, it is not necessary to keep vaccinated dogs separated from non-vaccinated dogs and domestic cats. The vaccine virus strain CPV-2b has not been tested in other carnivores (except dogs and domestic cats) that are known to be susceptible to canine parvoviruses. Therefore vaccinated dogs should be separated from them after vaccination. An appropriate warning is included in the SPC and package leaflet.

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

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product other than Versiguard Rabies and Versican Plus

L4. 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 by the veterinarian.

Field studies

Field studies were performed to assess the safety of the vaccine Versican Plus P.
Dogs of different breeds, genders and ages were vaccinated with Versican Plus P according to the vaccination scheme. All animals were observed for local or systemic reactions during the studies.
Overall, the vaccine Versican Plus P 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".

Environmental Risk Assessment

The applicant provided an environmental risk assessment in compliance with the relevant guideline 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 Clinical Studies Laboratory Trials

Versican Plus P is a monovalent live virus vaccine indicated for the immunisation of healthy puppies from six weeks of age and dogs against canine parvovirosis. The vaccine was developed as part of a larger combination (Versican Plus DHPPi/L4R) consisting of live virus components (canine distemper virus (CDV), canine adenovirus type 2 (CAV-2), canine parvovirus (CPV), canine parainfluenzavirus (CPiV)) presented in freeze-dried form in a vial to be reconstituted with a vial of the inactivated components (rabies virus, *Leptospira* Canicola, *Leptospira* Icterohaemorrhagiae, *Leptospira* Bratislava and *Leptospira* Grippotyphosa) presented in liquid form. The adjuvant of the liquid fraction is aluminium hydroxide. Therefore, many studies presented have been conducted with the larger combination. According to the CVMP guideline on multi-component vaccines these can be used to fully support the safety and efficacy of the smaller fall-out combinations.
The live virus component of Versican Plus P (canine parvovirus type 2b (CPV-2b)) is presented in freeze-dried form in a vial to be reconstituted with a vial of the diluent (water for injection). The vaccine Versican Plus P itself does not contain any adjuvant.

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

- Canine parvovirus type 2b: Monograph 0964

The efficacy in the target species dog was demonstrated by means of challenge trials.

Onset of immunity

CPV-2b:
Seven 6-week old dogs (5 vaccinates and 2 control dogs), tested seronegative against CPV (haemagglutination inhibition (HAI) and virus neutralisation (VN)), were administered the vaccine Versican Plus DHPPi/L4R subcutaneously. They were challenged oronasally with the challenge strain CPV-2b strain 212/98 at Day 21 after vaccination. After challenge the vaccinated group showed no clinical signs and no increase of rectal temperature. There was a further increase in antibody titres against CPV-2b while the white blood cell count demonstrated no leukopenia.
On virus isolation and HA 3/5 dogs excreted virus on one day between 3 and 5 days after challenge. This was less than 1/100 of the geometric mean of the maximum titres found in control animals by HA. No isolation of infectious CPV-2b was found in cell culture. This study is considered valid because it fulfils the requirements of Ph. Eur. monograph 0964.

Equivalence study
The objective of this study was the evaluation of the serological and clinical responses to non-adjuvanted Versican Plus DHPPi and Versican Plus Pi fall-out products of the Versican Plus DHPPi/L4R vaccine range after primary vaccination and by challenge with a virulent, heterologous strain of canine parainfluenza virus. As the vaccine Versican Plus P does not contain canine parainfluenzavirus, results pertaining to the challenge are not relevant and are therefore not summarised below.

Twenty-five 6-week old dogs (10 dogs vaccinated with Versican Plus DHPPi, 10 dogs vaccinated with Versican Plus Pi and 5 control dogs) were administered the vaccines subcutaneously at Day 0 and Day 21. The serological responses against CPV following primary vaccination with the non-adjuvanted Versican Plus DHPPi and Versican Plus Pi fall-out products of Versican Plus DHPPi/L4R vaccine were evaluated and visually compared to the results of historical data from studies with adjuvanted Versican Plus DHPPi/L4R. If the 95% confidence interval of the geometric mean titre of the non-adjuvanted component of the fall-out product in this study overlap the 95% confidence intervals of the geometric means of the adjuvanted components of Versian Plus DHPPi/L4R in historic studies on at least one time point after primary immunisation, responses were considered to be equivalent.

CPV serology results:
At the time of the second vaccination all animals had seroconverted. However, after the second vaccination the titres increased which demonstrates the booster effect of this vaccination.

