Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

Versican Plus BbPi IN

Zulassungsdatum:	.2020
Zulassungsnummer:	PEI.V.12002.01.1
Datum der Erstellung des öffentlichen Beurteilungsberichts:	12 February 2020
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 BbPi IN

PRODUCT SUMMARY

EU Procedure number	DE/V/0288/001/DC
Name, strength and pharmaceutical form	Versican Plus BbPI IN nasal drops, lyophilisate and solvent for suspension for dogs
Applicant	Zoetis Belgium s.a. Rue Laid Burnait, 1 1348 Louvain-la-Neuve Belgium
Active substance(s)	Each dose of 0.5 ml contains: Live attenuated *Bordetella bronchiseptica* strain MSLB 3096 $10^{8.0}$ – $10^{9.8}$ CFU* Live attenuated canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15 $10^{3.5}$ – $10^{5.8}$ $CCID_{50}$** * CFU: Colony forming unit ** $CCID_{50}$: Cell culture infectious dose 50% <u>Solvent:</u> Water for injections (WFI): 0.5 ml
ATC Vetcode	QI07AF01
Target species	Dogs
Indication for use	Active immunisation of dogs from 3 weeks of age: - to reduce clinical signs and bacterial excretion after infection with *Bordetella bronchiseptica* and - to reduce clinical signs and viral excretion after infection with canine parainfluenza virus.

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

PUBLIC ASSESSMENT REPORT

Legal basis of decentralised procedure application	Decentralised procedure application in accordance with Article 12 (3) and Article 32 (3) of Directive 2001/82/EC as amended.
Date of completion of the decentralised procedure	5th February 2020
Concerned Member States for mutual recognition procedure	AT, BE, CY, CZ, EE, EL, ES, FR, HR, HU, IE, IT, LT, LU, LV, NL, PL, RO, SI, SK, UK

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 0.5 ml dose:

Each dose of 0.5 ml contains:

Active substances:
Live attenuated *Bordetella bronchiseptica* strain MSLB 3096
$10^{8.0}$ – $10^{9.8}$ CFU*
Live attenuated canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15
$10^{3.5}$ – $10^{5.8}$ $CCID_{50}$**

*	CFU:	Colony forming unit
**	$CCID_{50}$:	Cell culture infectious dose 50%

Excipients:

Solvent:
Water for injections (WFI) 0.5 ml

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 strains (*Bordetella bronchiseptica* strain MSLB 3096 and canine parainfluenza Type 2 virus, strain CPiV-2 Bio 15) are 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 “Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010-Rev.1”.
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

Canine parainfluenzavirus:

- sterility according to Ph. Eur. 2.6.1
- test for mycoplasma according to Ph. Eur. 2.6.7
- determination of virus titre
- virus identity (CPiV-2)

Bordetella bronchiseptica:
- purity
- germ count

Vaccine bulk after blending:
- pH determination according to Ph. Eur. 2.2.3
- purity

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
- purity: according to Ph. Eur. 2.6.1
- test for mycoplasma: according to Ph. Eur. 2.6.7
- virus identity (CPiV-2)
- determination of virus titre (CPiV-2)
- *Bordetella bronchiseptica* identity/purity
- *Bordetella bronchiseptica* germ count
- determination of residual humidity
- vacuum test

Solvent
- appearance
- sterility: according to Ph. Eur. 2.6.1
- test for air tightness
- volume according to Ph. Eur. 2.9.17
- 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 according to Ph. Eur. 2.2.3

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 BbPi IN is a bivalent bacterial and viral vaccine for dogs containing live attenuated canine parainfluenza virus and live attenuated *Bordetella bronchiseptica*. It is intended for stimulation of an active immunity against infections with canine parainfluenza virus and *Bordetella bronchiseptica*. The lyophilisate is solved with a solvent (water for injection) and subsequently administered intranasally. Dogs from an age of 3 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 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 an overdose or repeat single dose with an interval of two weeks. Unvaccinated animals were used as control groups. All animals were monitored for systemic reactions during the studies.

Overall, the vaccine Versican Plus BbPi IN proved to be well tolerated in the target species dog. The 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.

The active components of Versican Plus BbPi IN are not known to have any adverse effects on the immune functions of infected animals. Therefore, no investigations of adverse effects on immunological functions were undertaken.

