1. NAME OF THE MEDICINAL PRODUCT

STAMARIL

Powder and solvent for suspension for injection in pre-filled syringe. Yellow fever vaccine (Live).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:

Yellow fever virus[1] 17D-204 strain (live, attenuated), not less than 1,000 IU

[1] produced in specified pathogen-free chick embryos

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Before reconstitution, the powder is homogeneous, beige to orange beige, and the solvent is a limpid solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STAMARIL is indicated for active immunization against yellow fever in persons:

- travelling to, passing through or living in an endemic area,
- travelling to any country that requires an International Certificate of Vaccination for entry (which may or may not depend on the previous itinerary).
- handling potentially infectious materials (*e.g.* laboratory personnel).

See sections 4.2, 4.3 and 4.4 regarding the minimum age for vaccination of children under special circumstances and guidance for vaccination of other specific patient populations.

In order to comply with vaccine regulations and to be officially recognized, yellow fever vaccines must be administered in an approved World Health Organization (WHO) vaccination center and registered on an International Certificate of Vaccination. The validity period of this certificate is established according to International Health Regulations (IHR) recommendations, and starts 10 days after primary vaccination and immediately after re-vaccination (see Section 4.2).

4.2 Posology and method of administration

Posology*:*

- Primary vaccination

The vaccine should be given at least 10 days before entering an endemic area since protective immunity may not be achieved until at least this time has elapsed.

Adults: a single dose of 0.5 ml of the reconstituted vaccine.

Paediatric population

- *Children aged 9 months and older: a single dose of 0.5 ml of the reconstituted vaccine.*
- *Children from 6 to 9 months of age:* Vaccination against yellow fever is not recommended in children aged from 6 months up to 9 months except in specific circumstances and in accordance with available official recommendations (see Section 4.4), in which case the dose is the same as in older children and adults.
- *Children under 6 months of age:* STAMARIL is contraindicated in children less than 6 months of age (see Section 4.3).

Older people

The dose is the same as for adults. However due to a potentially higher risk of yellow fever vaccine-associated severe and potentially fatal disease in persons from 60 years of age, the vaccine should only be given when it is considered that there is a significant and unavoidable risk of acquiring yellow fever infection (see Sections 4.4 and 4.8).

- *Re-vaccination*

The duration of protection following administration of one single 0.5 ml dose of STAMARIL is expected to be at least 10 years and may be life-long.

Re-vaccination with one dose of 0.5 ml.

Re-vaccination may be required, depending on official recommendations of local Health Authorities, as a condition of entry in some countries.

Method of administration:

It is preferable that the vaccine is injected by the subcutaneous route.

Intramuscular injection may be performed if this is in accordance with applicable official recommendations.

For intramuscular use, the recommended injection sites are the anterolateral aspect of the thigh in children less than 12 months of age, the anterolateral aspect of the thigh (or the deltoid muscle if muscle mass is adequate) in children 12 months through 35 months of age, or the deltoid muscle in children from 36 months of age onwards and adults.

DO NOT INJECT INTRAVASCULARLY

Precautions to be taken before handling or administering the medicinal product

For instructions on reconstitution of the medicinal product before administration, see Section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 or to eggs or chicken proteins.
- Severe hypersensitivity reactions (e.g., anaphylaxis) after a previous dose of any yellow fever vaccine.
- Age less than 6 months (see Sections 4.2 and 4.4).
- 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 myasthenia gravis, thymoma, thymectomy)
- Symptomatic HIV infection.
- Asymptomatic HIV infection when accompanied by evidence of impaired immune function (see Section 4.4).
- Moderate or severe febrile illness or acute 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.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injury from faints and manage syncopal reactions.

DO NOT INJECT INTRAVASCULARLY.

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.

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 (YEL-AND)

Very rarely, YEL-AND has been reported following vaccination, with sequelae or with fatal outcome in some cases (see Section 4.8). To date most of cases of YEL-AND have been reported in primary vaccinees with an onset within 30 days of vaccination. The risk appears to be higher in those aged over 60 years and below 9 months of age (including infants exposed to vaccine through breastfeeding) although cases have been also reported in other age groups. Congenital or acquired immunodeficiency has also been recognized as a potential risk factor (see Section 4.3).

Yellow Fever Vaccine-Associated Viscerotropic Disease (YEL-AVD)

Very rarely, YEL-AVD resembling fulminant infection by wild-type virus has been reported following vaccination (see

section 4.8). The mortality rate has been around 60%. To date, most of cases of YEL-AVD have been reported in primary vaccinees with an 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 other age groups. History of thymus dysfunction has also been recognized as a potential risk factor (see Section 4.3).

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

- Paediatric population: children less than 9 months of age

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.

STAMARIL is contraindicated in children less than 6 months of age (see Section 4.3).

- Older people: persons aged 60 years and older

Persons aged 60 years and older may have an increased risk of serious and potentially fatal adverse reactions (including systemic and neurological reactions persisting more than 48 hours, YEL-AVD and YEL-AND) when compared to other age groups. Therefore, the vaccine should only be given to those who have a significant risk of acquiring yellow fever (see above and Section 4.8).

