Institute for State Control of Veterinary Biologicals and Medicines
Ústav pro státní kontrolu veterinárních biopreparátů a léčiv

Ústav pro státní kontrolu veterinárních biopreparátů a léčiv

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DECENTRALISED PROCEDURE (DCP)

CZ/V/0119/001/DC

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Biocan Novel DHPPi/L4R,
lyophilisate and solvent for suspension for injection for dogs

MODULE 1

PRODUCT SUMMARY

EU Procedure number	CZ/V/0119/001/DC
Name, strength and pharmaceutical form	**Biocan Novel DHPPi/L4R,** **lyophilisate and solvent for suspension for injection for dogs**
Applicant	Bioveta a.s. Komenského 212 683 23 Ivanovice na Hané Czech Republic
Active substance(s)	Live Canine Distemper virus, strain CDV Bio 11/A Live Canine Adenovirus Type 2, strain CAV-2-Bio 13 Live Canine Parvovirus Type 2b, strain CPV-2b-Bio 12/B Live Canine Parainfluenza virus, strain CPiV-2-Bio 15 Inactivated *Leptospira interrogans* serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae, strain MSLB 1089 Inactivated *Leptospira interrogans* serogroup Australis serovar Bratislava, strain MSLB 1088 Inactivated *Leptospira interrogans* serogroup Canicola serovar Canicola, strain MSLB 1090 Inactivated *Leptospira kirschneri* serogroup Grippotyphosa serovar Grippotyphosa, strain MSLB 1091 Inactivated Rabies Virus, strain SAD Vnukovo-32
ATCvetcode	QI07AJ06
Target species	Dogs
Indication for use	Active immunization of dogs from 8-9 weeks of age. - to prevent mortality and clinical signs caused by canine distemper virus - to prevent mortality and clinical signs caused by canine adenovirus type 1 - to prevent clinical signs and reduce viral excretion caused by canine adenovirus type 2 - to prevent clinical signs, leukopenia and viral excretion caused by canine parvovirus - to prevent clinical signs (nasal and ocular discharge) and reduce viral excretion caused by canine parainfluenza virus - to prevent clinical signs, infection and urinary excretion caused by *L. interrogans* serogroup

	Australis serovar Bratislava - to prevent clinical signs and urinary excretion and reduce infection caused by *L. interrogans* serogroup Canicola serovar Canicola and *L. interrogans* serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae - to prevent clinical signs and reduce infection and urinary excretion caused by *L. kirschneri* serogroup Grippotyphosa serovar Grippotyphosa - to prevent mortality, clinical signs and infection caused by rabies virus

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	decentralised application according to Article 32(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	18/06/2014
Concerned Member States for original procedure	BG,CY,EE, HR, HU, LT, LV,MT,PL,RO,SI, SK

I. SCIENTIFIC OVERVIEW

The vaccine **Biocan Novel DHPPi/L4R** is live and inactivated viral and inactivated bacterial multivalent vaccine which is intended for the active immunisation of healthy puppies and dogs against diseases caused by canine distemper virus (CDV), canine parvovirus (CPV), canine adenovirus type 1 and 2 (CAV1 and CAV2), canine parainfluenza virus (CPiV), Leptospira interrogans serogroup Icterohaemorrhagiae serovar Icterohaemorrhagiae, Leptospira interrogans serogroup Canicola serovar Canicola, Leptospira interrogans serogroup Australis serovar Bratislava, Leptospira kirschneri serogroup Grippotyphosa serovar Grippotyphosa, and rabies virus (RV).

Active immunity starts:

- 2 weeks after a single vaccination from 12 weeks of age for rabies,

- 3 weeks after the first vaccination for CDV, CAV, CPV,

- 3 weeks after completion of the primary course for CPiV and

- 4 weeks after completion of the primary course for Leptospira components.

and persists at least one year following the primary vaccination course for all components of Biocan Novel DHPPi/L4R. Duration of immunity for rabies was demonstrated after one vaccination at 12 weeks of age.

