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# MUTUAL RECOGNITION PROCEDURE

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Eurican DAPPi$_2$-LR in the MA dossier

## Eurican DAPPi-LR since 2016 in all CMS

## Previously Eurican CHPPi$_2$-LR for France and Portugal
## Eurican SHPPi$_2$LT for Austria, Germany
## Eurican DHPPi$_2$-LR for Cyprus, Denmark, Greece, Poland
## Eurican MHPPi$_2$-LR for Spain

# MODULE 1

## PRODUCT SUMMARY

| | |
|---|---|
| EU Procedure number | FR/V/0267/001/MR |
| Name, strength and pharmaceutical form | Eurican DAPPi-LR<br>Lyophilisate and suspension for suspension for injection |
| Applicant | MERIAL<br>29 AVENUE TONY GARNIER<br>69007 LYON<br>FRANCE |
| Active substances | One dose of lyophilisate vaccine contains:<br>Attenuated Distemper strain BA5 : $10^{4,0}$ $CCID_{50}$-$10^{6,0}$ $CCID_{50}$*<br>Attenuated Canine Adenovirus type 2 strain DK13: $10^{2.5}$ $CCID_{50}$-$10^{6,3}$ $CCID_{50}$*<br>Attenuated Canine Parvovirus strain CAG2: $10^{4.9}$ $CCID_{50}$-$10^{7.1}$ $CCID_{50}$*<br>Attenuated Canine Parainfluenza type 2 strain CGF 2004/75: $10^{4.7}$ $CCID_{50}$-$10^{7.1}$ $CCID_{50}$*<br>* $CCID_{50}$: 50% cell culture infective dose<br><br>One dose of suspension contains:<br>Inactivated *Leptospira interrogans* serogroup Canicola strain 16070 : Activity according to Ph. Eur.447*<br>Inactivated *Leptospira interrogans* serogroup Icterohaemorrhagiae strain16069 : Activity according to Ph. Eur.447*<br>Inactivated rabies virus, strain G52 $\geq$ 1 IU<br>*80% of protection in hamsters |
| ATC Vetcode | QI07AJ06 |
| Target species | Dogs |
| Indication for use | Active immunisation of dogs to:<br>-prevent mortality and clinical signs caused by Distemper virus<br>-prevent mortality and clinical signs linked to canine contagious hepatitis,<br>- reduce clinical signs and viral excretion during respiratory disease caused by canine adenovirus type 2,<br>- prevent mortality, clinical signs and viral excretion linked to canine |

| | |
|---|---|
| | parvovirus type 2b et 2c,<br>- reduce clinical signs and viral excretion linked to canine parainfluenza virus,<br>- reduce mortality, clinical signs and bacterial excretion linked to Leptospira interrogans serogroup Canicola and Leptospira interrogans serogroup Icterohaemorrhagiae,<br>-prevent rabies. |

# MODULE 2

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

# 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 | 25th September 2013 |
| Date product first authorised in the Reference Member State (MRP only) | 13th May 2005 |
| Concerned Member States for original procedure | AT, CY, DE, DK, EL, ES, PL, PT |

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

## II. QUALITY ASPECTS

### *A. Composition*

One dose of lyophilisate 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 .....≥ $10^{4,9}$ $CCID_{50}$(*)
Attenuated Canine Parainfluenza type 2 strain CGF 2004/75 .....≥ $10^{4,7}$ $CCID_{50}$(*)
(* $CCID_{50}$: 50% cell culture infective dose)

One dose of suspension contains:

**Active substances:**

Inactivated *Leptospira interrogans* serogroup Canicola strain 16070 Activity acc. to Ph. Eur.447*
Inactivated *Leptospira interrogans* serogroup Icterohaemorrhagiae
strain16069 .....Activity acc. to Ph. Eur.447*

Inactivated rabies virus,, strain G52 .....≥ 1 UI
*80% of protection in hamsters

**Adjuvant:**

Aluminium hydroxide ..... 0,6 mg

The vaccine is filled in glass type I containers, closed with a butyl 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 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 practices from 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*

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 conform to 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 mycoplasma
- determination of residual humidity

**Suspension**
- appearance
- pH
- volume
- compatibility
- potency
- determination of aluminium content
- determination of thiomersal content
- sterility: according to Ph. Eur. 2.6.1
- demonstration of inactivation

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 broaching.

## III. SAFETY ASSESSMENT

### *Laboratory trials*

The safety of the subcutaneous administration of one dose, an overdose and the repeated administration of one dose in the target species (dog) 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 two laboratory studies. 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 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 (canine distemper virus, adenovirus type 2, parvovirus und 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.

No specific assessment of the interaction of this product with other medicinal products was made. Therefore, the safety and efficacy of this vaccine when used together with other medicinal products are not 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)*

*In very rare cases (less than 1 animal in 10,000 animals, including isolated reports):*

- *Slight itching and pain at injection site may occur immediately after the injection*
- *Slight swelling (≤ 4 cm) may occur after the injection at injection site, regressing generally within 1-4 days*
- *A small and transient nodule (maximum size 1.5 cm) at the injection site may be induced due to the presence of aluminium hydroxide*
- *A transient apathy lasting at most 1 day can be observed*
- *A hypersensitivity reaction may occur. In such a case, an appropriate symptomatic treatment should be provided*

### *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*

*No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product (except Eurican CHPPi$_2$-L as recommended under the primary vaccination schedule). 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*

*The injection of an overdose of vaccine may induce a transient local reaction similar to the one described in section 4.6 "Adverse reactions" as well as slight apathy (1 day) and a transient hyperthermia.*

