FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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35306 Fougères
FRANCE

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Eurican DAP in the MA dossier

French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0305/001/MR
Name, strength and pharmaceutical form	Eurican DAP lyophilisate and solvent for suspension for injection
Applicant	MERIAL 29 AVENUE TONY GARNIER 69007 LYON FRANCE
Active substances	One dose of lyophilisate vaccine contains: Attenuated Distemper virus strain BA5 : $10^{4,0}$ $CCID_{50}$-$10^{6,0}$ $CCID_{50}$* Attenuated Canine Adenovirus type 2 strain DK13: $10^{2.5}$ $CCID_{50}$-$10^{6,3}$ $CCID_{50}$* Attenuated Canine Parvovirus strain CAG2: $10^{4.9}$ $CCID_{50}$-$10^{7.1}$ $CCID_{50}$* * $CCID_{50}$: 50% cell culture infective dose
ATC Vetcode	QI07AD02
Target species	Dogs
Indication for use	Active immunisation of dogs to: - prevent mortality and clinical signs caused by canine distemper virus (CDV), - prevent mortality and clinical signs caused by infectious canine hepatitis virus (CAV), - reduce viral excretion during respiratory disease caused by canine adenovirus type 2 (CAV-2), - prevent mortality, clinical signs and viral excretion caused by canine parvovirus (CPV)*, *Protection has been demonstrated against canine parvovirus type 2a, 2b and 2c either by challenge (type 2b) or serology (type 2a and 2c).

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 32 (3) of Directive 2001/82/EC as amended.
Date of completion of the original procedure	24th February 2016
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece Hungary, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, Spain, United Kingdom

I. SCIENTIFIC OVERVIEW

The vaccine is a multivalent live virus vaccine which is indicated for the immunisation of healthy puppies from seven weeks of age and dogs against canine distemper, adenovirus hepatitis, adenovirus respiratory disease and parvovirosis. The components of the vaccine (canine distemper virus (CDV), canine adenovirus type 2 (CAV-2), canine parvovirus (CPV) are presented in freeze-dried form in a vial to be reconstituted with a vial of diluent (sterile water) presented in liquid form.
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 (Summary of Product Characteristics).
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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

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One dose of freeze-dried vaccine contains:

Active substances:

Attenuated Distemper strain BA5 ..... $\geq 10^{4.0}$ $CCID_{50}$(*)
Attenuated Canine Adenovirus type 2 strain DK13 ..... $\geq 10^{2.5}$ $CCID_{50}$(*)
Attenuated Canine Parvovirus strain CAG2 ..... $\geq 10^{4.9}$ $CCID_{50}$(*)
(* $CCID_{50}$: 50% cell culture infective dose)

The vaccine is filled in glass type I containers, closed with a chlorobutyl stopper and sealed with an aluminium cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strains 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 practices in a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with 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 “Table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines” (Note for Guidance III/3427/93, 7Blm10a).

Seed lots and cell banks have been produced as described in the relevant guideline.

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

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

E. Control tests during production

The tests performed during production are described 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 are in line with the relevant requirements; any deviation from these requirements is justified. The tests performed are as follows:

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

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier.

G. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (2 years) when stored under the approved conditions (at 2-8° C).

The vaccine must be used immediately after reconstitution.

III. SAFETY ASSESSMENT

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Laboratory trials

The safety of the subcutaneous administration of one dose, an overdose and the repeated administration of one dose in the target species (70 dogs) is demonstrated in three laboratory studies. Safety was assessed clinically in Specific Pathogen Free (SPF) dogs, over an appropriate time course, through observation and physical examination. Unvaccinated animals were used as control group. The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

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

Effects on reproductive performance were examined in three laboratory studies on 19 vaccinated bitches and 17 controls. As the vaccine proved to be safe in pregnant bitches, the vaccine can be used during pregnancy. A corresponding note is included in the SPC and package leaflet.

As only the canine parvovirus may have immunosuppressive properties, a laboratory study was performed on 5 vaccinated dogs and 5 controls to investigate the immunological properties of the canine parvovirus component. It could be shown that the canine parvovirus has no negative impact on the immune system of the vaccinated dogs.

For each live strain included in the vaccine (5 vaccinates and 5 controls for canine distemper virus, 5 vaccinates and 3 controls for adenovirus type 2, 6 vaccinates and 6 controls for parvovirus, 5 vaccinates and 2 controls for parainfluenza virus type 2), 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 the studies. Vaccinated animals may shed the live CAV-2 and CPV vaccine strains following vaccination. However, as the strains are not pathogenic, it is not necessary to keep vaccinated animals separated from non-vaccinated animals. An appropriate warning is included in the SPC and package leaflet.

