FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
La Haute Marche
Javené BP 90203
35302 FOUGERES cedex
FRANCE

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CANIGEN DHPPi/L - CANIXIN DHPPi/L - CANIGEN CHPPi/L

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0237/001/MR
Name, strength and pharmaceutical form	CANIGEN DHPPi/L, lyophilisate and suspension for suspension for injection, for dogs
Applicant	VIRBAC, France
Active substance(s)	Attenuated canine distemper virus (CDV) – Lederle strain Attenuated canine adenovirus type 2 (CAV-2) – Manhattan strain Attenuated canine parvovirus (CPV) – CPV780916 strain Attenuated canine parainfluenza virus (CPiV) – Manhattan strain Inactivated leptospira interrogans serogroup canicola serovar canicola Inactivated Leptospira interrogans serogroup icterohaemorrhagiae serovar icterohaemorrhagiae
ATC Vetcode	QI07AI02
Target species	dogs
Indication for use	For active immunisation of dogs from 8 weeks of age to : - Prevent mortality and clinical signs of canine distemper - Prevent mortality and clinical signs caused by canine adenovirus type 1 - Prevent clinical signs and mortality and reduce excretion caused by canine parvovirus in a challenge study performed with a CPV2b strain - Prevent clinical signs and reduce excretion caused by canine parvovirus in a challenge study performed with a CPV2c strain - Reduce respiratory clinical signs and viral excretion caused by canine parainfluenza virus and canine adenovirus type 2 - Prevent mortality and reduce infection, clinical signs, kidney colonisation, renal lesions and urine shedding of *L. canicola* - Reduce infection, clinical signs, kidney colonisation and urine shedding of *L. icterohaemorrhagiae*

	The onset of immunity has been demonstrated from 3 weeks after the primary vaccination for CDV, CAV-2 and CPV, 4 weeks for CAV-1 and CPiV, 5 weeks for *L.canicola* and 2 weeks for *L. icterohaemorrhagiae.* Duration of immunity : After the primary vaccination course, the duration of immunity lasts for one year for all components.. In the duration of immunity studies there was not significant difference between vaccinated and control dogs in viral excretion for CPiV or CAV-2, in reduction of kidney colonisation for *L.canicola* and *L.icterohaemorrhagiae*, nor in renal lesions and urine shedding for *L.canicola.* After the annual booster, the duration of immunity lasts for 3 years for CDV, CAV-1, CAV-2 and CPV. For CAV-2, the duration of immunity after the annual booster was not established by challenge and is based on the presence of CAV-2 antibodies 3 years after the booster vaccination.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/ and http://www.hma.eu/vmriproductindex.html

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 32 (2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	16/12/2011
Date product first authorised in the Reference Member State (MRP only)	26/05/2011
Concerned Member States for original procedure	UK
Date of completion of the repeat-use procedure	21/10/2015
Concerned member states	AT,BE,BG,CY,CZ,DE,DK,EE,EL,ES,FI,HR,IE,IS,IT,LT,LU,LV,MT,NL,NO,PL,PT,RO,SE,SI,SK

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.
The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product is constituted of a freeze-dried fraction containing the following live attenuated active ingredients :

ingredients	Quantity per dose
attenuated canine distemper virus, strain Lederle attenuated canine adenovirus type 2, Manhattan strain attenuated canine parvovirus, CPV 780916 strain attenuated canine parainfluenza virus, Manhattan strain	$10^{3.0}$ to $10^{4.9}$ $CCID_{50}$ $10^{4.0}$ to $10^{6.0}$ $CCID_{50}$ $10^{5.0}$ to $10^{6.8}$ $CCID_{50}$ $10^{5.0}$ to $10^{6.9}$ $CCID_{50}$
Stabilisant Buffered isotonic solution	

This fraction is to be reconstituted with liquid fraction containing the following inactivated active ingredients :

ingredients	Quantity per dose
Leptospira canicola Leptospira icterohaemorrhagiae	Not less than 8.33 10^8 bacteria before inactivation conferring ≥ 80% protection* Not less than 8.33 10^8 bacteria before inactivation conferring ≥ 80% protection*
Excipients	

*According to Eur. pharmacopeia monograph 447, Hamster potency test

The 2 fractions of the vaccine are filled in 3 ml insulin type flasks made of neutral borosilicate type 1 glass closed with a butyl elastomer stopper. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains, the production process and the formulation are justified.

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

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.

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

C. Control of Starting Materials

The active substances (canine distemper virus, canine adenovirus, canine parvovirus, canine parainfluenza virus, Leptospira canicola & Leptospira icterohaemorrhagiae) are established active substance described in the European Pharmacopoeia. 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.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

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

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. ; any deviation was adequately justified

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

Scientific data and certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

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

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular :

- Physicochemical tests,
- Identification and assay of the active ingredient
- Bacterial, fungal and mycoplasmic sterility according to Ph. Eur.

- Viral purity
- Control of inactivation (liquid fraction)
- Residual humidity (lyophilised fraction)

The demonstration of the batch to batch consistency is based on the results of 3 batches of vaccine (liquid fraction and lyophilised fraction) produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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 when stored under the approved conditions.

III. SAFETY ASSESSMENT

Vaccine batches used in the following studies are representative of the production process. For the live components, vaccine batches contain the maximal claimed titres.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the dogs is demonstrated in groups of 8 weeks old vaccinated dogs (1 dose, 10 doses of lyophilisate reconstituted in 2 doses of liquid fraction, administration of 3 doses 2 weeks apart and 4 doses 3 weeks apart). The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines and according to the relevant European Pharmacopoeia monographs when applicable. Transient mild local reactions after vaccination have been observed in most of the vaccinated dogs. These reactions have been adequately described in the SPC.

