Professional information for STAMARIL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

STAMARIL, powder and solvent for suspension for injection

Descriptive name of medicine:

Live, attenuated yellow fever virus strain 17D-204.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each immunising dose (0,5 mL) contains at least 1 000 IU of live, attenuated yellow fever virus (strain 17D-204) produced in specified pathogen free chick embryos.

Excipients with known effects:

Contains sugar (16 mg lactose per 0,5 mL) and sugar alcohol (8 mg sorbitol per 0,5 mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Freeze-dried vaccine: Beige to orange beige and homogeneous.

Solvent: Clear and colourless.

Reconstituted vaccine: A beige to pink beige suspension, more or less opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

STAMARIL is indicated in persons over 9 months of age for active immunisation against yellow fever in:

- Persons living in, travelling to or passing through an area where there is a current or periodic risk of yellow fever transmission.
- Persons moving from an endemic to a potentially receptive non-endemic area.
- Laboratory workers handling potentially infectious materials.

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 (IHR). 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 4.4).

For updated yellow fever vaccination requirements and recommendations consult the WHO dedicated website or refer to resources provided by national health authorities.

In order to comply with vaccine regulations and be officially recognised, the yellow fever vaccination must be administered at an approved World Health Organization (WHO) vaccination centre by a qualified and trained health care professional and registered on an International Certificate of Vaccination issued by Department of Health.
The validity period of the certificate is established according to IHR recommendations and starts 10 days after primary vaccination and immediately after revaccination.

4.2 Posology and method of administration

Posology

Primary vaccination

For adults and children over 9 months of age, a 0,5 mL single injection of the reconstituted vaccine provides protection for at least 10 years and may be life-long protection.

Paediatric population

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 children aged 9 months and older.

Children under 6 months of age: STAMARIL is contraindicated in children less than 6 months of age (see section 4.3).

Re-vaccination

The duration of protection is expected to be at least 10 years and may be life-long protection.

In accordance with World Health Organization (WHO) advice and International Health Regulations (IHR) recommendations, the validity of a certificate of vaccination against yellow fever shall extend for the life of the person vaccinated. However, re-vaccination may be needed in individuals who had an insufficient immune response after primary vaccination if they continue to be at risk for yellow fever virus infection.

Re-vaccination may also be required, depending on local official recommendations.

Method of administration

The reconstituted vaccine is administered via the intramuscular or the subcutaneous route.

The preferred sites for intramuscular injections are:

- the anterolateral aspect of the thigh in children from 9 to 11 months of age,
- the anterolateral aspect of the thigh (or the deltoid if muscle mass is adequate) in children 12 months through 35 months of age,
- the deltoid muscle in older children from 36 months of age, and adults.

Do not administer STAMARIL by intravascular injection.

STAMARIL must not be mixed with any other injectable vaccine(s) or medicinal product(s).

Separate syringes, separate injection sites and preferably separate limbs must be used in case of concomitant administration.

4.3 Contraindications

- STAMARIL should not be administered to individuals with history of severe allergic reaction to egg or chicken proteins or any component of the vaccine (see section 6.1) or after previous administration of the vaccine or a vaccine containing the same components.
- Administration of STAMARIL should be postponed in individuals suffering from moderate or severe febrile or acute illness.
- STAMARIL should not be administered to individuals with a congenital or acquired immune deficiency that impairs cellular immunity. This includes individuals receiving immunosuppressive therapies such as chemotherapy, or high doses of systemic corticosteroids (e.g. daily dose of 20 mg or 2 mg/kg body mass of prednisone or equivalent for 2 weeks or more, or daily dose of 40 mg or more of prednisone for more than one week), or any other medicines including biologicals with known immunosuppressive or immunomodulating properties, radiotherapy, cytotoxic medicines or any other condition which may result in immunocompromised status.
- STAMARIL should not be administered to individuals with a history of thymus dysfunction (including myasthenia gravis, thymoma) or thymectomy (for any reason). Thymectomy or thymic disease has been identified as potentially influencing the development of yellow fever vaccine-associated viscerotropic disease (see section 4.8). Health care providers are advised to ask for a history of thymus dysfunction prior to administering yellow fever vaccine. Alternative means of prevention in such patients are to be considered.
- Symptomatic HIV-infected individuals.
- Asymptomatic HIV infection when accompanied by evidence of impaired immune function (see section 4.4).
- Children less than 6 months old should not be administered the vaccine due to the risk of encephalitis.

4.4 Special warnings and precautions for use

Do not administer STAMARIL by the intravascular route: ensure the needle does not penetrate a blood vessel.

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 receiving anticoagulant therapy. The subcutaneous route of administration should be used instead.