The assessment of the interaction of this product with the Merial rabies vaccine Rabisin and the Eurican range vaccines containing Leptospira and rabies components (Eurican LR, Eurican L or Eurican Lmulti) was made. The safety and efficacy of these associations of vaccines are demonstrated. Suitable warnings are included in the SPC and package leaflet.

Details are given in the Summary of Product Characteristics (SPC) as follows:

4.6 Adverse reactions (frequency and seriousness)

Immediately after injection, a slight swelling (≤ 2 cm) may commonly be observed at the injection site, usually regressing within 1-6 days. This can, on some occasions, be accompanied by slight pruritus, heat and pain at the injection site. Transient lethargy and emesis may also be commonly observed.

Uncommon reactions such as anorexia, polydipsia, hyperthermia, diarrhoea, muscle tremor, muscle weakness and injection site cutaneous lesions may be observed.

As with any vaccine, rare hypersensitivity reactions may occur. In such cases, appropriate symptomatic treatment should be provided.

The frequency of adverse reactions is defined using the following convention:
- *very common (more than 1 in 10 animals displaying adverse reaction(s) 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

Can be used during pregnancy

4.8 Interaction with other medicinal products and other forms of interaction

Safety and efficacy data are available which demonstrate that this vaccine can be administered with Eurican LR, Eurican L or Eurican Lmulti vaccines (used as diluent) where available.
Safety and efficacy data are available which demonstrate that this vaccine can be administered on the same day but not mixed with Rabisin.
When administered with Merial's vaccines containing rabies, the minimum age for vaccination is 12 weeks of age.
When administered reconstituted with the Eurican LR vaccine a small and transient nodule (maximum size 1.5 cm) at the injection site may be induced due to the presence of aluminium hydroxide and a slight swelling (~4 cm) may occur after the injection at injection site, regressing generally within 1-4 days. 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.

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

No adverse reactions other than those mentioned in section 4.6 were observed after administration of a 10-fold overdose of the lyophilisate.

Field studies

Nine field studies were performed to assess the safety of the vaccine. Dogs of different breeds, genders and ages (391 puppies and 361 adults) were vaccinated with the product under test. All animals were observed for local or systemic reactions during the studies.
Overall, the vaccine Eurican DAP proved to be well tolerated in the target species. The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under "adverse reactions".

Ecotoxicity

The close relationship between parvovirus of cats, mink and dogs as well as the high susceptibility of Mustelidae to distemper virus has warranted trials performed in cats and mink. The live components of the vaccine Eurican DAP proved to be safe for cats and minks.

The applicant provided an environmental risk assessment which showed that the risk for the environment and other animals and species posed by this vaccine can be considered as very low.

Warnings and precautions as listed in the product literature for its disposal are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

Laboratory Trials

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

- Canine distemper virus (CDV): Monograph 448
- Canine adenovirus type 2 (CAV2): Monograph 1951
- Canine parvovirus (CPV): Monograph 964

Twenty two studies were performed in laboratory conditions. The efficacy in the dog was demonstrated by means of challenge trials.

- Efficacy of the Canine distemper virus component:

The onset of immunity was established based on the results of a randomised blinded trial in which 12 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of three dogs was included. All the dogs were challenged at 14 days after the second vaccination. All the controls had to be euthanized while all the vaccinates remained in good general conditions.

The duration of immunity was established based on the results of 3 randomised blinded trials in which seronegative puppies 7-9 weeks old (27 dogs) were vaccinated twice (at 4 weeks interval). A control group (21 dogs)was included in all studies. The dogs were challenged at 12 or 13 months after the primovaccination or 36 months after a yearly booster following primovaccination.. After the challenge performed 3 years after the booster all the controls had to be euthanized while all the vaccinates remained in good general conditions.

- Efficacy of the Canine adenovirus component:

  • Against the canine contagious hepatitis due to the Canine adenovirus type 1:

The onset of immunity was established based on the results of 2 randomised blinded trials in which 18 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of 6 dogs was included. All the dogs were challenged at 14 days after the second vaccination. All the controls had to be euthanized while all the vaccinates remained in good general conditions.

The duration of immunity was established based on the results of 3 randomised blinded trials in which seronegative puppies 7-9 weeks old (18 dogs) were vaccinated twice (at 4 weeks interval). A control group (15 dogs)was included. The dogs were challenged at 12, 13 and 20 months after the second vaccination with a canine adenovirus type 1. After the challenge performed 20 months after the primovaccination, all the vaccinated dogs survived and showed no signs of disease while all the control dogs died of canine adenovirosis.

