What is behind the new EURICAN?

September 2016 - CROATIA
EURICAN®, following high standards in canine infectious disease prevention

EURICAN® is providing a modern and committed range of canine vaccines providing unique characteristics consistent with Merial’s high standards as a world leader in Companion Animal Health

The wide* range and broad* coverage against specific canine infectious diseases
Merial is a leading animal health company that develops innovative solutions and offers a comprehensive range of vaccines to prevent a large number of infectious canine diseases.

The vaccine range with excellence in clinical efficacy
EURICAN® DHPpi-Lmulti ensures early and strong protection with 2 weeks onset of immunity for all key components. Beyond adding a new lepto serovar, Merial has also focused on the quality of protection against all considered lepto serovars. The vaccine has proven cross-protection against major circulating variants of canine parvovirus (CPV-2a, 2b and 2c).

Proven compatibility between EURICAN® DHPpi-Lmulti and RABISIN®
Demonstrated through safety and efficacy data, EURICAN® DHPpi-Lmulti and RABISIN®, Merial’s rabies vaccine, can be administered concomitantly§ in dogs from 12 weeks of age.

Improvement of safety
EURICAN® DHPpi-Lmulti offers improved purity thanks to an innovative patented leptospira technology

- § At 2 injection sites
### Epidemiological occurrences of canine diseases

Percentage of clinics having diagnosed dogs with the following diseases in a period of 12 months*

<table>
<thead>
<tr>
<th>Country</th>
<th>Parvovirosis</th>
<th>Leptospirosis</th>
<th>Hepatitis (all)</th>
<th>Distemper</th>
<th>Lyme Disease</th>
<th>Kennel Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK</strong></td>
<td>52.9% (1-20 cases) 1.7% (&gt;20 cases)</td>
<td>32.2% 0.8%</td>
<td>20.7% 0.8%</td>
<td>4.1% 0.8%</td>
<td>9.1% -</td>
<td>50.4% 48.8%</td>
</tr>
<tr>
<td><strong>Belgium</strong></td>
<td>62.5% (1-20 cases) 2.5% (&gt;20 cases)</td>
<td>50% 2.5%</td>
<td>3% -</td>
<td>15% -</td>
<td>42.5% -</td>
<td>65% 35%</td>
</tr>
<tr>
<td><strong>France</strong></td>
<td>54.1% (1-20 cases) 1.6% (&gt;20 cases)</td>
<td>59.1% -</td>
<td>12.5% -</td>
<td>10.8% -</td>
<td>19.1% -</td>
<td>87.5% 6.6%</td>
</tr>
<tr>
<td><strong>Germany</strong></td>
<td>37.5% -</td>
<td>33.3% -</td>
<td>10.8% -</td>
<td>14.2% -</td>
<td>52.5% 0.8%</td>
<td>61.7% 23.3%</td>
</tr>
<tr>
<td><strong>Portugal</strong></td>
<td>72% 20%</td>
<td>-</td>
<td>-</td>
<td>36% -</td>
<td>40% 2%</td>
<td>82% 16%</td>
</tr>
<tr>
<td><strong>Spain</strong></td>
<td>73.3% 11.7%</td>
<td>17.5% -</td>
<td>23.3% -</td>
<td>37.5% -</td>
<td>20.8% -</td>
<td>60.8% 34.7%</td>
</tr>
<tr>
<td><strong>Italy</strong></td>
<td>67.5% 1.7%</td>
<td>38.3% 0.8%</td>
<td>18.3% -</td>
<td>34.2% 0.8%</td>
<td>25% -</td>
<td>75% 13.3%</td>
</tr>
<tr>
<td><strong>Poland</strong></td>
<td>73.8% 1.3%</td>
<td>21.3% -</td>
<td>27.5% -</td>
<td>38.7% -</td>
<td>32.5% 1.2%</td>
<td>73.7% 16.2%</td>
</tr>
</tbody>
</table>

*Bio’sat. Annual quantitative survey about vaccines for pets performed in October 2014, 771 online interviews were conducted - European comparison.*
What is behind the new EURICAN® DHPPi-Lmulti?

