**ALPHA JECT micro® 1Noda**

- **Reduces mortality** caused by RGNNV in sea bass.
- A new generation of PHARMAQ’s **micro dose** (0.05 ml per fish) vaccines.
- Reduces fish size at vaccination to 12 g.
- **Onset of immunity**: 466 degree days.
- **Duration of immunity**: 1 year.

**PACKAGING**: Flexible and robust injection bags easy to handle and store.

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**REFERENCES:**

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**THE FIRST COMMERCIAL VACCINE AGAINST RGNNV IN EUROPE**

**ALPHA JECT micro® 1Noda**, emulsion for injection for sea bass. Composition per dose (0.05 ml):

- Inactivated Red-spotted Grouper Nervous Necrosis Virus (RGNNV) strain ALV1107 ≥ 0.07 antigenicity units. 1 quantity of antigen measured in vaccine (short version AgU).

**Indications for use:**
For active immunisation of sea bass to reduce mortality caused by Red-spotted Grouper Nervous Necrosis Virus (RGNNV).

**Contraindications:**
None.

**Amounts to be administered and administration route:**
The recommended dose is 0.05 ml per fish of a minimum weight of 12 g. Should be administered by intraperitoneal (IP) injection. Should be left to slowly reach 15 – 20 °C by keeping it at room temperature and should be well shaken prior to use.

**Special warnings:**
Vaccinate healthy animals only.

**Withdrawal period:**
Zero degree days.

**Onset of immunity:**
466 degree days.

**Duration of immunity:**
1 year.

**Special storage precautions:**
Store and transport refrigerated (2 °C – 8 °C). Do not freeze. Protect from light.

**Package sizes:**
- 250 ml bag (5 000 doses)
- 500 ml bag (10 000 doses)

**Spanish MA no.:**
3597 ESP

**Italian MA no.:**
Sacca da 250 ml A.I.C. n.105071017
Sacca da 500 ml A.I.C. n.105071029

**Croatian MA no.:**
UP7I-322-05/17-01/405

**Greek MA no.:**
108576/1-12-2017

**Marketing Authorisation Holder:** PHARMAQ AS, 7863 Overhalla, Norway.

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www.pharmaq.com
PHARMAQ is the global leader in vaccines and innovation for aquaculture and part of Zoetis, the world leader in animal health. The company provides environmentally sound, safe and efficacious health products to the global aquaculture industry through targeted research and the commitment of dedicated people. Production facilities, administration and research and development activities are based in Norway.

Our focus on quality is absolute in all steps of production, from raw materials to finished products. Quality is built in every operation, from development to the final product is approved by the authorities and released.

As a pharmaceutical company, we are subject to very stringent demands, regulated in the principles and guidance of Good Manufacturing Practice (GMP) and are on a regular basis, approved according to GMP by the Norwegian Medicines Agency (NoMA).

“A ALPHA JECT micro® 1 Noda has been developed in response to fish farmers’ needs in the Mediterranean to fight against the most common viral disease affecting farmed sea bass in the Mediterranean. PHARMAQ is committed to the continuous development and supply of innovative health solutions for fish farmers globally.”

Morten Nordstad,
President of PHARMAQ
Viral Nervous Necrosis (VNN), also called Viral Encephalopathy and Retinopathy (VER), is considered the most important disease in the Mediterranean area; this is linked to the economic impact of the disease, caused both by the mortality rate and the growth reduction in the affected batch.

Viral Nervous Necrosis caused by an RNA virus belonging to Betanodavirus genus and may affect different fish species and all production stages of sea bass. Due to its viral nature, no treatments are feasible neither prevention tool was available up to date.

Officially reported from most worldwide regions except South America, linked to intensive production of marine species.

RGNNV genotype is the most common in the Mediterranean area due to its broader host range and to the specific higher water temperature requirements.

**VIRAL NERVOS NECROSIS, A TECHNICAL UPDATE**

**AETIOLOGICAL AGENT**

The causative agent of VNN is classified into the genus Betanodavirus within the family Nodaviridae.

**VIRUS DESCRIPTION**

Nodavirus is a small, non-enveloped virus with an icosahedral-shaped capsid of 25 nm diameter that surrounds the genetic material. This genetic material is made up of two molecules of single-stranded positive-sense RNA.

**NODAVIRUS CLASSIFICATION**

Betanodaviruses are clustered in four different genotypes, based on a variable region of RNA1, and in three serotypes according to polyclonal antibodies virus neutralization.