The recommended basic vaccination scheme is: two doses of Biocan Novel DHPPi/L4R 3–4 weeks apart from 8–9 weeks of age. The second dose should not be given before 12 weeks of age.

Administration route is subcutaneous injection.

Stability data, which support the proposed shelf-life of 2 years, have been provided.

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.

The efficacy of the product was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

Composition:

One vaccination dose (1 ml) contains:

Active substances:

Lyophilisate (live attenuated):	**Minimum**	**Maximum**
Canine Distemper virus, strain CDV Bio 11/A	$10^{3.1}$ $TCID_{50}$*	$10^{5.1}$ $TCID_{50}$*
Canine Adenovirus Type 2, strain CAV-2 Bio 13	$10^{3.6}$ $TCID_{50}$*	$10^{5.3}$ $TCID_{50}$*
Canine Parvovirus Type 2b, strain CPV-2b Bio 12/B	$10^{4.3}$ $TCID_{50}$*	$10^{6.6}$ $TCID_{50}$*
Canine Parainfluenza Type 2 virus, strain CPiV-2 Bio 15	$10^{3.1}$ $TCID_{50}$*	$10^{5.1}$ $TCID_{50}$*

Solvent (inactivated):	
Leptospira interrogans serogroup Icterohaemorrhagiae	
serovar Icterohaemorrhagiae, strain MSLB 1089	GMT** ≥ 1:51 ALR***
Leptospira interrogans serogroup Canicola	
serovar Canicola, strain MSLB 1090	GMT** ≥ 1:51 ALR***
Leptospira kirschneri serogroup Grippotyphosa	
serovar Grippotyphosa, strain MSLB 1091	GMT** ≥ 1:40 ALR***
Leptospira interrogans serogroup Australis	
serovar Bratislava, strain MSLB 1088	GMT** ≥ 1:51 ALR***
Inactivated rabies virus, strain SAD Vnukovo-32	> 2.0 IU****

Adjuvant:	
Aluminium hydroxide (quantified as Al_2O_3)	1.8-2.2 mg

* Tissue culture infectious dose – 50%

** Antibody micro agglutination-lytic reaction (serology in rabbits)

*** Geometric mean titre

**** International Units; batch potency test performed by serological testing according to Ph. Eur. monograph 0451

The vaccine is presented in type I glass vials complying with Ph. Eur. Vials of the lyophilisate are closed with a bromobutyl rubber stopper and aluminium cap. Vials of the solvent are closed with a chlorobutyl rubber stopper and aluminium cap. The vaccine is supplied in quantities of 10x1, 25x1 and 50x1 ml vials of each fraction (i.e. lyophilisate and solvent) in transparent plastic cartons.

Package leaflet is included in each package.

The particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1 and 3.2.9 of the European Pharmacopoeia.

The choice of the vaccine strains, of the vaccine composition, adjuvant, inactivating agent, preservative, of the dose volume and vaccination schedule 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 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. For the purposes of authorization procedure the validation data have been sufficiently documented.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substances are manufactured in accordance with the principles of good manufacturing practice.

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

Starting materials of non-biological origin used in production comply with indicated pharmacopoeia monographs.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened and appropriately treated for the absence of extraneous agents according to the Ph. Eur monographs.

- **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.

D. Control tests during production

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

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E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. Relevant validations are provided.

F. Batch to batch consistency

The demonstration of the batch to batch consistency on Finished Freeze-dried Fraction (DHPPi) and on the Finished Liquid Fraction (L4R) is based on the results of 3 batches produced according to the method described in the dossier.

G. Stability

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

For the purposes of authorization procedure the stability data on the active substances have been sufficiently documented.

Shelf life of the veterinary medicinal product as packaged for sale is 2 years.
The vaccine should be used immediately after reconstitution according to directions.

III. SAFETY

The vaccine is recommended for dogs from 8-9 weeks of age. The recommended basic vaccination scheme is: two doses of Biocan Novel DHPPi/L4R 3–4 weeks apart from 8–9 weeks of age. The second dose should not be given before 12 weeks of age.