In individuals who have a history of serious or severe reaction with a previous injection of a vaccine containing similar components, the course of the vaccination must be carefully considered.

Before the injection of any biological, the person responsible for administration must take all precautions known for the prevention of allergic or any other reactions. 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 STAMARIL.

As a precautionary measure, adrenaline (epinephrine) injection (1:1 000) must be immediately available in case of unexpected anaphylactic or serious allergic reactions.

Syncope (fainting) may occur following or even before any vaccination as a psychogenic response to the needle injection. Procedures should be in place to prevent injuries due to falling and to manage syncopal reactions.

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

Yellow fever vaccine-associated neurotropic disease (YEL-AND)

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).

To date, most 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 the vaccine through breastfeeding), although cases have also been reported in other age groups. Congenital or acquired immunodeficiency has also been recognised as a predisposing condition (see section 4.3).

However, cases of YEL-AND have also been reported in individuals with no identified risk factors. Vaccinees should be instructed to seek medical attention if they experience any symptoms suggestive of YEL-AND after vaccination, such as high fever with headache or confusion, personality change or if they experience extreme tiredness, stiff neck, fits, loss of movement or feeling in part or all of the body, and they should also be reminded to inform their health care professional that they received the yellow fever vaccine.

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)

Very rarely, yellow fever vaccine-associated viscerotropic disease (YEL-AVD) resembling fulminant infection by wild-type virus has been reported following vaccination. The mortality rate has been around 60 %. To date, most 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.

Thymectomy or history of thymus dysfunction has also been recognised as predisposing conditions (see section 4.3). However, cases of YEL-AVD have also been reported in individuals with no identified risk factors. Vaccinees should be instructed to seek medical attention if they experience any symptoms suggestive of a YEL-AVD after vaccination, such as pyrexia, myalgia, fatigue, headache or hypotension, as these can potentially progress quickly to liver dysfunction with jaundice, muscle cytolysis, thrombocytopenia, and acute respiratory and renal failure, and they should also be reminded to inform their health care professional that they received the yellow fever vaccine.

Immune status of the person

STAMARIL must not be administered to immunosuppressed persons (see section 4.3).

Patients under immunosuppressive treatments:

For patients receiving immunosuppressive treatment, vaccination should be delayed until the immune function has recovered. Patients taking high doses of systemic corticosteroids for 14 days or more should postpone vaccination for at least 1 month after completing the course.
Patients receiving other immunosuppressive treatments should obtain advice from their specialist.

HIV infection:

STAMARIL must not be administered to persons with symptomatic HIV infection, or with asymptomatic HIV infection when accompanied by evidence of impaired immune function. 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 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:

It is necessary to obtain confirmation of the child's HIV status:

1. If the child is not infected, the normal vaccination timetable applies (see section 4.2 and 4.3).
2. If the child is infected, it is essential to seek the opinion of a specialised paediatric team.

Age

Children between 6 and 9 months of age:

Only children over 9 months of age should be vaccinated, however, during outbreak control, vaccination of children aged 6 to 9 months could be considered in accordance with official recommendations.

Persons aged 60 and older:

Individuals aged 60 years and older have an increased risk of serious and potentially fatal adverse events (including neurological or systemic reactions persisting more than 48 hours, YEL-AVD and YEL-AND) compared to other age groups. In this population, the risk of a rare serious reaction to yellow fever vaccine must be balanced against the risk of yellow fever infection. Therefore, the vaccine should only be given to those who are visiting areas where there is an ongoing risk of yellow fever transmission at the time of travel. Countries designated by WHO as where vaccination is not generally recommended, or not recommended, should be considered as not representing a significant and unavoidable risk (refer to the updated WHO list of countries with risk of yellow fever transmission).

Excipients with known effect

STAMARIL contains less than 1 mmoL sodium (23 mg) per dose, that is to say essentially sodium free.

STAMARIL contains less than 1 mmoL potassium (39 mg) per dose, that is to say essentially potassium free.

STAMARIL contains 8 mg sorbitol per 0,5 mL.

4.5 Interaction with other medicines and other forms of interaction

STAMARIL may be administered at the same time as measles vaccines, typhoid Vi capsular vaccines polysaccharide and/or inactivated hepatitis A vaccines but with separate syringes, into separate sites (and preferably into separate limbs)(see section 4.2).

STAMARIL must not be administered to persons who are receiving immunosuppressive therapies such as high-dose systemic corticosteroids (e.g. daily dose of 20 mg or 2 mg/kg body mass of prednisone or equivalent for 2 weeks or more, or daily dose of 40 mg or more of prednisone for more than one week), any other medicinal products including biologicals with known immunosuppressive properties, radiotherapy, cytotoxic drugs or any other condition which may result in immunocompromised status (see section 4.3).

