REMINDER ON THE CONTRAINDICATIONS AND WARNINGS FROM SUMMARY OF PRODUCT CHARACTERISTICS

4.3 Contraindications

- Hypersensitivity reaction to eggs, chicken proteins or to any component of STAMARIL
- Serious hypersensitivity reactions (*e.g.*, anaphylaxis) after a previous dose of any yellow fever vaccine.
- Immunosuppression, whether congenital, idiopathic or as a result of treatment with systemic steroids (greater than the standard dose of topical or inhaled steroids), radiotherapy or cytotoxic drugs.
- History of thymus dysfunction (including thymoma, thymectomy)
- Symptomatic HIV infection
- Asymptomatic HIV infection when accompanied by evidence of impaired immune function (see section 4.4).
- Age less than 6 months (see sections 4.2 and 4.4).
- Current severe febrile illness.

4.4 Special warnings and precautions for use

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of anaphylaxis or other severe hypersensitivity reaction following administration of the vaccine.
STAMARIL should be administered only to persons who are/will be at risk of infection with yellow fever virus or who must be vaccinated to comply with international health regulations. Before considering administration of yellow fever vaccine, care should be taken to identify those who might be at increased risk of adverse reactions following vaccination (see section 4.3 and below).

Yellow fever vaccine associated neurotropic disease

Very rarely, yellow fever vaccine-associated neurotropic disease (YEL-AND) has been reported following vaccination, with sequelae or with fatal outcome in some cases (see section 4.8). Clinical features have appeared within one month of vaccination and include high fever with headache that may progress to include one or more of the following: confusion, encephalitis/encephalopathy, meningitis, focal neurological deficits, or Guillain Barré syndrome. To date, those affected have been primary vaccinees. The risk appears to be higher in those aged over 60 years, although cases have been also reported in younger persons or following transmission from nursing mothers to the infants.

Yellow fever vaccine-associated viscerotropic disease

Very rarely, yellow fever vaccine-associated viscerotropic disease (YEL-AVD) resembling fulminant infection by wild-type virus has been reported following vaccination (see section 4.8). The clinical presentation may include fever, fatigue, myalgia, headache, hypotension, progressing to one or more of metabolic acidosis, muscle and liver cytolysis, lymphocytopenia and thrombocytopenia, renal failure and respiratory failure. The mortality rate has been around 60%. To date, all cases of YEL-AVD have been in primary vaccinees with onset within 10 days of vaccination. The risk appears to be higher in those aged over 60 years although cases have also been reported in younger persons. Disease of the thymus gland has also been recognised as a potential risk factor (see section 4.3 and section 4.8).

Immunosuppressed persons

STAMARIL must not be administered to immunosuppressed persons (see section 4.3).
If the immunosuppression is temporary, vaccination should be delayed until the immune function has recovered. In patients who have received systemic corticosteroids for 14 days or more, it is advisable to delay vaccination until at least one month after completing the course.

HIV infection

STAMARIL must not be administrated to persons with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function (see section 4.3).
However, there are insufficient data at present to determine the immunological parameters that might differentiate persons who could be safely vaccinated and who might mount a protective immune response from those in whom vaccination could be both hazardous and ineffective. Therefore, if an asymptomatic HIV-infected person cannot avoid travel to an endemic area available official guidance should be taken into account when considering the potential risks and benefits of vaccination.

Children born to HIV positive mothers

Children aged at least 6 months (see sections 4.2 and 4.3 and below) may be vaccinated if it is confirmed that they are not infected with HIV.
HIV infected children aged at least 6 months who are potentially in need of protection against yellow fever should be referred to a specialist paediatric team for advice on whether or not to vaccinate.

Age

Children aged 6 to 9 months

STAMARIL must not be administered to children before the age of 6 months (see section 4.3). Children aged from 6 months up to 9 months should only be vaccinated under special circumstances (e.g. during major outbreaks) and on the basis of current official advice.