In the absence of the required demonstration data, it is recommended not to use the vaccine during pregnancy or lactation.

For each live strain included in the vaccine (canine distemper virus - Lederle strain, canine adenovirus type 2 – Manhattan strain, canine parvovirus – CPV780916 strain and canine parainfluenza virus – Manhattan strain), specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain(s). The live viral vaccinal strain canine adenovirus type 2 and

canine parvovirus have been demonstrated to spread from vaccinated dogs to animals put-in contact without leading to any pathological effects for these in-contact animals.

The excipients used are in annex II of MRL regulation and live components are not associated to zoonotic diseases. Based on this information, no withdrawal period is proposed.

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

Field studies

Safety of the vaccine was confirmed in field situation where puppies aged 8 weeks from 6 veterinary clinics were vaccinated as recommended. Data complete also pharmacovigilance data available for this vaccine which is authorised for years in many European countries.
Most of the vaccinated dogs presented transient mild local reactions. In very rare cases, general post vaccine reactions could be observed in vaccinated dogs, including hyperthermia, limited and brief digestive signs such as vomiting, diarrhoea or signs of lethargy. All these reactions resolve spontaneously within few days and are regarded as not uncommon and acceptable post-vaccination reactions for a canine vaccine. They are adequately described in the SPC.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.B Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show the efficacy of the vaccine with regard to the claims. For live components, vaccines used in these studies were formulated to contain minimal claimed titres.

Efficacy of the vaccine against distemper virus (prevention of mortality and clinical signs) is established according to the requirements of the European Pharmacopoeia in clinical studies including challenge performed 3 weeks after vaccination. Duration of immunity has been established through a challenge protection study conducted one year after vaccination.

Efficacy of the vaccine against canine type 1 adenovirus (prevention of mortality and clinical signs) is established according to criteria defined in the European Pharmacopoeia in the corresponding monograph in a clinical study including challenge performed 4 weeks after vaccination. 1 year duration of immunity is estimated from antibody levels that do not decline during this period.

Efficacy of the vaccine against canine type 2 adenovirus (reduction of clinical signs and viral excretion) is established according to the requirements of the European Pharmacopoeia in a clinical study including challenge performed 3 weeks after vaccination. 1 year duration of immunity has been established through a challenge protection study conducted one year after vaccination.

Efficacy of the vaccine against parvovirus (prevention of mortality and clinical signs, reduction of excretion) is established in conformity with the European Pharmacopoeia in a clinical study including challenge with parvovirus type 2b performed 3 weeks after vaccination. In an additional study including challenge with parvovirus type 2c, efficacy of the vaccine to prevent clinical signs and reduction of excretion has also been established. 1 year duration of immunity is estimated for these 2 parvovirus strains from antibody levels that do not decline during this period.

Efficacy of the vaccine against canine parainfluenza virus (reduction of clinical signs and viral excretion) is established in conformity with the European Pharmacopoeia in a clinical study including challenge performed 4 weeks after vaccination. Duration of immunity has been established through a challenge protection study conducted one year after vaccination.

Efficacy of the vaccine against Leptospira canicola and Leptospira icterohaemorrhagiae (reduction of infection, clinical signs, kidney colonisation, renal lesions and urine shedding) is established in clinical studies including challenge performed 5 weeks after vaccination for Leptospira canicola and 2 weeks after vaccination for Leptospira icterohaemorrhagiae. Duration of immunity has been established through challenge protection study (for each serovar) conducted one year after vaccination.

Data and analysis of serological response have been provided that suggest that maternally derived antibodies may in some cases influence the immune response to vaccination (CAV-2 and CPV in particular). Based on the available data, it is justified to recommend in presence of such antibodies to perform three vaccine injections.

Additional study has been provided to increase duration of immunity for CPV, CDV & CAV components.

23 SPF puppies, seronegative, 9 weeks old were vaccinated 2 times 3 weeks apart with CANIGEN DHPPi/L and received a booster vaccination 1 year after the initial vaccination.
The puppies were monitored for 3 years after the annual booster and received annual CANIGEN Pi/L vaccination.
A 3 years lasting serological response was observed in all vaccinated dogs for CPV, CAV and in 91% of the dogs for CDV.

Vaccinated dogs were protected :
. against challenge with CDV (5 vaccinates / 5 controls – prevention of mortality and clinical signs),
. against challenge with CAV-1 (6 vaccinates / 6 controls – prevention of mortality and clinical signs)
. against challenge with CPV-2c (6 vaccinates / 6 controls – prevention of clinical signs, reduction of excretion).

Field Trials

Laboratory studies are completed by field studies relying on observation of the serological response after vaccination of puppies of minimal age, various breeds and from 6 veterinary clinics. Supportive pharmacovigilance data are also provided as this vaccine which is authorised for years in many European countries.

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

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product.

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

2012 : increase of the production capacity and batch size for leptospira antigens

2014 : reduction of stability of the product to 18 months

2014 : update of efficacy claims according to new studies for CAV-2 and CPV strain 2c. Decrease of the minimal titre for CDV. Additional investigation on influence of presence of maternal dervived antibody on response to vaccination.

2015 : update of SPC after repeat-use procedure to better reflect efficacy data

2017 : increase of the duration of immunity to 3 years after the booster vaccination for CAV (CAV-1 & CAV-2), CDV and CPV.