Assessment of the equivalence of the serological data:
Based on the results of this assessment it can be concluded that the CPV component used in the Versican Plus range vaccines protect against canine parvovirosis irrespective of whether they are adjuvanted or non-adjuvanted (95% confidence interval of geometric mean antibody titre against CPV-2 of seronegative, vaccinated dogs). This was considered acceptable.

Influence of maternally derived antibodies on the efficacy of the vaccine

The presented studies clearly show the influence of maternally derived antibodies (MDA) regarding CPV antigen. While MDA negative dogs seroconvert after the first vaccination and are boostered after the second vaccination, MDA positive dogs show a titre decrease until Days 28–35. Seroconversion is observed from Days 35–42 onwards. Although the animals were protected against challenges with virulent CPV strain, the possible interference of MDA should always be taken into consideration when vaccinating very young puppies. The studies demonstrate the importance of the second vaccination as part of the primary vaccination: animals with MDA do not seroconvert after the first vaccination but after the second one. As immunological response to CPV may be delayed due to MDA the vaccination scheme for young dogs - especially for puppies at 6 weeks of age - should be planned carefully. This has been reflected in the SPC.

Duration of immunity

CPV-2b:
Seven 6-week old dogs (5 vaccinates and 2 control dogs), tested seronegative against CPV (HAI and VN) were administered the vaccine Versican Plus DHPPi/L4R subcutaneously at Day 0 and Day 21. They were challenged oronasally with the challenge strain CPV-2b strain 212/98 at 12 months after the second vaccination. Control animals remained seronegative until challenge. As they were housed together with vaccinated animals, these results confirm that vaccine induced immunity to CPV was not further boosted through concurrent infections with field strains during the study. After challenge the vaccinated group showed no clinical signs and no increase of rectal temperature. Virus isolation: by HA, 3/5 animals

showed CPV excretion for 2 days between 5 and 10 days after challenge. This was less than 1/100 of the geometric mean of the maximum titres found in control animals by HA. By cell culture, 0/5 vaccinated animals excreted infectious CPV.
The control group showed no abnormal clinical signs, there was hyperthermia in 1/2 controls 10 and 11 days after challenge. White blood cell count: leukopenia - white blood cell numbers decreased more than 50% compared to pre-challenge mean values (leukopenia) in 2/2 controls. Virus isolation: by HA, 2/2 controls showed CPV excretion starting 5 days and peaking from 7 to 10 days after challenge. By cell culture, 2/2 controls started to excrete CPV 5 days and peaked 7 days postchallenge.

Immunity after revaccination – response to booster

To demonstrate protective immunity of the components of Versican Plus DHPPi/L4R following re-vaccination (annual booster) with a single dose 12 months after completion of the primary vaccination course laboratory response-to-booster studies in dogs were performed. For the CPV component, protective immunity following an annual booster was demonstrated serologically by comparing antibody titres in response to the annual booster with those after primary vaccination.
The antibody titres against **CPV** of vaccinated animals 12 months after the second vaccination have declined slightly. After a single booster vaccination the titres increased again and were comparable to those observed three weeks after primary vaccination course.

Three-year duration of immunity studies

CPV-2b:
Nine 6-7-week old dogs (6 vaccinates and 3 control dogs), tested seronegative against CPV (HAI and VN) were administered the vaccine Versican Plus DHPPi/L4R subcutaneously at Day 0 and Day 21. Three years after the second vaccination 7 dogs (5 vaccinates and 2 control dogs) were challenged oronasally with the challenge strain CPV-2b strain 212/98.
Control animals remained seronegative until challenge. As they were housed together with vaccinated animals, these results confirm that vaccine induced immunity to CPV was not further boosted through concurrent infections with field strains during the study. After challenge the vaccinated group showed no clinical signs, no increase of rectal temperature and no leukopenia. Virus isolation: by HA, 4/5 animals showed CPV excretion for 1-3 days between 3 and 10 days after challenge. This was less than 1/100 of the geometric mean of the maximum titres found in control animals by HA. By cell culture, 0/5 vaccinated animals excreted infectious CPV.
The control group showed clinical signs of canine parvovirosis. There was hyperthermia in 1/2 controls 8 days after challenge. White blood cell count: leukopenia - white blood cell numbers decreased more than 50% compared to prechallenge mean values (leukopenia) in 1/2 controls. Virus isolation: by HA, 2/2 controls showed CPV excretion starting 3 days and peaking from 12 days after challenge. By cell culture, 2/2 controls started to excrete CPV 3 days and peaked 12 days post-challenge.

Immunity after revaccination – response to booster

To demonstrate protective immunity of the components of Versican Plus DHPPi/L4R following re-vaccination with a single dose 3 years after completion of the primary vaccination course a laboratory response-to-booster study in dogs was performed.