Persons aged 60 years and older

Some serious and potentially fatal adverse reactions (including systemic and neurological reactions persisting more than 48 hours, YEL-AVD and YEL-AND) appear to occur at higher frequencies after the age of 60 years. Therefore, the vaccine should only be given to those who have a considerable risk of acquiring yellow fever (see above and section 4.8).

Because intramuscular injection can cause injection site haematoma, STAMARIL should not be given by the intramuscular route to persons with any bleeding disorder, such as haemophilia or thrombocytopenia, or to persons on anticoagulant therapy. The subcutaneous route of administration should be used instead.

Patients with rare hereditary problems of fructose intolerance should not take this vaccine.

Pregnancy (Section 4.6)

No animal reproduction studies have been conducted with Stamaril and the potential risk for humans is unknown. Data on a limited number of exposed pregnancies indicate no adverse effects of Stamaril on pregnancy or the health of the fetus/newborn child. Nevertheless, Stamaril should be given to pregnant women only when clearly needed and only after careful consideration of the potential risks and benefits.

Lactation (Section 4.6)

As there is a probable risk of transmission of the vaccine virus strain to the infants from breastfeeding
mothers, Stamaril should not be given to nursing mothers unless when clearly needed
such as during an outbreak control, and following an assessment of the risks and benefits. There are very few reports suggesting that transmission of Yellow Fever vaccine virus may occur from nursing mothers, who received Yellow Fever vaccine postpartum, to the infant. Following transmission the infants may develop yellow fever vaccine associated neurotropic disease (YEL-AND) from which the infants recover (see section 4.6).

FOR THE FULL INFORMATION ON STAMARIL™, PLEASE REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS http://www.medicinesauthority.gov.mt/search-medicine-results?modSearch=adv

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Healthcare professionals may also report suspected adverse reactions to Sanofi Pasteur by calling at **Cherubino Ltd. on +356 21343270** or mailing at **pharmacovigilance@cherubino.com.mt**

NON PROMOTIONAL MATERIAL

EDUCATIONAL MATERIAL

ENHANCED PROGRAM TO INVESTIGATE POTENTIAL RARE SERIOUS ADVERSE REACTIONS FOLLOWING YELLOW FEVER (YF) VACCINATION WITH STAMARIL™

THIS EDUCATIONAL MATERIAL AIMS AT

• Informing the Healthcare Professionals (HCP) of the existence of a YF IdentificationProgramme for detection and analysis of the potential cases of Yellow Fever Vaccine-Associated Neurotropic Disease (YEL-AND) and Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD) after Stamaril™

• Highlighting the available safety key data on Stamaril™, the contraindications and warnings in specific population

The participation in this program (samples shipment and analysis) is free of charge on condition of signature of the informed consent form

Cherubino Ltd. Since 1906 YOUR HEALTH AT HEART

SANOFI PASTEUR

THE YF NATURAL INFECTION

Infection with yellow fever virus can cause severe illness and death. Up to 50% of severely affected persons without treatment will die from yellow fever. There are an estimated 200 000 cases of yellow fever, causing 30 000 deaths, worldwide each year[1].

THE YF PREVENTION

Stamaril™ is a live attenuated viral vaccine against yellow fever distributed by Sanofi Pasteur in Europe. According to the World Health Organization (WHO), vaccination is the single most important preventive measure against yellow fever[1].

THE VACCINE SAFETY PROFILE

Stamaril™ vaccine was proved to be highly effective and to present a good and well-documented safety profile over 17 years of experience with more than 280 million doses distributed worldwide[2].

As with any vaccine, adverse event can be observed after the use of Stamaril™. The most frequent adverse reactions are local reactions (reported in approximately 16% of subjects across clinical studies), and headache (very frequent)[2].

In very rare instances (0.4 -0.8 cases/100,000 doses), serious pathological conditions have been reported following yellow fever vaccination: Yellow Fever Vaccine-Associated-Neurotropic disease (YEL-AND) and Yellow Fever Vaccine-Associated-Viscerotropic disease (YEL-AVD) [2,3].

