DOCUMENT 7.

PRODUCT INFORMATION
STAMARIL®
[YELLOW FEVER VACCINE (LIVE), STABILISED]

NAME OF PREPARATION

Yellow Fever Vaccine (Live), Stabilised

DESCRIPTION

Each 0.5mL dose of reconstituted vaccine from the freeze-dried product contains an injectable suspension in stabiliser of the attenuated 17 D strain of yellow fever virus. The virus has been propagated in specific pathogen-free chick embryos, in particular free from avian leucosis viruses. Each dose contains not less than 1000 mouse LD_{50} units.

Other ingredients;

Stabilising medium:	16.0 mg lactose, 8.0 mg sorbitol, 833 µg L-histidine hydrochloride, 362 µg L-alanine, 1.6 mg sodium chloride, 54 µg potassium chloride, 598µg sodium phosphate-dibasic dodecahydrate, 63 µg potassium phosphate-monobasic, 39 µg calcium chloride, 29µg magnesium sulfate.
Diluent:	0.4% sodium chloride solution.

STAMARIL® has been manufactured in a facility approved by the World Health Organization.

The manufacture of this product includes exposure to bovine materials. No evidence exists that any case of vCJD (considered to be the human form of bovine spongiform encephalopathy) has resulted from the administration of any vaccine product.

PHARMACOLOGY

STAMARIL® is a live stabilised vaccine for active immunisation against yellow fever. Immunity appears 7 to 10 days after injection and lasts at least 10 years.

INDICATIONS

Prevention of yellow fever. Vaccination is recommended for:

- Every person over 9 months of age living or travelling through an endemic area.
- Non-vaccinated persons moving from an endemic to a potentially receptive non-endemic area.

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- Laboratory workers handling potentially infected materials.

- In order to be officially recognised, the yellow fever vaccination must be administered in an approved vaccination centre and registered on an international certificate. This certificate is valid from the 10th day after vaccination for 10 years.

CONTRAINDICATIONS

Pregnancy constitutes a contraindication considering the data available at the present time. However, a vaccination carried out during an unsuspected pregnancy, even during the first trimester, does not justify a termination of pregnancy. In case of outbreaks, the vaccine may be administered in pregnant women after the assessment of the risk related to the epidemiological context.

Not for use in children under 6 months of age.

Allergy to any components of the vaccine, especially eggs and egg protein (including ovalbumin) or severe reaction after previous administration of the vaccine.

Vaccination should be postponed in the case of fever, acute illness or chronic disease in evolution.

STAMARIL® should not be administered to the following individuals:

- patients receiving high-dose oral or injectable corticosteroids or other immunosuppressive treatment, including radiation therapy;

- those suffering from malignant conditions such as lymphoma, leukaemia, Hodgkin's disease or other tumours of the reticuloendothelial system, including those in remission who have received chemotherapy within the last 6 months;

- patients with impaired immunological mechanisms, such as severe combined immunodeficiency, symptomatic HIV-positive individuals or patients who have established laboratory verification of non-adequate immune system function as per specialist assessment, and patients who have had recent bone marrow or other organ transplants.

PRECAUTIONS

It is important to evaluate whether the person to be vaccinated plans to live in or travel to a yellow fever endemic or epidemic country or area. It is also important to evaluate whether the person may have pre-disposing risk factors (see below).

- **Yellow fever vaccine associated neurotropic disease**

Yellow fever vaccine-associated neurotropic disease (YEL-AND) has been reported to occur within a month of vaccination (refer to ADVERSE REACTIONS). Known risk factors for this adverse event are children aged less than 9 months and persons with congenital or acquired immunodeficiency.

- **Yellow fever vaccine-associated viscerotropic disease**

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) has been reported to occur within 10 days of vaccination (refer to ADVERSE REACTIONS). The risk appears to be higher in those aged 60 years and older although cases have been reported also for younger vaccinees.

Thymic disease has been identified as potentially influencing the development of yellow fever vaccine-associated viscerotropic disease (refer to ADVERSE REACTIONS). It is advised to enquire for a history of thymus disorder, such as thymoma or prior thymectomy, including for treatment of myasthenia gravis, before administering the yellow fever vaccine. Alternative means of prevention in such patients must be considered.

- **Immune status of the person**

Children born to HIV-positive mothers
The inevitable passage of maternal IgG antibodies through the placenta makes the child's serology uninterpretable until the age of about 9-10 months. NOTE: the persistence of circulating antibodies of maternal origin has been detected at up to 14 months of age. It is therefore necessary to obtain confirmation of the child's HIV status, determined by immunotransfer (Western Blot), possibly using viral genome detection techniques:

- If the child is not infected with HIV: STAMARIL® can be administered as routinely advised.
- If the child is infected with HIV: the advice of specialist paediatric team must be sought.

Patient under immunosuppressive treatments
For patients following an immunosuppressive treatment, it is recommended to delay the vaccination until the immune function has recovered.

In patients taking high doses of systemic corticosteroids given for 14 days or more, it is advisable to wait for at least one month.

Patients following other immunosuppressive treatments should seek advice from a specialist.

- Age

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Children aged 6 to 9 months
Routinely, only children aged 9 months and above should be vaccinated. However, during outbreak control when mass vaccination campaigns are needed in order to interrupt the circulation of yellow fever virus, vaccination of children aged 6 to 9 months could be considered.

Persons aged 60 years and older
Analyses of yellow fever vaccines adverse events demonstrated an increased frequency of serious adverse events (systemic and neurologic reaction persisting more than 48hours), including viscerotropic disease, in persons 60 years of age and older when compared to other age groups.