Twelve 6-7-week old dogs (10 vaccinates and 2 control dogs), seronegative against CPV were vaccinated with Versican Plus DHPPi/L4R at Day 0 and Day 21. Three years after the second vaccination 9 dogs (7 vaccinates and 2 control dogs) received a booster vaccination. The titres against **CPV** declined over time until booster vaccination 3 years after the second vaccination. After booster vaccination, anamnestic responses were observed in all animals against this antigen. The mean titres against CPV after booster vaccination were higher than those after primary vaccination.

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 immunisation of dogs from 6 weeks of age:

- to prevent clinical signs, leucopoenia and viral excretion caused by canine parvovirus.

Onset of immunity:
3 weeks after the first vaccination

Duration of immunity:
At least three years following the primary vaccination course

Vaccination scheme:

Primary vaccination scheme:
Two doses of Versican Plus P 3–4 weeks apart from 6 weeks of age.

Revaccination scheme:
A single dose of Versican Plus P should be given every 3 years.

Compatibility

Versican Plus P is compatible with Versican Plus L4 and Versiguard Rabies. As mentioned in Part 3.A, the SPC will include an option to use Versican Plus P in combination with these vaccines. The manufacturing processes of Versiguard Rabies are identical to those of the rabies component of Versican Plus DHPPi/L4R. This means that it will only be the number of active ingredients which will be different between Versican Plus DHPPi/L4R and Versican Plus L4 or Versiguard Rabies, and consequently there is no reason to believe that a combination of Versican Plus P and Versiguard Rabies or Versican Plus L4 could result in any safety issues. No compatibility studies of Versican Plus P with other products were undertaken.
Section 4.8 of the SPC contains the following text:
No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product other than Versiguard Rabies and Versican Plus L4. 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 by the veterinarian.

Field Trials

Two field studies were performed to demonstrate safety and efficacy of Versican Plus P:
The first one was a multi-centre, positively controlled, randomised, blinded field study in two countries (France and Germany), in compliance with CVMP/VICH/595/98 "VICH Topic GL9 Step 7 - Guideline on Good Clinical Practices".
Field trials (cohort study 1, cohort study 2 and cohort study 3) were carried out in 3 centres in France (FR) and 3 centres in Germany (DE). A total of 128 dogs (FR 63, DE 65) were included in the field trials, i.e. 45 mixed bred and 83 pure bred dogs of 28 breeds including toy breeds, utility/hunting breeds and large breeds; 50 females, 23 neutered females, 41 males and 14 neutered males. Cohorts were composed as follows:

- Cohort 1: 54 naïve dogs (FR 27, DE 27) with an age range of 8 weeks to 15 years. The dogs were administered two doses of vaccine (V1= Versican Plus DHPPi/L4; V2= Versican Plus DHPPi/L4R) 3–4 weeks apart followed by the owner observations;
- Cohort 2: 41 dogs (FR 21, DE 20) with an age range of 1 year to 11 years. The dogs were administered one annual booster vaccination (Versican Plus DHPPi/L4R), followed by the owner observations;
- Cohort 3: 33 naïve puppies (FR 15, DE 18) with an age range of 8 to 9 weeks. The dogs were administered two doses of vaccine (V1= Versican Plus DHPPi/L4; V2= Versican Plus DHPPi/L4R) 3–4 weeks apart, followed by observations through trained personnel.

For ethical reasons no unvaccinated dogs were included in the study and competitor vaccines were used in the controls for antibody comparison. Competitors vaccines used in France were Enduracell 7 and Enduracell 8 and in Germany were Vanguard 7 and Vanguard R.
Serological control tests were performed on cohort 1 and 3 before the first and the second vaccination (V1 and V2) (on the same day of vaccinations) and 21 days after the second vaccination (V2+21). Serological control tests were performed on cohort 2, before the annual booster vaccination (V1) (on the same day of vaccination) and 21 days after it (V1+21). Efficacy was assessed by measuring antibody responses and comparing titres before and after vaccination with Versican Plus DHPPi/L4R or the comparator vaccine. The antibody response by means of seroneutralisation (SN) test was categorised as follows:

- No increase.
- Increase 1: < 2-fold increase of CPV antibodies (SN).
- Increase 2: ≥ 2-fold increase of CPV antibodies (SN).

Only results relevant to the components of Versican Plus P are summarised below.