Safety clinical findings have been based on the recommended vaccination scheme.

Laboratory trials

Safety studies have been performed with a vaccine batch (containing maximum content of the antigens) produced according the described production process.

Verification of safety of the administration of one dose and the repeated administration of one dose in the target animal was demonstrated in controlled laboratory study. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

The safety study demonstrates that the administration of one dose and the repeated administration of one dose can be considered to be safe, when used in accordance with the recommended vaccination schedule. The observed reactions are reflected in the relevant SPC and package leaflet sections:

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

The most common side effect (seen in more than 1 in 100 dogs) with Biocan Novel DHPPi/L4R is a short lived swelling of up to 5 cm which may occur at the injection site after vaccination.

In situations where puppies are expected to inherit very high antibody levels from the bitch the vaccination protocol should be planned accordingly.

Examination of reproductive performance

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.

Special requirements for live vaccines

Specific studies were carried out to describe the spread, dissemination and reversion to virulence. The studies were designed to demonstrate compliance with the relevant European Pharmacopoeia monographs.
These data indicate a negligible potential for animal-to-animal spread or reversion to virulence under conditions of field use for CDV, CAV-2 and CPiV.
The CPV-2b strain has also been shown to be stably attenuated, but regarding spread of this vaccine strain the SPC reflects the following warning:

The live virus vaccine strains CAV-2, CPiV and CPV-2b may be shed by vaccinated dogs for a number of days following vaccination. Due to the low pathogenicity of the strain, it is not necessary to keep vaccinated dogs separated from non-vaccinated dogs.

Since the vaccine virus strain CPV-2b has not been tested in domestic cats and other carnivores (except dogs) that are known to be susceptible to canine parvoviruses, it is recommended vaccinated dogs to be separated from other canine and feline species after vaccination.

Study of residues
A withdrawal period is not applicable since the vaccine is not for use in food producing species.

Interactions
No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

User risk assessment
Given the nature of the vaccine, and its mode of administration, the risk to the user is characterised as low.
An appropriate warning in the SPC is included:

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Ecotoxicity

The applicant provided a phase 1 environmental risk assessment in compliance with the relevant guideline. Ecotoxicity was adequately addressed, and the risk to the environment is considered negligible. Therefore no further assessment is required.

IV. EFFICACY

All experiments conducted with **Biocan Novel DHPPi/L4R** in laboratory and field conditions were designed to meet the requirements of the relevant veterinary legislation, including European Directive 2001/82/EC, as amended (2009/9/ES). More detailed guidance is provided by various CVMP guidelines and European Pharmacopoeia (Ph Eur) monographs.

Laboratory Trials

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

Onset of immunity

Following one administration of vaccine DHPPi/L4R with the CDV, CAV-2, CPV-2b and CPiV components at the minimum titre and maximum passage to six week old naive dogs, animals were protected against a heterologous CDV virus challenge and heterologous CAV-1 virus challenge, that resulted in clinical signs and death of control animals.
Six week old naive dogs, animals were protected against heterologous CAV-2 virus challenge and against a heterologous CPiV virus challenge that resulted in clinical signs and virus shedding of control animals. Six week old naive dogs, animals were protected against heterologous CPV-2b challenge too that resulted in typical signs of parvovirosis in control animals. All these study fulfilled the efficacy requirements of the European Pharmacopoeia Monographs.

30 seronegative dogs, 12 to 13-weeks of age, were vaccinated once with Biocan Novel DHPPi/L4R containing the rabies component at minimum potency and maximum passage that will be present in a batch of commercial vaccine. As part of this study antibody titres against rabies were determined at multiple time points post vaccination and pre challenge. Time points 3 to 35 days after vaccination were the most relevant to assess onset of immunity for the rabies component of **Biocan Novel DHPPi/L4R**.

Following the vaccination scheme of the **Biocan Novel DHPPi/L4R** vaccine containing the *L. Icterohaemorrhagiae* component at the minimum potency and maximum passage to naive dogs from six weeks of age, animals were protected against challenge with a heterologous *L.Icterohaemorrhagiae* strain, that resulted in typical signs of leptospirosis in control animals.