### *Field studies*

Three field studies were performed to assess the safety of the vaccine. Dogs of different breeds, genders and ages were vaccinated according to the vaccination scheme. All animals were observed for local or systemic reactions during the studies.
Overall, the vaccine Eurican DAPPi$_2$-LR 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 DAPPi$_2$-LR 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 on 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:

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|---|---|
| - Canine distemper virus: | Monograph 448 |
| - Canine adenovirus type 2: | Monograph 1951 |
| - Canine parvovirus: | Monograph 964 |
| - Canine parainfluenza virus type 2: | Monograph 1955 |
| - Leptospirosis: | Monograph 447 |
| - Rabies | Monograph 451 |

In laboratory conditions, 15 studies were performed with the vaccine Eurican DAPPi$_2$-LR and 7 studies with close products in order to further complete the efficacy data.
The efficacy in the dog was demonstrated by means of challenge trials. In these trials, seronegative animals at the minimum vaccination age of 12 weeks were

vaccinated with Eurican DAPPi$_2$-LR and subsequently challenged with virulent canine distemper virus, canine adenovirus type 2, canine parvovirus, canine parainfluenza virus type 2, Leptospira, or rabies virus. Unvaccinated animals served as controls.
The results clearly demonstrate the efficacy of Eurican DAPPi$_2$-LR.

The immunogenicity of the vaccine was evaluated by a serological follow up in two laboratory studies. Based on theses studies, the onset of immunity for distemper virus, canine parvovirus type 2b, canine adenovirus type 2 and rabies was set at 2 weeks.

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 to:*
- *prevent mortality and clinical signs caused by Distemper virus*
- *prevent mortality and clinical signs linked to canine contagious hepatitis,*
- *reduce clinical signs and viral excretion during respiratory disease caused by canine adenovirus type 2,*
- *prevent mortality, clinical signs and viral excretion linked to canine parvovirus type 2b et 2c,*
- *reduce clinical signs and viral excretion linked to canine parainfluenza virus,*
- *reduce mortality, clinical signs and bacterial excretion linked to Leptospira interrogans serogroup Canicola and Leptospira interrogans serogroup Icterohaemorrhagiae,*
- *prevent rabies.*

*Onset of immunity : 2 weeks after primo-vaccination demonstrated:*
- *by challenge for canine contagious hepatitis, canine parvovirus type 2c, canine parainfluenza virus, Leptospira interrogans serogroup Canicola and Leptospira interrogans serogroup Icterohaemorrhagiae*
- *by serology and proof of a seroprotective titre for Distemper virus, canine parvovirus type 2b, canine adenovirus type 2 and rabies.*

*Duration of immunity: at least one year after the second injection of the primo-vaccination demonstrated by challenge for all strains. For the canine parainfluenza virus, the reduction of clinical signs could not be demonstrated in the duration of immunity study because adult dogs did not sufficiently express clinical signs after challenge. For the canine parvovirus type 2c, the duration of immunity is not established.*

*Active immunisation of dogs to:*
*- prevent mortality and clinical signs caused by 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)*,*
*- reduce clinical signs and viral excretion linked to canine parainfluenza virus type 2 (CPiV)**,*
*- reduce mortality, clinical signs and bacterial excretion linked to Leptospira interrogans serogroup Canicola and Leptospira interrogans serogroup Icterohaemorrhagiae,*
*- prevent rabies.*

*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 made on 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).*
***For the canine parainfluenza virus, the reduction of clinical signs could not be demonstrated in the duration of immunity study because adult dogs did not sufficiently express clinical signs after challenge.*

### *4.9 Amounts to be administered and administration route*

*Inject by subcutaneous route a 1-ml dose according to the following schedule:*

***Primary vaccination:***

*One injection of Eurican CHPPi$_2$-LR from the 12$^{th}$ week of age, 3 to 5 weeks before or after an injection of Eurican CHPPi$_2$-L vaccine.*

*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.*

***Boosters:***

*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.*

### *Field Trials*

The applicant has conducted a field study in France and Belgium on the efficacy of Eurican DAPPi$_2$-LR.
Dogs of different breeds, genders and ages were vaccinated with Eurican DAPPi$_2$-LR according to the vaccination scheme. All animals were regularly bled during the study to determine antibodies to canine distemper virus, adenovirus, parvovirus, parainfluenza virus type 2, Leptospira, and rabies virus. The results confirm the immunogenicity of the vaccine and the good take of the vaccine in field conditions.

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

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.

### Quality changes

| Summary of change | Approval date |
|---|---|
| Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability<br>Change in the specification parameters and/or limits of the finished product | 2016 |
| Update of the composition with regard to the quantitative particulars of the freeze-drying substrate of the “DAPPI” fraction. | 2016 |
| Addition of an alternative manufacturing site for the Leptospira active ingredients. | 2016 |
| Addition of two new TSE certificates of suitability from EDQM for the starting material “Foetal Calf serum” | 2015 |
| Addition of a new TSE certificate of suitability from EDQM for the starting material “Foetal Calf serum<br>Omission of the Target Animal Batch Safety Test | 2015 |
| Addition of a starting material for culture medium for vaccine production | 2015 |

### Safety/efficacy changes

| Summary of change | Approval |
|---|---|

| | **date** |
|---|---|
| Alignement across the Eurican range of the indications and the vaccination schedule related to the 3 core components D, A and P. | 2016 |
| Change of the invented name in order to have consistent denominations for products of the same range (MERIAL canine vaccines): Eurican DAPPi-LR | 2016 |
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