- **LEPTO**
  - Updated component

- **Safety**
  - Optimized purification

- **EURICAN DHPPi-Lmulti**

- **PARVO**
  - Confirmation of efficacy

- **RABIES**
  - Compatibility
LEPTOSPIROSIS
UPDATED COMPONENT
Leptospirosis

Leptospirosis is the most widespread bacterial zoonosis mainly transmitted by rodents that affects around one million people a year worldwide with 48,000 estimated deaths\textsuperscript{36,37}

Percentage of clinics having diagnosed dogs with leptospirosis

![Percentage of clinics](chart)

TABLE 1. Some serogroups and serovars of *L. interrogans* sensu lato

<table>
<thead>
<tr>
<th>SEROGROUP</th>
<th>SEROVAR(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Icterohaemorrhagiae</em></td>
<td>Icterohaemorrhagiae, Copenhageni, Lai, Zimbabwe</td>
</tr>
<tr>
<td><em>Hebdomadis</em></td>
<td>Hebdomadis, Jules, Kremastos</td>
</tr>
<tr>
<td><em>Autumnalis</em></td>
<td>Autumnalis, Fortbragg, Bim, Weerasinghe</td>
</tr>
<tr>
<td><em>Pyrogenes</em></td>
<td>Pyrogenes</td>
</tr>
<tr>
<td><em>Bataviae</em></td>
<td>Bataviae</td>
</tr>
<tr>
<td><em>Grippotyphosa</em></td>
<td>Grippotyphosa, Canalzonae, Ratnapura</td>
</tr>
<tr>
<td><em>Canicola</em></td>
<td>Canicola</td>
</tr>
<tr>
<td><em>Australis</em></td>
<td>Australis, Bratislava, Lora</td>
</tr>
<tr>
<td><em>Pomona</em></td>
<td>Pomona</td>
</tr>
<tr>
<td><em>Javanica</em></td>
<td>Javanica</td>
</tr>
</tbody>
</table>

Adapted from. Ref 38. Levett PN. *Clin Microbiol Rev* 2001; 14:296-326

Bio'sat. Annual quantitative survey about vaccines for pets performed in October 2014, 771 online interviews were conducted - European comparison.
Leptospirosis

Distribution of the infecting *Leptospira* serogroups of dog in Europe between 2004 and 2014
to discover and imagine new antigens for vaccines providing a large spectrum of protection against leptospirosis
First step of Lmulti
3 serovars
L. Icterohaemorrhagiae
L. Canicola
L. grippotyphosa
Leptospirosis is particularly difficult to diagnose and to prevent due to the variability of clinical signs and its heterogeneous geographical distribution.

Based on recent literature, serogroups Icterohaemorrhagiae, Grippotyphosa and Canicola belong to the most prevalent and clinically relevant serogroups.

The three major challenges of Leptospiral vaccination:

1. Provide clinical protection against the major pathogenic serovars
2. Avoid lesions on key organs involved in homeostasis such as the kidney
3. Control bacterial shedding in the environment to reduce the zoonotic risk
LEPTO EFFICACY

Infection

Clinical signs

Renal lesions

Renal carriage

Mortality

Urinary excretion

Setting new standards of leptospirosis protection
Setting new standards of leptospirosis protection

The only vaccine* to offer prevention/reduction of mortality, renal carriage and renal lesions

Prevention of renal carriage is a prerequisite to control zoonotic risk

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Clinical signs</th>
<th>Infection</th>
<th>Excretion</th>
<th>Renal carriage</th>
<th>Renal lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Icterohaemorragiae</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>L. Canicola</td>
<td>P</td>
<td>P</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>L. grippotyphosa</td>
<td>P</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
</tr>
</tbody>
</table>

P: Prevent    R: Reduce

* In EU as of 2015
Adapted from. Ref 43 SPC EURICAN® Lmulti
Exceptional clinical protection obtained for all targeted serovars

- No clinical signs in challenges performed in young dogs as early as 2 weeks after vaccination with EURICAN DPPPI-Lmulti<sup>1</sup>
- Full prevention of mortality both in onset of immunity and duration of immunity

Adapted from Ref 2. EURICAN<sup>®</sup> DPPPI-Lmulti Registration File
* In EU as of 2015
Setting new standards of leptospirosis protection

Significant reduction of shedding

 sterility immunity for all serovars demonstrated in challenges performed as early as 2 weeks after primary vaccination

Percentage of dogs shedding leptospira after a strong challenge

Adapted from Ref 2. EURICAN® DHPPi Lmulti. Registration File
Setting new standards of leptospirosis protection