For each live strain included in the vaccine (canine parainfluenza virus type 2 and *Bordetella bronchiseptica*) 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 strains. No reversion to virulence of the vaccine antigens was observed in these studies. The live attenuated virus vaccine strain CPiV-2 and the *Bordetella bronchiseptica* vaccine strain may be shed by vaccinated animals following vaccination. Unvaccinated dogs can manifest mild clinical signs such as sneezing and nasal and ocular discharge after contact with vaccinated dogs. These findings are reflected in the SPC. The transmission of vaccine strains to cats, pigs and rodents could not be demonstrated. However, as the possibility of transmission to non-target species cannot be rejected, it is recommended to keep non-vaccinated animals out of close contact with vaccinated dogs for at least 4 weeks. An appropriate warning is included in the SPC and package leaflet.

A compatibility study was performed which demonstrated that this product is safe in dogs from 8 weeks of age when given at the same time as vaccines of the Versican Plus/Biocan Novel and Vanguard ranges containing live canine parvovirus, adenovirus, distemper virus, parainfluenza virus as well as inactivated *Leptospira* and rabies virus. Mild (< 1 ºC), transient increases in temperature were very commonly observed following co-administration of these vaccines.

Efficacy after concurrent use has not been tested. Therefore, while safety of concurrent use has been demonstrated, the veterinarian should take this into account when deciding to administer the products at the same time.

Although proven safe it should not be necessary to give a parainfluenza vaccine twice by two different routes, therefore the veterinarian should consider vaccination options based on local availability of core vaccines without parainfluenza and monovalent Bordetella vaccines.

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 field study was performed to assess the safety of the vaccine Versican Plus BbPi IN. Dogs of different breeds, genders and ages were vaccinated with Versican Plus BbPi IN according to the vaccination scheme. All animals were observed for adverse reactions during the study.
Overall, the vaccine Versican Plus BbPi IN proved to be well tolerated in the target species dog. The results confirm the observations made in the laboratory studies. The adverse 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.
As the vaccine strains are shed by vaccinated dogs, an appropriate warning is included in the SPC and package leaflet.

IV. EFFICACY

IV.B Clinical Studies

Laboratory Trials

Versican Plus BbPi IN is a bivalent live vaccine indicated for the intranasal immunisation of healthy puppies and dogs against canine parainfluenza and *Bordetella bronchiseptica* (*Bb*).
The live virus and bacterial components of Versican Plus BbPi IN (canine parainfluenza virus type 2 (CPiV-2) and *Bordetella bronchiseptica* (*Bb*) are presented in freeze-dried form in a vial to be reconstituted with a vial of the diluent (water for injection). The vaccine Versican Plus BbPi IN itself does not contain any adjuvant.

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

- Canine parainfluenza virus: Monograph 1955
- *Bordetella bronchiseptica*: Monograph 2525

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

Onset of immunity

CPiV-2:
Sixteen 3-week old dogs (10 vaccinates and 6 control dogs), tested seronegative against CPiV-2 were administered the vaccine Versican Plus BbPi IN intranasally. They were challenged intranasally with the canine parainfluenza challenge virus strain D008 on Day 7 after vaccination. After challenge the vaccinated group showed mild nasal and ocular discharge. There was no increase in the rectal temperature. All vaccinated animals excreted CPiV-2 challenge virus between 2 and 5 days after challenge. The antibody titres of the vaccinates increased slightly after challenge. All control animals showed notable clinical signs of upper respiratory disease and excreted challenge virus. The number of days of viral excretion was significantly higher in the control group compared to the vaccinated group. All control dogs seroconverted after challenge against CPiV-2.
This study is considered valid because it fulfils the requirements of Ph. Eur. monograph 1955.

Bb:
Sixteen 3-week old dogs (10 vaccinates and 6 control dogs), tested seronegative against *Bb* were administered the vaccine Versican Plus BbPi IN intranasally. They were challenged intranasally with the *Bordetella bronchiseptica* challenge strain MSLB 8182 01/16 on Day 3 after vaccination. After challenge the vaccinated group showed mild to moderate nasal discharge and mild ocular discharge. Two animals coughed for one day. There was no increase in the rectal temperature. All vaccinated animals excreted *Bb* challenge strain between 2 and 17 days after challenge. Their antibody titre level increased after challenge. All control animals showed notable clinical signs of upper respiratory disease and excreted challenge virus. The number of days of bacterial excretion and the excreted bacteria number were significantly higher in the control group compared to the vaccinated group. 3/6 controls seroconverted against *Bb*.
This study is considered valid because it fulfils the requirements of Ph. Eur. monograph 2525.