  • Against the respiratory disease due to the Canine adenovirus type 2:

The onset of immunity was established based on the results of a randomised blinded trial in which 11 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of eleven dogs was included. All the dogs were challenged at 14 days after the second vaccination. The results of the study demonstrated that there was a notable decrease in the incidence and severity of signs (even if not statistically significant) and in virus excretion (statistical difference) in vaccinates compared to controls.

The duration of immunity was established based on the results of a randomised

blinded trial in which 12 seronegative puppies 7-9 weeks old were vaccinated twice

(at 4 weeks interval). A control group of eleven dogs was included. All the dogs were challenged at 12 months after the second vaccination with a canine adenovirus type 2. The results of the study demonstrated that the vaccination reduced significantly the virus excretion.
Another study was provided to establish the duration of immunity. Ten seronegative puppies 8-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of ten dogs was included. All the dogs were challenged at 13 months after the second vaccination with a canine adenovirus type 2. The results of the study demonstrated that the vaccination reduced significantly the virus excretion.

- Efficacy of the Canine parvovirus virus component:

The onset of immunity was established based on the results of a randomised blinded trial in which 5 seronegative puppies 7-9 weeks old were vaccinated with one dose of vaccine. A control group of two dogs was included. All the dogs were challenged at 14 days after the vaccination with a canine parvovirus type 2b. After challenge, the control dogs showed typical signs of the disease, leucopenia and excretion of the virus and all the vaccinated dogs survived and showed no sign of disease nor leucopenia and no virus was excreted in the faeces.

A second study with a challenge with a canine parvovirus type 2c was performed. Six seronegative puppies 12-13 weeks old were vaccinated with one dose of vaccine. A control group of six dogs was included. All the dogs were challenged at 14 days after the vaccination. The control dogs showed typical signs of the disease, leucopenia and excretion of the virus and all the vaccinated dogs survived and showed no sign of disease nor leucopenia and the virus excretion in the faeces was significantly reduced.

The duration of immunity was established based on the results of 3 randomised blinded trials in which seronegative puppies 7-9 weeks old (32 dogs) were vaccinated twice (at 4 weeks interval). A control group (11 dogs) was included in all studies. The dogs were challenged at 12, 17 and 25 months months after the second vaccination with a canine parvovirus type 2b. All the controls showed typical signs of disease or died. All the vaccinated dogs survived and showed no sign of disease nor leucopenia and the maximal viral titre in the faeces was lower than 1/100th of the geometric mean of maximal titres found in the controls.

The impact of maternally derived parvovirus antibodies was studied. Six conventional puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval). A control group of three dogs was included. All the dogs were challenged at 14 days after the vaccination with a canine parvovirus type 2b. All the control dogs had to be euthanised or died due to canine parvovirosis six days post-challenge. All vaccinated dogs, (except one that died 6 days post-challenge in a group vaccinated with another experimental vaccine containing the CPV strain), remained in good health with no clinical signs of parvovirosis and no parvovirus excretion in faeces throughout the challenge phase was observed. This study

showed that the presence of CPV antibodies at vaccination did not affect the efficacy induced by the vaccine.

Serological results against parvovirus (anti-CPV2, anti-CPV2a, anti-CPV2b and anti-CPV2c) were determined from three different studies (1 onset of immunity and 1 duration of immunity pivotal study and 1 field study) after dog vaccination with Eurican DAPPi-L_{multi}. The results showed that the anti-CPV2 titers measured shift similarly for CPV2a, CPV2b and CPV2c antibody titers in animals vaccinated in different clinical studies. Serological profiles against 4 CPV2 variants (CPV2, CPV2a, CPV2b, CPV2c) were equivalent in the sera of these animals. Thus, the CPV2 strain of Eurican DAPPi-L_{multi} vaccine induces in animals antibodies able to cross react, with similar extent and kinetics, against different field variants like CPV2a, CPV2b and CPV2c.

- Association of the vaccine with a Merial rabies vaccine

A serological monitoring of one year was performed on 42 seronegative puppies 7-9 weeks old randomized into 3 groups: 14 dogs were vaccinated twice (at 4 weeks interval), first with Eurican DAPPi-L_{multi} and then with Eurican DAPPi-L_{multi} associated (but not mixed) with Rabisin; 14 dogs were vaccinated twice (at 4 weeks interval) with Eurican DAPPi-L_{multi} ; 14 dogs were vaccinated once with Rabisin.
Serological responses against the viral components of the vaccine (CDV, CAV, CPV and CPiV) and Rabisin (rabies virus) was significantly non inferior in dogs vaccinated with Eurican DAPPi-L_{multi} and Rabisin when compared to that in dogs vaccinated with only one of the 2 vaccines. The applicant has shown that the titers obtained are above serological protective threshold for the CDV, CAV and CPV components and therefore the challenge for these components can be omitted.