Pregnant and breast-feeding women

STAMARIL should not be used in pregnant and breast-feeding woman unless when clearly needed and following an assessment of the risks and benefits (see Section 4.6).

Transmission

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 YEL-AND from which the infants recover (see section 4.6.)

As with any vaccine, vaccination with STAMARIL may not protect 100% of vaccinated individuals.

4.5 Interaction with other medicinal products and other forms of interaction

STAMARIL must not be mixed with any other vaccine or medicinal product in the same syringe.

If there is a need to administer another injectable vaccine(s) at the same time as STAMARIL each vaccine should be injected into a separate site (and preferably a separate limb).

This vaccine may be administered at the same time as measles vaccine if this is in accordance with official recommendations.

It may be administered at the same time as vaccines containing typhoid Vi capsular polysaccharide and/or inactivated

hepatitis A virus.

It must not be administered to persons who are receiving immunosuppressant therapy (e.g., cytotoxic agents, systemic steroids, greater than standard dose of topical or inhaled steroids or other agents), (see Section 4.3).

It can induce false positive results with laboratory and/or diagnostic tests for other flavivirus related diseases such as dengue or Japanese encephalitis.

4.6 Fertility, pregnancy and lactation

Pregnancy

No animal developmental and reproductive 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.

Breast-feeding

As there is a probable risk of transmission of the vaccine virus strain to the infants from breast-feeding 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 (see section 4.4).

Fertility

No animal fertility studies have been conducted with STAMARIL and no fertility data are available in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

In all clinical studies, 4896 subjects (all ages) received STAMARIL.

In the most representative study in general population, the most frequently reported reactions (between 12% and 18% of subjects) were headache, asthenia, injection site pain and myalgia.

In the most representative study in toddler population, the most frequently reported reactions (between 32% and 35% of toddlers) were irritability, crying and appetite loss.

Adverse reactions usually occurred within the first three days following vaccination except pyrexia, which occurred between Day 4 and Day 14.

These reactions usually lasted for not more than 3 days.

Both local and systemic reactions were usually of mild intensity; however at least one severe injection site reaction was reported in 0.8% of subject in general population and in 0.3% of toddlers and at least one severe systemic reaction was reported in 1.4% of subjects in general population and 4.9% in toddlers.

Cases of serious adverse events such as severe hypersensitivity or anaphylactic reactions, neurotropic or viscerotropic disease (YEL-AND; YEL-AVD) have been reported from post-marketing experience (see subsections ***b. Tabulated list of adverse reactions*** and ***c. Description of selected adverse reactions***).

b. Tabulated list of adverse reactions

The table below summarizes the frequencies of the adverse reactions that were recorded following vaccination with STAMARIL during clinical studies and worldwide post-marketing experience.

The adverse reactions are ranked under headings of frequency using the following convention:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from available data)

System Organ Class	Frequency	Adverse reactions
Infections and infestations	Rare	Rhinitis
	Very rare	YEL-AVD‡
Blood and Lymphatic System Disorders	Not known	Lymphadenopathy
Immune System Disorders	Not known	Anaphylactoid reaction including angioedema
Metabolism and nutrition disorders	Very common	Appetite loss*
Nervous System Disorders	Very common	Drowsiness*, Headache
	Uncommon	Dizziness
	Very rare	YEL-AND‡
	Not known	Paresthesia
Gastrointestinal disorders	Very common	Vomiting†
	Common	Nausea
	Uncommon	Abdominal pain
	Rare	Diarrhea
Skin and Subcutaneous tissue Disorders	Common	Rash
	Uncommon	Pruritus
	Not known	Urticaria
Musculoskeletal and Connective Tissue Disorders	Very common	Myalgia
	Common	Arthralgia
General Disorders and Administration Site Conditions	Very common	Irritability*, Crying*, Pyrexia†, Asthenia, Injection site pain/tenderness
	Common	Injection site erythema/redness, Injection site hematoma, Injection site induration; Injection site oedema/swelling
	Uncommon	Injection site papule
	Not known	Influenza-like illness

*Specific to paediatric population, (see Section ***d. Paediatric population***)

‡ For clinical features see Section ***c. Description of selected adverse reactions***

† Very common in toddlers (see Section ***d. Paediatric population***), Common in general population

c. Description of selected adverse reactions

Cases of neurotropic disease (known as YEL-AND), some of which have had a fatal outcome, have been reported to occur within 30 days following vaccination with STAMARIL, and other yellow fever vaccines. YEL-AND may manifest as high fever with headache that may progress to include one or more of confusion, lethargy, encephalitis, encephalopathy and meningitis. Other neurological signs and symptoms have been reported and include convulsion, Guillain-Barré syndrome and focal neurological deficits (see Section 4.4).

Cases of viscerotropic disease (known as YEL-AVD and formerly described as “Febrile Multiple Organ-System Failure”) have been reported following vaccination with STAMARIL, and other yellow fever vaccines, some of which have been fatal. In the majority of cases reported, the onset of signs and symptoms was within 10 days after the vaccination.