Influence of maternally derived antibodies on the efficacy of the vaccine

The duration of protection through maternally derived antibodies (MDAs) in new-born dogs can vary depending on the titres contained in the colostrum. Puppies vaccinated at a minimum age of 3 weeks may still have MDAs against CPiV-2, which potentially interfere with vaccination. No published information could be obtained on MDAs against *Bb* in dogs. In the field study no MDAs against *Bb* were detected in 30 puppies aged 3-8 weeks. Maternally derived antibodies (IgG) do not interfere with mucosal IgA, which follows on intranasal vaccination. Given that MDAs are not likely to interfere with intranasally administered vaccine a corresponding study was not performed.

Duration of immunity

One-year duration of immunity studies

CPiV-2:
Twenty 3-week-old dogs (12 vaccinates and 8 control dogs), tested seronegative against CPiV-2 were administered the vaccine Versican Plus BbPi IN intranasally. They were challenged intranasally with the canine parainfluenza challenge virus strain D008 one year after vaccination. After challenge the vaccinated group showed mild nasal discharge, coughing and a slight increase in the rectal temperature. Six vaccinated animals excreted CPiV-2 challenge virus between 2 and 6 days after challenge. The antibody titres of the vaccinates increased after challenge. The control

animals showed mild nasal discharge, coughing and a slight increase in the rectal temperature. All control dogs excreted challenge virus. The number of days of viral excretion was significantly higher in the control group compared to the vaccinated group. All control dogs seroconverted after challenge against CPiV-2.
This study is considered valid because it fulfils the requirements of Ph. Eur. monograph 1955. The study confirms a duration of immunity of 1 year.

Bb:
Twenty 3-week-old dogs (12 vaccinates and 8 control dogs), tested seronegative against *Bb* were administered the vaccine Versican Plus BbPi IN intranasally. One animal of the vaccinated group died because of congenital heart defect. The dogs were challenged intranasally with the *Bordetella bronchiseptica* challenge strain MSLB 8182 01/16 one year after vaccination. After challenge 4/11 vaccinated dogs showed mild nasal discharge between 3 and 9 days after challenge. One animal had diarrhea 10 days after challenge. Two dogs had a slight increase in the rectal temperature for not more than 2 days. All vaccinated animals excreted *Bb* challenge strain between 2 and 9 days after challenge. Their antibody titre level increased after challenge. The control animals showed mild nasal discharge, coughing and a slight increase in the rectal temperature. All control dogs excreted challenge virus. The number of days of viral excretion was significantly higher in the control group compared to the vaccinated group. 3/6 controls seroconverted against *Bb*.
This study is considered valid because it fulfils the requirements of Ph. Eur. monograph 2525. The study confirms a duration of immunity of 1 year.

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 3 weeks of age:
- to reduce clinical signs and bacterial excretion after infection with *Bordetella bronchiseptica* and
- to reduce clinical signs and viral excretion after infection with canine parainfluenza virus.

Onset of immunity: 3 days after primary vaccination for *Bordetella bronchiseptica.*
7 days after primary vaccination for canine parainfluenza virus.

Duration of immunity: 1 year.

Vaccination scheme:

Primary vaccination scheme:
A single dose from 3 weeks of age.

Re-vaccination scheme:
A single dose to be given annually.

Compatibility

Versican Plus BbPi IN is compatible with Versican Plus/Biocan Novel and Vanguard ranges containing live canine parvovirus, adenovirus, distemper virus, parainfluenza virus as well as inactivated *Leptospira* and rabies virus.
The SPC will include an option to use Versican Plus BbPi IN in combination with these vaccines. No compatibility studies of Versican Plus BbPi IN with other products were undertaken.
Section 4.8 of the SPC contains the following text:
"*This product has been shown safe in dogs from 8 weeks of age when given at the same time as vaccines of the Versican Plus/Biocan Novel and Vanguard ranges containing live canine parvovirus, adenovirus, distemper virus, parainfluenza virus as well as inactivated Leptospira and rabies virus. Mild (< 1 ºC), transient increases in temperature were very commonly observed following co-administration of these vaccines.*
Efficacy after concurrent use has not been tested. Therefore, while safety of concurrent use has been demonstrated, the veterinarian should take this into account when deciding to administer the products at the same time.
Although proven safe it should not be necessary to give a parainfluenza vaccine twice by two different routes, therefore the veterinarian should consider vaccination options based on local availability of core vaccines without parainfluenza and monovalent Bordetella vaccines.
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 Trials

A field study to assess the efficacy of the vaccine Versican Plus BbPi IN was undertaken in compliance with the guidance of CVMP/VICH/595/98 "VICH Topic GL9

Step 7 - Guideline on Good Clinical Practices (CVMP approved July 2000). The study was a multi-centre, positively and negatively controlled, randomised, blinded field study in dogs. 150 dogs of different breeds, different breeds, genders and ages were included in the study:
70 puppies: 30 vaccinated with Versican Plus BbPi IN, 40 controls (20 animals were administered water for injection, 20 dogs were vaccinated with a competitor product (Nobivac KC)).
80 adult dogs: 40 vaccinated with Versican Plus BbPi IN, 40 controls (20 animals were administered water for injection, 20 dogs were vaccinated with a competitor product (Nobivac KC)). Blood samples for determination of the antibody titres were taken on Days 0, 3, 7 and 28. At one study site 31 out of 35 puppies were re-homed before the end of the study (Day 28). Therefore, only sera of 39 puppies were available at the two study sites on Day 28.