With regard to the CPiV component, the demonstration of the compatibility is based on the results of a trial using puppies issued from the serological monitoring in which 14 seronegative puppies 7-9 weeks old were vaccinated twice (at 4 weeks interval), first with Eurican DAPPi-L_{multi} and then with Eurican DAPPi-L_{multi} associated (but not mixed) with Rabisin. A control group of twelve dogs was vaccinated with Rabisin. All the dogs were challenged at 12 months after the second vaccination with a CPiV strain. All the control dogs showed excretion of the challenge virus and the scores for virus excretion for the vaccinated dogs were significantly lower than in the controls.

In the efficacy studies provided, the different vaccines of the Eurican range were used. The vaccine Eurican DAPPi was diluted with Eurican LR, Eurican L or Eurican Lmulti and therefore the safety and efficacy of these associations are

demonstrated.

- Efficacy of the booster vaccination

Fourteen SPF puppies were primovaccinated with Eurican DAPPi$_2$-L$_{multi}$ vaccine at the age of 8 and 12 weeks. A booster vaccination was carried out between 12 and 15 months after the second injection of primovaccination.
The results of this study show that the dogs receiving a booster vaccination present antibody titres above the protective thresholds for CDV, CAV and CPV components. The results of the serological follow up showed that the vaccination could boost the immune response against all strains in dogs.

Field Trials

Three field studies were carried out to demonstrate the safety and the efficacy of the vaccine under field conditions.
The first study was performed in 10 veterinary practices in France. 93 puppies of various breeds never vaccinated before (7 to 24 weeks old, average 10.7 weeks) were vaccinated twice with Eurican DAPPi-L$_{multi}$ vaccine at 4 weeks interval. The results of the serological follow up showed that primovaccination with the vaccine induced a good immune response in puppies.
The second study was performed in 10 veterinary practices in France. 108 dogs of various breeds (more than 12 months old, average 5.7 years) previously vaccinated were vaccinated once with Eurican DAPPi-L$_{multi}$ vaccine. The results of the serological follow up showed that the vaccination could boost the immune response in dogs previously vaccinated with a commercial vaccine.
The third study was performed in 10 veterinary practices in France. 93 puppies of various breeds (7 to 24 weeks old, average 10.7 weekks) never vaccinated were vaccinated twice with Eurican DAPPi-L$_{multi}$ vaccine. The results of the serological follow up showed that the vaccination induced a good immune response in puppies and that the serological titres obtained are above the protective thresholds.

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

Active immunisation of dogs to:

- *prevent mortality and clinical signs caused by canine distemper virus (CDV),*
- *prevent mortality and clinical signs caused by infectious canine hepatitis virus (CAV),*
- *reduce viral excretion during respiratory disease caused by canine adenovirus type 2 (CAV-2),*
- *prevent mortality, clinical signs and viral excretion caused by canine*

*parvovirus (CPV)**

Onset of immunity : 2 weeks for all strains

Duration of immunity: at least one year after the second injection of the primary vaccination course for all strains.
Current available challenge and serological data show that protection for distemper virus, adenovirus and parvovirus lasts for 2 years after primary vaccination course followed by a first annual booster.*
Any decision to adapt the vaccination schedule of this veterinary medicinal product needs to be madeon a case by case basis, taking into account the vaccination history of the dog and the epidemiological context.
**Protection has been demonstrated against canine parvovirus type 2a, 2b and 2c either by challenge (type 2b) or serology (type 2a and 2c).*

4.9 Amounts to be administered and administration route

Aseptically reconstitute the contents of the lyophilisate with either sterile diluent or a compatible Merial vaccines (Eurican LR, Eurican L or Eurican Lmulti) where available. Shake well before use. The entire contents of the reconstituted vial should be administered as a single dose.

The reconstituted content shall be an opalescent yellow to orange suspension.

Inject a 1-ml dose subcutaneously according to the following schedule:

Primary vaccination:

Two injections separated by an interval of 4 weeks from 7 weeks of age. When administered with Merial's vaccines containing rabies, the minimum age for vaccination is 12 weeks of age.

In cases where high levels of maternally derived antibodies are suspected by the veterinarian and the primary vaccination course was completed before 16 weeks of age, a third injection using a Merial vaccine containing Distemper, Adenovirus and Parvovirus is recommended from 16 weeks of age, at least 3 weeks after the second injection.

***Revaccination:** Administer one dose 12 months after completion of the primary vaccination course. Dogs should be revaccinated with a single booster dose on an annual basis.*

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.

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. The current SPC is available on the veterinary Heads of Agencies website (http://www.hma.eu/vmriproductindex.html).

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