Significant reduction of shedding

- Sterile immunity/substantial reduction of shedding both in duration and frequency obtained for all serovars 12 to 14 months after primary vaccination for all serovars demonstrated in challenges performed as early as 2 weeks after primary vaccination.
Setting new standards of leptospirosis protection

What is the Merial’s strategy for the Lepto component?
- In a willing of continuous improvement of vaccines, Merial works on Lepto component following two axis: adding serovars (Lmulti), creation of a large spectrum vaccine (Covalept)

What are the characteristics of the Lmulti component?
- Inactivated non adjuvanted component with 3 serovars: Li, Lc, Lg

What are the parameters that aim to evaluate the efficacy of a Lepto vaccine?
- Clinical signs/Mortality/infection/urinary excretion/Renal carriage/Renal lesions

What are the claims in term of efficacy of Eurican Lmulti?
- Prevention/Reduction for all parameters for all included serovars

EURICAN® DHPPi-Lmulti is the only vaccine* against leptospiral infection claiming up to 6 protection criteria including, prevention of mortality and prevention/reduction of renal carriage, renal lesions and urinary shedding for all considered serovars
PARVOVIROSIS
CONFIRMATION OF EFFICACY
Parvovirosis

Evolution of CPV2 – new variants CPV2a, CPV2b and CPV2c

CPV2

1980

CPV2a

1990

CPV2b

2000

CPV2c

Canine Parvovirosis

Feline Parvovirosis Panleucopenia
Parvovirus infection is a major concern for vets and pet owners with several variants present in Europe. The table below shows the distribution of canine parvovirus variants in the world:

<table>
<thead>
<tr>
<th>Continent/country</th>
<th>Number of strains detected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPV-2a</td>
</tr>
<tr>
<td>Europe</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>56</td>
</tr>
<tr>
<td>Portugal</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>3</td>
</tr>
<tr>
<td>France</td>
<td>0</td>
</tr>
<tr>
<td>UK</td>
<td>117</td>
</tr>
<tr>
<td>Belgium</td>
<td>17</td>
</tr>
<tr>
<td>Germany</td>
<td>13</td>
</tr>
<tr>
<td>Greece</td>
<td>81</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1</td>
</tr>
<tr>
<td>Romania</td>
<td>2</td>
</tr>
<tr>
<td>Hungary</td>
<td>27</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>31</td>
</tr>
<tr>
<td>Slovenia</td>
<td>1</td>
</tr>
<tr>
<td>Africa</td>
<td></td>
</tr>
<tr>
<td>Tunisia</td>
<td>15</td>
</tr>
<tr>
<td>North America</td>
<td>1</td>
</tr>
<tr>
<td>USA</td>
<td>1</td>
</tr>
<tr>
<td>South America</td>
<td>1</td>
</tr>
<tr>
<td>Uruguay</td>
<td>1</td>
</tr>
<tr>
<td>Argentina</td>
<td>9</td>
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<tr>
<td>Brazil</td>
<td>37</td>
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<tr>
<td>Asia</td>
<td></td>
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<tr>
<td>India</td>
<td>37</td>
</tr>
<tr>
<td>India b</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>2</td>
</tr>
<tr>
<td>Korea</td>
<td>119</td>
</tr>
<tr>
<td>Japan</td>
<td>4</td>
</tr>
<tr>
<td>China</td>
<td>27</td>
</tr>
<tr>
<td>Thailand</td>
<td>19</td>
</tr>
<tr>
<td>Oceania</td>
<td>41</td>
</tr>
</tbody>
</table>


Adapted from. Bio’sat. Annual quantitative survey about vaccines for pets performed in October 2014, 771 online interviews were conducted - European comparison.
Parvovirosis

Challenges for achieving an optimal protection against parvovirus:
- Providing broad cross-protection
  - The continuous spread of different antigenic variants like CPV-2a, 2b and 2c requires vaccines that provide broad cross-protection
- Bridging the immunity gap at a young age

High titre vaccines help to reduce the immunity gap

Studies performed on nearly 1,000 field sera from dogs of breeding age indicated that approximately 25% would not be expected to respond until after 12 weeks of age.\(^2\)
Outstanding efficacy for very early vaccination

The efficacy of EURICAN® Primo (PRIMODOG®) in the face of Maternally Derived Antibodies (MDA) has been proven in an independent field trial.³