<u>Results in naïve puppies</u>
Forty-four dogs aged from 8 weeks to 6 months, (without a previous history of vaccination were selected from cohort 1 (11 dogs, 7 of which vaccinated with Versican Plus DHPPi/L4R and 4 with a competitor vaccine) and cohort 3 (33 dogs vaccinated with Versican Plus DHPPi/L4R). Serological results are reported hereafter:
Puppies without MDA:

- 100% of the puppies showed full serological response (Increase 2) against the live viral component CPV - the proportions of puppies without MDA responding to

Versican Plus DHPPi/L4R were greater and their responses generally higher than those following vaccination with comparator products.

Puppies with MDA:

− 20% of puppies did not show an antibody increase against CPV (n=5): In three puppies MDA interfered with responses after both vaccinations leaving the puppies without any protective antibody levels (< 2) after primary immunisation. The other two pups had higher than average MDA titres before the first vaccination which decreased to levels that allowed them to respond to the second vaccination.

Results in naïve dogs (adults and puppies)

Fifty-four unvaccinated dogs (cohort 1) divided in 43 dogs over 6 months of age without a previous history of vaccination or with a previous history of vaccination that had lapsed by more than 14 months and 11 naïve puppies younger than 6 months, showed the following serological results:

Dogs without pre-existing antibodies:

- 100% showed full serological response (Increase 2) after primary immunisation (V1+V2).

Dogs with pre-existing antibodies:

− The proportion of dogs with pre-existing antibodies showed lower serological response (Increase 1 or no increase) if compared to dogs without pre-existing antibodies.

Results in previously vaccinated adult dogs

Forty-one dogs of more than 6 months of age, with a previous history of vaccination and requiring an annual booster (cohort 2), showed the following serological results:

Dogs without pre-existing antibodies:

− 100% showed full serological response (Increase 2) against CPV.

Dogs with pre-existing antibodies:

− The proportion of dogs with pre-existing antibodies showed lower serological response (Increase 1 or no increase) if compared to dogs without pre-existing antibodies.

Conclusions

Evaluable serological data from 86 (out of 128) animals were generated. Since antibody titres from field and laboratory studies were determined using the same assay systems in the same laboratory, it was possible to directly compare field titres with minimum protective titres established in laboratory studies.

The applicant summarised all serological data irrespective of their antibody status pre-vaccination via descriptive statistics and compared the minimally induced antibody titre per antigen with the titre that was fixed as minimum protective titre in the challenge studies.

Against CPV, 100% of the adult dogs were protected following an annual booster vaccination (cohort 2) and all adult dogs of cohort 1 were protected following a primary immunisation. Puppies did not all respond with protective antibody levels against CPV (cohorts 1 and 3) because of pre-existing MDA.

The presented field study clearly shows the influence of MDA regarding CPV antigen. While the MDA negative dogs mostly seroconvert after the first vaccination and are boostered after the second vaccination, MDA positive dogs react after the second vaccination and in general have lower titres than those without MDAs. The study demonstrates again the importance of the second vaccination as part of the primary vaccination scheme. As immunological response to CPV may be delayed due to MDA,

the vaccination scheme for young dogs should be planned carefully. This has been reflected in the SPC.
The second field trial was performed in UK with 1 center. 20 dogs (40-44 days of age, Labrador retrievers, Border collies, 14 females, 6 males) were divided into two groups. 14 dogs were vaccinated with Versican Plus DHPPi/L4 on Day 0 and Day 28. For ethical reasons no unvaccinated dogs were included in the study. Therefore, a competitor vaccine (Duramune DAPPi+LC) was used in the 6 control dogs for antibody comparison. Antibody titres against CPV were determined on the days of vaccinations and 21 days after the second vaccination.
Evaluation:

- CPV antibodies by virus neutralisation
- cut-off points: < 1:2 or, if not enough serum <1:5
- success criteria: 2-fold increase if seronegative pre first vaccination any titre increase if seropositive pre first vaccination

All dogs reached protective antibody titres against the live viral component CPV after primary vaccination with Versican Plus DHPPi/L4.
The majority of puppies (15 of 20 puppies; 75%) had MDAs to at least one vaccine component at the time of the first vaccination when they were around 6 weeks of age. MDAs against CPV were found in the majority of puppies (68%). The highest MDA titres were found directed against CPV.
All puppies without MDAs responded fully to vaccination with Versican Plus DHPPi/L4 against the live viral component CPV.
Puppies with MDAs fully responded to primary immunisation, which consisted of two vaccine administrations 4 weeks apart, against CPV.

The results confirm the observations made in the laboratory studies. The vaccine Versican Plus P 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 and the quality and safety of the product for humans and the environment is acceptable.