If there is uncertainty about the level of immunosuppression, vaccination should be withheld, and advice sought from a specialist.

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 from post-marketing surveillance and literature are not sufficient to demonstrate whether STAMARIL can affect pregnancy and embryo/fetal development, parturition and postnatal development. The potential risk is unknown.

STAMARIL is a live attenuated vaccine, it should not be given during pregnancy unless clearly needed and following an assessment of the risks and benefits.

Pregnancy should be avoided for one month following vaccination.

Lactation

As there is a probable risk of transmission of vaccine components to the infants from breastfeeding mothers, STAMARIL should not be given to nursing mothers unless when clearly needed, and following an assessment of the risks and benefits, including those to the breastfed child. In case vaccination is needed, it is recommended to interrupt breastfeeding for at least 2 weeks following vaccination.

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 a vehicle or use machines have been performed.

4.8 Undesirable effects

Adverse event information is derived from clinical studies and worldwide post-marketing experience.

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

Very common: ≥ 1/10 (≥ 10 %)

Common: ≥ 1/100 to < 1/10 (≥ 1 % and < 10 %)

Uncommon: ≥ 1/1 000 to < 1/100 (≥ 0,1 % and < 1 %)

Rare: ≥ 1/10 000 to < 1/1 000 (≥ 0,01 % and < 0,1 %)

Very rare: < 1/10 000 (< 0,01 %)

Unknown: Cannot be estimated from available data.

Data from clinical studies:

In all clinical studies, 4 896 subjects of all ages received STAMARIL.

Data from the 2 most representative studies for safety profile of STAMARIL are presented below.

General population: aged 1 – 85 years

Safety data of STAMARIL were collected in 1 252 subjects during a blind observer, randomised safety study conducted on 2 514 subjects from 1 to 85 years old receiving STAMARIL or another yellow fever vaccine. The safety profile was assessed during the first 3 weeks following vaccination as follows:

- Solicited injection site and local reactions within 8 days (D0 – 7) post-vaccination.
- Unsolicited and serious adverse events and reactions within 21 days from vaccination.

Solicited reactions

Headache, asthenia and injection site pain were the most frequently reported adverse reactions in the STAMARIL group.

Solicited local reactions usually occurred within the first 3 days following vaccination, and usually lasted for not more than 3 days following vaccination, except pyrexia, which occurred between Day 4 and Day 7. These events usually lasted for not more than 3 days.

The percentage of subjects experiencing at least one solicited local or systemic reaction was 15,3 % and 30,4 %, respectively. Both local and systemic reactions were usually of mild intensity; only 0,8 % of subjects had at least one severe solicited injection site reaction and 1,4 % of subjects had at least one severe solicited systemic reaction.

Serious adverse events:

There were no serious events reported in STAMARIL group.

The summary of adverse reactions to STAMARIL from this study is as follows:

Infections and infestations

- *Rare:* rhinitis

Nervous system disorders

- *Very common:* headache
- *Uncommon:* dizziness

Gastrointestinal disorders

- *Common:* nausea and vomiting
- *Uncommon:* abdominal pain

- *Rare:* diarrhoea

Skin and subcutaneous tissue disorders

- *Common:* rash
- *Uncommon:* pruritus

Musculoskeletal and connective tissue disorders

- *Very common:* myalgia
- *Common:* arthralgia

General disorders and administration site conditions

Local reactions:

- *Very common:* pain/tenderness
- *Common:* erythema, haematoma, induration, swelling

Systemic complaints:

- *Very common:* asthenia
- *Common:* pyrexia.

Paediatric population: toddlers aged 12 – 13 months

The safety of STAMARIL in paediatric population has been recently studied through a clinical study performed in 393 toddlers aged 12 to 13 months.

They received STAMARIL and placebo concomitantly at different sites. The safety profile was assessed during the first 4 weeks following vaccination as follows:

- Solicited injection site and local reactions within 8 days (D0 – 7) and 15 days (D0 – 14) post-vaccination, respectively.
- Unsolicited and serious adverse events and reactions within 28 days from vaccination.

Solicited reactions:

Irritability, appetite loss and crying were the most frequently reported reactions.

Solicited local reactions usually occurred within the first 3 days following vaccination, and usually lasted for not more than 3 days. Solicited systemic reactions usually occurred within first 3 days following vaccination except pyrexia, which occurred with similar rates from Day 0 to Day 3 as from Day 4 to Day 7 and Day 8 to Day 14. These events usually lasted for no more than 3 days.

The percentage of subjects experiencing at least one solicited local or systemic reaction was 30,6 % and 63,5 %, respectively. Both local and systemic reactions were usually of mild intensity; only one toddler (0,3 %) experienced a severe solicited injection site reaction (at both STAMARIL and placebo administration sites) and 19 toddlers (4,9 %) had at least 1 severe solicited systemic reaction.