Results:

64/70 puppies (91%) did not have maternally derived antibodies (MDAs) against CPiV-2 and 69/70 (98.6%) puppies did not have MDAs against *Bordetella bronchiseptica*.
At the beginning of the study 66 out of 80 adult dogs (83%) had pre-existing antibodies against CPiV-2 and 68 out of 80 dogs (85%) against *Bordetella bronchiseptica*, respectively. Due to the high prevalence of seropositive dogs, it was difficult to show differences in serological responses between the beginning and the end of the study. Statistical analysis of antibody increases against *Bordetella bronchiseptica* between Day 0 and Day 28 was performed separately for each site. No significant increases were detected. Furthermore, no significant differences were detected between groups on Study Days 0 or 28.

<u>Antibody response against CPiV-2:</u>

Puppies

Versican Plus BbPi IN: On Day 28 sera from 17 animals were available. Seroconversion was observed in all 17 puppies.
Nobivac KC: On Day 28 sera from 10 animals were available. Seroconversion was observed in all 10 puppies.
Water for injection: On Day 28 sera from 12 animals were available. Seroconversion was observed in all 10 puppies of one study site. The two animals of the other study site remained negative.

Adults

Versican Plus BbPi IN: 34 out of 36 animals (94% both sites) were seropositive for CPiV-2 on Day 28. One dog remained seronegative throughout the whole study and is considered to be a non-responder.

Nobivac KC: All dogs either seroconverted or remained seropositive.
Water for injection: All dogs were either already seropositive at the beginning of the study or seroconverted to CPiV-2 during the study except for two dogs, one at each site, that were seronegative at enrolment and remained seronegative until the end of the study.

Antibody response against *Bordetella bronchiseptica*:

Puppies
Versican Plus BbPi IN: On Day 28 sera from 17 animals were available. Seroconversion was observed in 6 out of 17 puppies (35%) at the two study sites.
Nobivac KC: On Day 28 sera from 10 animals were available. Seroconversion was observed in 9 out of 10 puppies (90% both sites).
Water for injection: On Day 28 sera from 12 animals were available. Seroconversion was observed in 5 out of 12 puppies (42%) at the two study sites. Probably, Bb circulated in the kennels of mock-vaccinated puppies.

Adults
Versican Plus BbPi IN: On Day 28 sera from 36 animals were available. Seroconversion was observed in 33 out of 36 dogs (92% both sites).
Nobivac KC: On Day 28 sera from 17 animals were available. Seroconversion was observed in all 17 animals.
Water for injection: On Day 28 sera from 16 animals were available. Seroconversion was observed in 15 out of 16 dogs (94%) at the two study sites. Probably, Bb circulated in the kennels of mock-vaccinated dogs.

Conclusions:
Puppies:
Most of the puppies were MDA negative at D0. As regards CPiV-2 all vaccinated puppies at one test site (Versican Plus BbPi IN and Nobivac KC groups) showed seroconversion on D28. However, as regards *Bordetella bronchiseptica* only 27% of the puppies vaccinated with Versican Plus BbPi IN and 90% of the puppies vaccinated with Nobivac KC had seroconverted on D28.
It should be noted that the majority of the puppies which received only WFI seroconverted on D28. The applicant states that the circulating CPiV-2 and *Bordetella bronchiseptica* originated from vaccination as no disease outbreak was observed during the study. Given that two vaccines were involved (Versican Plus BbPi IN and Nobivac KC), it cannot be distinguished which one may have induced the seroconversion.

Adult dogs:
Most of the dogs at one test site had antibodies against CPiV-2 and *Bordetella bronchiseptica* on D0. No significant increase in titres could be observed on D28. Therefore, no booster effect after vaccination could be shown. Most of the dogs that were seronegative before vaccination seroconverted on D28. However, a few dogs did not show seroconversion. These dogs may be non-responders.

The results confirm the observations made in the laboratory studies. The vaccine Versican Plus BbPi IN 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.