Initial signs and symptoms are non-specific and may include pyrexia, myalgia, fatigue, headache and hypotension, potentially progressing quickly to liver dysfunction with jaundice, muscle cytolysis, thrombocytopenia and acute respiratory and renal failure (see Section 4.4).

d. Paediatric population

The safety of STAMARIL in paediatric population has been studied through a clinical study performed in 393 toddlers aged 12 to 13 months which received STAMARIL and placebo concomitantly.

The safety profile was assessed during the first 4 weeks following vaccination.

The following most frequently reported adverse reactions specific to the paediatric population were reported as “very common”: irritability (34.7%), appetite loss (33.7%), crying (32.1%) and drowsiness (22%).The other adverse reactions reported in toddlers were also reported from studies in general population:

- Injection site pain (17.6%), pyrexia (16.5%) and vomiting (17.1%) were reported as “very common” in toddlers. Pyrexia and vomiting were more frequently reported than in general population (see table in subsection ***b. Tabulated summary of adverse reactions***).

- Injection site erythema (9.8%) and injection site swelling (4.4%) were reported as “common” in toddlers, like in general population, however with significantly higher frequencies compared to general population.

e. Other special population

Congenital or acquired immunodeficiency has been recognized as a potential risk factor for serious adverse events, including YEL-AND (See Sections 4.3 and 4.4).

Age of more than 60 years (see section 4.4) has been recognized as a potential risk factor for YEL-AVD and YEL-AND.

Age below 9 months (including infants exposed to vaccine through breastfeeding) (see Section 4.4) has been recognized as a potential risk factor for YEL-AND.

A medical history of thymus dysfunction (see sections 4.3 and 4.4) has been recognized as a potential risk factor for YEL-AVD.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health (www.health.gov.il) according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

Cases of administration of more than the recommended dose (overdose) have been reported with STAMARIL. When adverse reactions were reported, the information was consistent with the known safety profile of STAMARIL described in Section 4.8.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Yellow Fever Vaccine (Live), ATC code: J07BL01

STAMARIL is a live attenuated yellow fever virus vaccine. As with other live attenuated viral vaccines, there is a sub-clinical infection in healthy recipients that results in the production of specific B and T cells and the appearance of specific circulating antibody. A neutralizing antibody titer of 1:10 is assumed to correlate with protection.

Protective immunity appears from about 10 days after vaccination, lasts at least 10 years and may be life-long.

In clinical studies in adults it has been shown that 28 days following vaccination with STAMARIL seroconversion rates

of 93% and 100% were obtained.

Paediatric population

In a clinical study conducted in 337 toddlers aged 12 to 13 months the yellow fever seropositivity rates 28 days post injection of STAMARIL were 99.7% (98.5; 100.0) and the Geometric Mean Titers were 423 (375; 478). In another clinical study conducted in 30 children and adolescents aged 2 to 17 years a seroconversion rate of 90 to 100% was observed confirming results observed in earlier clinical studies.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

No non-clinical studies have been performed.

6. Pharmaceutical particulars

6.1 List of excipients

Powder: Lactose, Sorbitol E420, L-Histidine hydrochloride, L-Alanine, Sodium chloride, Potassium chloride, Disodium phosphate dehydrate, Potassium dihydrogen phosphate, Calcium chloride, Magnesium sulphate

Solvent: Sodium chloride, Water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this vaccine must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution, the medicinal product must be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial of powder and the syringe of solvent in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3

6.5 Nature and contents of container

Powder in vial (type I glass), with a stopper and a flip-off cap + 0.5 ml of solvent in a pre-filled syringe (type I glass), with a plunger-stopper and an attached needle and needle-shield – pack size of 1, 10 or 20.

Powder in vial (type I glass), with a stopper and a flip-off cap + 0.5 ml of solvent in a pre-filled syringe (type I glass), with a plunger-stopper, and a tip-cap – pack size of 1 or 10.

Powder in vial (type I glass), with a stopper and a flip-off cap + 0.5 ml of solvent in a pre-filled syringe (type I glass), with a plunger-stopper and a tip cap with 1 or 2 separate needles attached in the blister – pack size of 1 or 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For syringe without attached needle only: after removing the syringe tip cap, a needle should be firmly placed on the tip of the syringe and secured by rotating a quarter of a turn (90°).

The vaccine is reconstituted by adding the solvent provided in the pre-filled syringe to the vial of powder. The vial is shaken and, after complete dissolution, the suspension obtained is withdrawn into the same syringe for injection.

Before administration, the reconstituted vaccine should be vigorously shaken. Use immediately after reconstitution.

After reconstitution the suspension is beige to pink beige, more or less opalescent.

Contact with disinfectants is to be avoided since they may inactivate the virus.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Manufacturer:

SANOFI PASTEUR, 14 Espace Henry Vallée, 69007 Lyon, France

8. License Holder:

Medici Medical Ltd, 3 Hamachshev St. Netanya 4250713, Israel

9. Marketing Authorisation Numbers

133-30-30951-00

The content of this leaflet was approved by the Ministry of Health in Feb 2016 and updated according to the guidelines of the Ministry of Health in April 2020