In this population, the risk of a rare reaction to yellow fever vaccine must be balanced against the risk of yellow fever infection.

In addition, vaccinees in this age group should be carefully monitored for adverse events up to 10 days after vaccination.

Only for intramuscular or subcutaneous injection. Do not inject by intravascular route.

STAMARIL® should be given with caution to patients with any bleeding disorder, such as haemophilia or thrombocytopenia, or to patients on anticoagulant therapy, because of the risk for haematoma formation after intramuscular injection. If the decision is made to administer STAMARIL® in such patients, the subcutaneous route should be considered as an alternative to the intramuscular route, and given with steps taken to avoid the risk of haematoma formation following injection.

As with other injectable vaccines, appropriate medical treatment and supervision should always be available in cases of anaphylactic reactions. Adrenaline should always be readily available whenever the injection is given.

Provided adequate provision is made for observation and any needed treatment of the patient, individuals with suspected allergy to the vaccine may have a skin test of 0.1mL of vaccine intradermally. If there has been no reaction within 15 minutes, the remainder of the dose (ie. 0.4mL) can be given subcutaneously.

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

Use in Pregnancy Category B2

As with all live vaccines, pregnancy constitutes a contraindication, particularly during the first trimester. However a vaccination carried out during an unsuspected pregnancy does not justify termination of pregnancy. In the case of outbreaks, the vaccine may be

administered in pregnant women after assessment of the risk related to the epidemiological context.

Use in Lactation

No data exists on the use of STAMARIL® during lactation. There is a theoretical risk of transmission of the live attenuated Yellow Fever virus in STAMARIL® from vaccinated breastfeeding mothers to the newborn. This applies particularly when the newborn is below 6 months of age.

Interactions With Other Drugs

To avoid reduction in serological responses:

- Another live vaccine, if not given concurrently with STAMARIL®, should be given after four weeks have elapsed.
- The administration of either injectable cholera vaccine or whole cell paratyphoid or typhoid vaccines concomitantly with STAMARIL® is not recommended. A period of 4 weeks is recommended between yellow fever vaccination and these other vaccinations.

Available data supports concomitant use of STAMARIL® with polysaccharide typhoid vaccine in separate syringes at separate sites. Data concerning other vaccines is limited. However, no interaction is anticipated when vaccines are given at separate sites using separate syringes.

ADVERSE REACTIONS

The reactions are listed within body systems and categorised by frequency according to the following definitions:

Very common:	>1/10
Common:	<1/10 and ≥1/100
Uncommon:	<1/100 and >1/1000
Rare:	<1/1000 and ≥1/10000
Very rare:	<1/10000, including isolated reports

Clinical Trial Experience

In clinical studies, the most common adverse events occurring after vaccine administration were local reactions, reported in 16% of subjects.

General disorders and administration site conditions

Very common:	local reactions (including pain, redness, haematoma, induration, swelling)
Common:	pyrexia, asthenia

Uncommon: malaise, influenza-like symptoms
Rare: fatigue

Nervous system disorders
Very common: headache

Gastro-intestinal system disorders
Common: nausea, diarrhoea
Uncommon: abdominal pain, vomiting

Musculo-skeletal and connective tissue disorders
Common: myalgia
Uncommon: arthralgia
Rare: arthritis

Post-Marketing Experience

Skin and subcutaneous tissue disorders
Rare: rash, urticaria
Very rare: eczema, oedema

Blood and lymphatic system disorders
Rare: lymphadenopathy

Immnue system disorders
Very rare: anaphylactoid reaction including angioedema

Nervous system disorders
Very rare: neurotropic disease, described as Yellow Fever Vaccine-Associated Neurotropic Disease (YEL-AND), has been reported to occur within 30 days following vaccination.
The clinical presentation has varied, and includes high fever with headache associated with one or more of confusion, lethargy, encephalitis, encephalopathy, and meningitis. Fatal outcome has been reported. Other neurological signs and symptoms have been reported and include convulsion, Guillain-Barré Syndrome or focal neurological deficit.

General disorders and administration site conditions
Very rare: Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD) (formerly described as "Febrile Multiple Organ-System Failure"). YEL-AVD, sometimes fatal, has been reported following STAMARIL® and also following administration of yellow fever vaccines from other manufacturers. In the majority of cases reported, the onset of signs and symptoms was within 10 days after the vaccination. Initial signs and

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symptoms are non-specific and may include pyrexia, myalgia, fatigue and headache. This may lead quickly to liver and muscle cytolysis and possibly to thrombocytopenia, lymphopenia, acute renal failure, metabolic acidosis and respiratory failure. The pathophysiological mechanism of such reactions has not been established. In some individuals with YEL-AVD a medical history of thymic disease has been reported. Age older than 60 years has also been identified as a risk factor for this event.

DOSAGE AND ADMINISTRATION

A single 0.5-mL dose given by intramuscular or subcutaneous injection provides protection for at least 10 years.

The vaccination schedule is identical for adults and children over 6 months.

The contents of each vial should be carefully rehydrated with the accompanying syringe diluent. After complete dispersion, the vaccine is withdrawn back into the syringe and is ready for injection. Strict aseptic technique should be employed when rehydrating and withdrawing the reconstituted product back into the syringe. The reconstituted vaccine should be used as soon as possible and must be used within one hour of reconstitution.

PRESENTATION AND STORAGE

1 single dose lyophilised vaccine vial + (0.5mL) diluent syringe.

Store at 2-8°C. Do not freeze. Protect from light.

MANUFACTURED BY

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