CLINICAL SYMPTOMS OF YEL-AND & YEL-AVD

- YEL-AND may manifest within one month of vaccination, as high fever with headache that may progress to include one or more of confusion, lethargy, encephalitis, encephalopathy and meningitis.
- YEL-AVD may manifest within 10 days of vaccination as fever, fatigue, myalgia, headache and hypotension progressing to one or more of metabolic acidosis, muscle and liver cytolysis, lymphocytopenia and thrombocytopenia, renal and respiratory failure.

Potential risk factors include age of more than 60 years for YEL-AVD and YEL-AND, although cases have also been reported in younger persons, and a medical history of thymic disease for YEL-AVD[2-3].

Although occurrence of YEL-AND and YEL-AVD after Stamaril™ vaccination is very rare, Sanofi Pasteur and Sanofi Pasteur MSD have invested in surveillance and research projects for exploring the possible pathogenesis mechanism of YEL-AND and YEL-AVD.

1. *WHO | Yellow fever Fact sheet N°100, Updated March 2014 [Internet]. WHO. [cited 2014 Jun 17]. Available from: http://www.who.int/mediacentre/factsheets/fs100/en/*
2. *Cottin P, Niedrig M, Domingo C. Safety profile of the yellow fever vaccine Stamaril®: a 17-year review. Expert Rev Vaccines. 2013 Nov;12(11):1351–68.*
3. *Staples JE, Gershman M, Fischer M, Centers for Disease Control and Prevention (CDC). Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2010 Jul 30;59(RR-7):1–27.*

THE YEL-AND and YEL-AVD SURVEILLANCE PROGRAMME

The objective of this programme is to improve early diagnosis and documentation of YEL-AND and YEL-AVD reported in Europe. This programme is offered as a service to the medical community and is considered to be of assistance in identifying post-vaccination events possibly associated with the vaccine.

RKI PRESENTATION – TESTING DETAILS

The RKI fulfils all requirements of standardisation, biosafety and quality control, standard assays according to defined quality control criteria. The RKI is a pre-qualified WHO laboratory, and is part of the European Network for the Diagnostics of "Imported" Viral Diseases, with the objective to improve the diagnostics of "imported" viral infections. Testing includes:

- Detection and qualification of YF IgM /IgG
- Quantification of YF antibody titers on acute- and convalescent-phase specimens
- Polymerase Chain Reaction (PCR) analysis and viral culture of acute-phase sera, cerebrospinal fluid (CSF), peritoneal fluid, pleural fluid, and fresh-frozen tissue samples
- Only when PCR is positive:
  - Immunohistochemical analysis of fixed tissue
  - Molecular analysis of vaccine virus from the same lot as administered to the patient

This list is not exhaustive. The types of samples to be shipped and panel of tests to be performed will be agreed on case-by-case basis between RKI and the reporter based on clinical description.

IN PRACTICE

When a patient presents with clinical features suggestive of YEL-AND or YEL-AVD, laboratory tests are generally performed to assess the diagnosis.

Doctors and clinicians are encouraged to investigate such events using samples already taken as part of routine care practice (such as serum, CSF or tissue samples) for additional yellow fever testings. Samples can be sent to the laboratory of the reporter's choice or to the laboratory of Robert Koch Institute (RKI) in Berlin (Germany).

However, only samples sent to the RKI are part of the programme. The shipment and the testings performed at the RKI lab will be free of charge for the patient and the reporter.

The RKI in Berlin already offers physicians the possibility to ask for specific testing in order to determine whether clinical features suggestive of YEL-AND and YEL-AVD are potentially related to yellow fever vaccination

INSTRUCTIONS FOR THE SAMPLES STORAGE AND SHIPMENT

The instructions are available on the following website: **http://www.enivd.de/index.htm**

In section **ongoing studies/yellow fever**

CONTACT DETAILS

For additional information, you may contact either the RKI at the following phone number (English/German speaking):
+49-30-18-754-2370 / 2321

Or

Cherubino Ltd. Delf Building, Sliema Road, Gzira

Tel: **+356 2134 3270**