Some breeds appear to be particularly susceptible to parvovirus infection, i.e. Rottweilers, German Shepherds, Doberman Pinschers, Labrador Retrievers, American Staffordshire terriers, Alaskan sled dogs, and require particular protection,³, ²², ²³

³

Strong seroconversion in all breeds* as early as 4 weeks of age

Outstanding efficacy in primary vaccination and boosters

Proven clinical protection after CPV-2c challenge performed as early as 14 days after a single dose of vaccine

Reduction of viral excretion after CPV-2c challenge

This trial also demonstrates absence of leucopenia in vaccinated puppies
Outstanding efficacy against all circulating variants

Proven clinical protection against CPV-2b and CPV-2c

- Proven clinical protection after CPV-2b challenge performed 2 years after vaccination
- Demonstrated cross-reactive antibody responses to CPV-2 subtypes-2a, 2b & 2c
  - Long-lasting protective neutralizing antibodies response

CPV-2 vaccination elicits similar kinetics and protective neutralizing Ab response against all heterologous antigenic variants
Outstanding efficacy against all circulating variants

- What are the parvovirosis strains in Europe?
  - CPV2a, CPV2b, CPV2c

- Which animals are affected?
  - Dogs = canine parvovirosis
  - Cats = can causes symptoms like panleucopenia

- Which strain is in the Merial’s vaccine?
  - CPV2

- What are the key assets of EURICAN® Primo
  - Efficacy in front of maternally antibodies
  - Quick onset of immunity
  - Strain with proven cross-protection against circulating variants CPV-2a, 2b and 2c

- What is the efficacy demonstrated in this vaccine for these strains?
  - Strong efficacy, for all strains (CPV2a, CPV2b, CPV2c)
  - Clear indication in the SPC (continuous improvement)
RABIES COMPATIBILITY
Rabies is still a threatening disease and is always fatal. However, it is fully preventable through vaccination.

Distribution of levels of risk for humans to contract rabies, worldwide in 2013*

Dogs are the main vector of the disease. This is why it is essential to ensure protection with highly immunogenic vaccines.44

* The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization Map Production: Control of Neglected Tropical Diseases (NTD) - World Health Organization
Decades of proven efficacy in the field

Early onset of *immunity*

- Fast titre build-up to reach protective levels in just fifteen days

![Graph showing mean FAVN rabies antibodies (log IU/ml) over days after vaccination.](image)

- **Significant difference**

Adapted from Ref 45. Minke J, Cliquet F, *et al*. Vet Microbiol 2008; 133:283-6

*Compatible with EURICAN® DHPPI-Lmulti range when administered concomitantly at 2 injection sites*
Decades of proven efficacy in the field

Early onset of immunity

- 3-year duration of immunity** after first year booster validated by a severe challenge
- Superior efficacy proven in numerous independent studies

*RABISIN® consistently shows a significantly lower proportion of failures in serological tests performed 4 months after a single injection\(^8,9,45,47\)


* Compatible with EURICAN® DHHPI-Lmulti range when administered concomitantly at 2 injection sites
** A 3-year interval vaccination schedule after a first annual booster is aligned with current international guidelines/ KOL recommendations
Compatible* with EURICAN® DHPPi-Lmulti, adding all the benefits of a powerful protection against rabies²

Dogs vaccinated with RABISIN® concomitantly to EURICAN® DHPPi-Lmulti had similar protective antibodies profile compared to those vaccinated with RABISIN® alone

* When administered concomitantly at 2 injection sites
SAFETY
OPTIMIZED PURIFICATION
Improving vaccine purity

As part of a global quality program, Merial continuously works on the process, research, and new technologies to improve purity and safety of canine vaccines

- No adjuvant
- Reduction of the protein load

Merial’s commitment to improve purity and safety of canine vaccines

Adapted from. Ref 2. EURICAN® DHPi-Lmulti Registration file
No adjuvant

Definition

- An adjuvant is a substance that can be co-administered with a vaccine to accelerate, prolong, or enhance the quality of an immune response to the antigen.
- Therefore, The main role of adjuvants is to induce a local reaction that mimics a local infection.

Consequences

- Local inflammation > mass, nodule
- Variable, depending of the vaccine
Improving vaccine purity

- Reduction of the protein load

Anaphylactic reaction
Facial oedema
Improving vaccine purity

Reduction of the protein load of the viral components
Improving vaccine purity

Reduction of the protein load of the viral components

Cells multiplication

Cells infection

Viral multiplication

Viral gathering

Rinsing and change of the culture environment

Stabilizers

Proteins, from stabilizers, environment...