Onset of immunity against other strains of leptospira (*L. Bratislava, L. Canicola* and *L. Grippotyphosa*) was demonstrated in the same way - challenge with a heterologous strain.

The results and conclusions of laboratory studies support the following label claim for section 4.2 of the SPC:

Onset of immunity:
- 2 weeks after a single vaccination from 12 weeks of age for rabies,
- 3 weeks after the first vaccination for CDV, CAV, CPV,
- 3 weeks after completion of the primary course for CPiV and
- 4 weeks after completion of the primary course for *Leptospira* components.

Duration of immunity

In ten challenge studies, duration of immunity (DOI) for one year was demonstrated for the CDV, CAV-2, CPV, CPiV, *Leptospira* and rabies components of Biocan Novel DHPPi/L4R. The results and conclusions of these studies support the following label claim for section 4.2 of the SPC:

Duration of immunity:
At least one year following the primary vaccination course for all components of Biocan Novel DHPPi/L4R. Duration of immunity for rabies was demonstrated after one vaccination at 12 weeks of age.

The influence of maternal antibody on the efficacy of the vaccine

The presented studies clearly show the influence of MDAs regarding CDV, CPV and CAV antigens. The possible interference of MDA should always be taken into consideration when vaccinating very young puppies. This study demonstrates the importance of the second vaccination as part of the primary vaccination because animals with MDAs do not seroconvert after the first vaccination but after the second one. As immunological responses to CDV, CPV and CAV-2 may be delayed due to MDAs the vaccination scheme for young dogs, especially for puppies at 6 weeks of age, should be planned carefully.
The data show that the interference of MDAs against CPiV does not play a considerable role. Therefore, a corresponding warning in the SPC is unnecessary.
Based on the data of the laboratory and field studies the applicant proposes the following wording of the SPC:

Special precautions for use in animals:

Immunological responses to the CDV, CAV-2 and CPV components of the vaccine 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 CDV, CAV and CPV at levels equal or higher to those likely to be encountered under field conditions. In situations where very high maternally derived antibodies levels are expected, the vaccination protocol should be planned accordingly.

Basic vaccination scheme:

Two doses of Biocan Novel DHPPi/L4R 3–4 weeks apart from 8–9 weeks of age. The second dose should not be given before 12 weeks of age.

Compatibility

No studies on immunological compatibility of Biocan Novel DHPPi/L4R with other products were undertaken. Section 6.2 of the proposed SPC for Biocan Novel DHPPi/L4R contains the following text:

Incompatibilities
Do not mix with any other veterinary medicinal product.

Field studies

The safety and effectiveness of **Biocan Novel DHPPi/L4R** was investigated in a field study involving 129 dogs. The dogs were either vaccinated twice with a three or four week interval or they received a single annual booster vaccination.

Safety was evaluated by the examination of the local and systemic effects following vaccination.

The measure of effectiveness was levels of antibodies before and after vaccination.

The field study showed that vaccination with **Biocan Novel DHPPi/L4R** resulted in levels of antibodies that were sufficient to protect against canine distemper virus and canine adenovirus in all dogs. The percentage of dogs with protective levels of antibodies for parvovirus ranged from 73 to 100%, for parainfluenza virus 73 to 97%, for leptospira 59 to 96% and for rabies virus 86 to 100%. Responses in puppies were lower than adult dogs in some cases, because of antibodies inherited from their mothers.

As regards rabies component, the following text was added to SPC:

In field studies 10% of seronegative dogs did not show seroconversion (> 0.1 IU/ml) 3–4 weeks after single primary vaccination against rabies. Another 17% did not show the 0.5 IU/ml rabies antibody titre required by some non-EU countries to travel in. In case of travelling to risk areas or for travel outside the EU veterinary surgeons may wish to use a two dose primary course including rabies or give an additional rabies vaccination after 12 weeks.

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