Serious adverse events:

There were no serious events reported in the STAMARIL group.

The summary of subjects with adverse reactions to STAMARIL (with concomitant administration with placebo at different sites) is as follows:

Metabolism and nutrition disorders

- *Very common:* appetite loss

Nervous system disorders

- *Very common:* drowsiness

Gastrointestinal disorders

- *Very common:* vomiting

General disorders and administration site conditions

Local reactions:

- *Very common:* pain/tenderness
- *Common:* erythema, swelling

- *Uncommon:* papule

Systemic complaints:

- *Very common:* pyrexia, crying, irritability.

Data from post-marketing experience:

Based on spontaneous reporting, the following adverse events have also been reported during the commercial use of STAMARIL. These events have been very rarely reported, however since exact incidence rates cannot be precisely calculated, their frequency is qualified as unknown.

Infections and infestations

- Yellow fever vaccine-associated viscerotropic disease (YEL-AVD, formerly described as febrile multiple organ-system failure). Yellow fever vaccine-associated viscerotropic disease, 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 symptoms are non-specific and may include pyrexia, myalgia, fatigue, headache and hypotension, potentially progressing quickly to liver dysfunction with jaundice, muscle cytolysis, thrombocytopenia, acute respiratory and renal failure.

Blood and lymphatic system disorders

- Transient moderate leucopenia, lymphadenopathy.

Immune system disorders

- Anaphylactoid reaction including angioedema.

Nervous system disorders

- Neurotropic disease, described as YEL-AND, sometimes fatal, has been reported to occur within 30 days following vaccination with STAMARIL and also with other yellow fever vaccines. The clinical presentation has varied, and includes either encephalitis (with or

without demyelination), or a neurological disease with peripheral nervous system involvement (e.g. Guillain-Barré syndrome). Encephalitis usually starts with high fever with headache that may progress to include encephalopathy (e.g. confusion, lethargy, personality change lasting more than 24 hours), focal neurological deficits, cerebellar dysfunction or seizures.

YEL-AND with peripheral nervous system involvement usually manifests as bilateral limb weakness or peripheral cranial nerve paresis with decreased or absent tendon reflexes.

- Neurological disease not meeting the criteria for YEL-AND has been reported. Manifestations may include cases of aseptic meningitis or seizure with no associated focal neurological symptoms. Those cases are usually of mild or moderate severity and resolve spontaneously.

Skin and subcutaneous tissue disorders

- Urticaria.

General disorders and administration site conditions

- Influenza-like illness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of STAMARIL is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Adverse Drug Reaction Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.
Side effects can be reported directly to Sanofi's Pharmacovigilance Unit at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Cases of overdosing have been reported with STAMARIL. Overdose symptoms are consistent with the adverse events (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 30.2 Antigens

Pharmacotherapeutic group: Yellow Fever Vaccine (Live)

ATC code: J07BL01.

Immunity appears 10 days after the injection and lasts for at least 10 years, and may be life-long.

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:

Calcium chloride

Disodium phosphate dihydrate

Lactose

L-Alanine

L-Histidine hydrochloride

Magnesium sulphate

Potassium dihydrogen phosphate

Potassium chloride

Sodium chloride

Sorbitol (E420)

Solvent:

Sodium chloride (0,4 %)

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

36 months.

The reconstituted vaccine must be used immediately after reconstitution.

6.4 Special precautions for storage

Store between 2 °C and 8 °C.

Do not freeze. Protect from light.

6.5 Nature and contents of container

Freeze-dried vaccine in a Type I glass vial with a chlorobutyl stopper and a purple flip-off cap.

0,5 mL of solvent in a Type I glass pre-filled syringe with a bromobutyl or chlorobutyl plunger-stopper, with a 25 G 16 mm stainless steel needle and needle-shield attached.

Pack size: singles.

6.6 Special precautions for disposal and other handling

The vaccine is reconstituted in its vial with the 0,4 % sodium chloride solvent contained in the syringe. The vial is shaken and, after complete dissolution, the suspension obtained is withdrawn

into the syringe for injection.

Before administration, the reconstituted vaccine should be vigorously shaken.

Use immediately after reconstitution.

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

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

8. REGISTRATION NUMBER

27/30.1/0532

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 April 1994

10. DATE OF REVISION OF THE TEXT

13 December 2021

SADC REGISTRATION DETAILS:

Botswana: S2

Reg. No.: BOT0300559

Namibia: NS2

Reg. No.: 04/30.1/1778

Zimbabwe: PP

Reg. No.: 99/18.2/3637