<table>
<thead>
<tr>
<th>GENOTYPE</th>
<th>SEROTYPE</th>
<th>TARGET HOST FISH</th>
<th>OPTIMUM GROWTH TEMPERATURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striped Jack Nervous Necrosis Virus - SJNNV</td>
<td>A</td>
<td>Striped jack</td>
<td>20-25°C</td>
</tr>
<tr>
<td>Tiger Puffer Nervous Necrosis Virus - TPNNV</td>
<td>B</td>
<td>Tiger puffer</td>
<td>20°C</td>
</tr>
<tr>
<td>Barfin Flounder Nervous Necrosis Virus - BFNNV</td>
<td>C</td>
<td>Cold-water fish: Atlantic halibut, Atlantic cod, flounders, etc.</td>
<td>15-20°C</td>
</tr>
<tr>
<td>Red-spotted Grouper Nervous Necrosis Virus - RGNNV</td>
<td>C</td>
<td>Warm-water fish: Asian sea bass, European sea bass, groupers, etc.</td>
<td>25-30°C</td>
</tr>
</tbody>
</table>

Every genotype correlates with different host species and in optimal growth temperature:

**EPIZOOTIOLOGY OF NODAVIRUS INFECTION**

Betanodaviruses are highly resistant in the aquatic environment and the disease has been reported in more than 50 fish species.

**INFLUENCING FACTORS IN BETANODAVIRUSES**

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mortality rate is age-dependent, so the earlier the disease signs occur, the greater is the rate of mortality, often reaching 100% mortality in larval stages.</td>
</tr>
<tr>
<td>Water temperature</td>
<td>Higher mortality at temperatures around 25°C, temperatures &gt; 31°C inhibit the proliferation of RGNNV.</td>
</tr>
<tr>
<td>Stress</td>
<td>Chronic stress may suppress the immune system of the fish and increase the probability of outbreaks</td>
</tr>
</tbody>
</table>

**INFECTION SPREADING**

- Horizontal transmission is the most common way of disease transmission. But also in some species vertical transmission may play a key role, being the virus detected in brood stock gonads and even in early stage development embryos.
- Water is the most important abiotic vector spreading the infection during a clinical outbreak.
- Cannibalism on dead fish may contribute to spreading the virus.
- Reservoirs in the wild are the original source of infection of farmed populations; trading of infected juveniles contributes to spread the virus geographically.
EMULSION FOR INJECTION FOR SEA BASS

ALPHA JECT micro® 1 Noda is the first vaccine licensed in EU to immunize sea bass against Nodavirus (RGNNV genotype). The first of a new micro-dose (0.05 ml) PHARMAQ generation vaccines at Mediterranean market, allowing vaccination of fish down to 12 g.

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MAIN PRODUCT CHARACTERISTICS

Composition

**Inactivated** Red-spotted Grouper Nervous Necrosis Virus (RGNNV) ≥ 0.07 antigenicity units per dose (quantity of antigen measured in vaccine) in *emulsion for injection.*

Adjuvant: Liquid paraffin (mineral oil)

Indication

For active immunization of *European sea bass* (*Dicentrarchus labrax*) to reduce mortality caused by Red-spotted Grouper Nervous Necrosis Virus (RGNNV).

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. 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.

Posology

The recommended dose is 0.05 ml per fish of a minimum weight of 12 g. The vaccine should be administered by intraperitoneal (IP) injection.

Technical features

Multiple efficacy and safety studies have been performed:

- Safety has been evaluated by scoring of local reactions (adhesions and pigmentation) in the abdominal cavity, and efficacy has been documented by challenges up to 12 months post vaccination.

- The vaccine reduces mortality caused by Nodavirus (RGNNV genotype) in European sea bass up to 12 months post vaccination.

- Onset of immunity is documented at 466 degree-days after vaccination.

VIRAL NERVOUS NECROSIS, A TECHNICAL UPDATE

CLINICAL SIGNS, LESIONS AND DIAGNOSIS

Quite unspecific external clinical signs are observed, barely a progressive change in pigmentation and some cutaneous erosion in cranial areas due to traumatic lesions caused by visual disturbances.

Main behaviour signs of the disease are caused by the viral replication in the cells of brain and retina, and include:

- Uncoordinated swimming and nervous signs, including erratic swimming behaviour patterns (spiralling, whirling or belly up at rest).
- Swim bladder hyperinflation, diseased fish are often seen at the surface.
- Flexing of the body, muscle tremors.
- Anorexia, lethargy, exophthalmus...

Histopathology reveals extensive vacuolation in nervous tissue, brain, spinal cord and nervous layer of the retina. Malacia and gliosis are also observed often with intracytoplasmic inclusions.

Diagnosis must be made after matching compatible clinical findings with positive results from different analysis:

- Behavioural signs.
- Microscopic findings (vacuolation and necrosis) and virus visualization by electron microscopy.
- Virus isolation from SSN-1 or E-11 cell lines culture (Gold Standard for VNN diagnosis).
- Agent detection tools like direct ELISA antigen detection method, Immunohistochemistry and Immunofluorescence technics from brain and retina tissue samples, and finally PCR-based methods (RT-PCR, Nested PCR or RealTime PCR).