PURITY IMPROVEMENT
Improving vaccine purity

Reduction of the protein load of the viral components

Evolution of total protein level per dose of EURICAN® DHPPi

-22% of total protein level for EURICAN® DHPPi

Evolution of total protein level per dose of EURICAN® DHPPi

Before

After
Merial culture process for leptospira

1. Pre-Culture
Low-scale multiplication of leptospira.

2. Fed-batch process
Fermenter process to increase the volume of relevant immunogenic ingredient in a low protein medium:
- Ensuring a proper balance between biomass and feeding
- Allowing to use a BSA-free medium thanks to the fed-batch process
- Selecting specific vegetable derived fatty acid with no need of SAO components

3. Culture Inactivation
Efficient leptospira chemical inactivation.

4. Concentration
Reduction of volume through ultrafiltration to concentrate the protective antigens.

5. Final product
Thanks to the patented fed-batch§ process, the loss of putative protective antigen is avoided. As a result, EURICAN® has a powerful profile for the leptospira vaccine.

*This currently applies to serovars Ictero and Grippotyphosa, Ongoing adaptation for Canicola
** BSA: Bovine serum albumin
# SAO: Substance animal origin
§ US patent
Improving vaccine purity

**Significant decrease of non-antigenic proteins in leptospiral component**

- An innovative and patented **fed-batch** process for the culture of leptospira
- Reduction of the use of serum protein in particular bovine serum albumin in the culture medium

![Graph showing percentage decrease of protein](image)

- **EURICAN® L to EURICAN® Lmulti**

- **-40%** of total protein level for EURICAN® Lmulti

Adapted from. Ref 2. EURICAN® DHPPi-Lmulti Registration file

* US patent
PROTOCOLS OF VACCINATION RECOMMENDATIONS
Primary vaccination: two injection from the 7th to 9th week of age, 3-5 weeks apart. 3rd injection after 16W recommended in case high level of Maternal Derived Antibodies are suspected *(claim)*

- 2Y DOI after a first annual booster for DHP component

- Onset of immunity: two weeks after primary vaccination

- Safe in pregnant animal

- Shelf life: 24 months
Recommended vaccination protocol

**DISTEMPER/ADENOVIRUS/PARVOVIRUS/PARAINFLUENZA/ LEPTOSPIROSIS (DHPPi-L)**

PRIMARY VACCINATION COURSE

- **≥ 8 w**
- **± 12 w**
- **± 16 w**
- **first annual booster**
- **annual boosters**

- **DHPPi L**
- **DHPPi L**
- **DHP**
- **DHPPi L**
- **DHPPi L**

**LIFETIME**

* Vaccination can be started at 7 weeks of age

** In cases where high levels of MDA 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. 

**PARVOVIRUS (P) for puppies in high risk environments**

PRIMARY VACCINATION COURSE

- **≥ 6 w**
- **≥ 8 w**
- **± 12 w**
- **± 16 w**
- **first annual booster**
- **annual boosters**

- **P**
- **DHPPi L**
- **DHPPi L**
- **DHP**
- **DHPPi L**
- **DHPPi L**

Dogs with community risks

**LIFETIME**

* Vaccination can be started at 7 weeks of age

** In cases where high levels of MDA 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.

Vaccination should be considered case by case, depending on risk exposure.
EURICAN® DHPPi-Lmulti:

- Achieving high quality of protection against targeted leptospira serovars
- Delivering outstanding parvovirus efficacy and cross-protection against major circulating strains (CPV-2a, 2b, 2c)
- Allowing concomitant use of RABISIN® for outstanding quality of protection against rabies
- New technology to improve purity of canine vaccines

*When administered concomitantly at 2 injection sites*
QUESTIONS ?
References

2. EURICAN® DHPP-I-Lmultii Registration File
5. Data on file at Merial
13. EURICAN® Pneumodog Registration File
15. Merilinm®3 Registration File
16. EURICAN® Pirodog Registration File
26. Primodog® Registration file
References


41. Ellis W. Control of canine leptospirosis in Europe, time for a change. *Vet Rec.* 2010; 167:602-5


43. SPC EURICAN® Multi, Versican L4 and Nobivac L4


46. RABISIN® Registration File


51. EURICAN® Herpes Registration file


