NEW ZEALAND DATA SHEET

1 STAMARIL® (SUSPENSION FOR INJECTION)

Yellow Fever Vaccine (Live)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mL dose of reconstituted vaccine from the freeze-dried product contains an injectable suspension in stabiliser of the attenuated 17D 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 IU.

Stamaril meets the World Health Organization (WHO) requirements for manufacture of biological substances.

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.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder and diluent for suspension for injection.

Stamaril is a beige to orange beige and homogenous powder, which after reconstitution with sodium chloride solution (a clear and colourless solution) forms a beige to pinked beige suspension, more or less opalescent.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Prevention of yellow fever. Vaccination is recommended for:

- Every individual aged 9 months and over living or travelling through an area where there is a current or periodic risk of yellow fever transmission.
- Non-vaccinated individual moving through an area where there is a current or periodic risk of yellow fever transmission to a potentially receptive non-endemic area where there is a current or periodic risk of yellow fever transmission.
- Laboratory workers handling potentially infectious materials.

In order to be officially recognised, the yellow fever vaccination must be administered in an approved vaccination centre by a qualified and trained health care professional

and registered on an international certificate. The validity period of the certificate is established according to International Health Regulations recommendations and starts 10 days after primary vaccination and immediately after re-vaccination.

4.2 DOSE AND METHOD OF ADMINISTRATION

For adults and children aged 9 months and over: a single 0.5 mL dose given by intramuscular or subcutaneous injection.

Do not administer by intravascular injection.

Stamaril must not be mixed with any other injectable vaccine(s) or medical product(s).

The freeze-dried powder is reconstituted with the accompanying 0.4% sodium chloride diluent contained in the syringe. The vial is shaken and, after complete dissolution, the suspension obtained is withdrawn into a separate syringe for injection.

Before administration, the reconstituted vaccine should be shaken vigorously.

Use immediately after reconstitution.

Product is for single use in one patient only. Discard any residue.

Use a separate, sterile syringe and needle for each patient to prevent transmission of blood borne infectious agents. Do not recap needles. Dispose of needles and syringes according to biohazard waste guidelines.

The duration of protection is expected to be at least 10 years and may be a life-long re-vaccination may be needed in individuals who had an insufficient immune response after their primary vaccination if they continue to be at risk for yellow fever virus infection.

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

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

4.3 CONTRAINDICATIONS

Stamaril should not be administered to individuals with a history of severe allergic reaction to eggs or chicken proteins or to any component of the vaccine or a history of severe allergic reaction 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 used in pregnant and breast-feeding women, unless when clearly needed, and following an assessment of the risks and benefits.

Stamaril should not be administered to children less than 6 months of age due to the risk of encephalitis.

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 or any other medicinal products including biologicals with known immunosuppressive or immunomodulating properties.

Stamaril should not be administered to symptomatic HIV-infected individuals.

Stamaril should not be administered to HIV-infected individuals who are asymptomatic when accompanied by evidence of impaired immune function.

Stamaril should not be administered to individuals with a history of thymus dysfunction (including myasthenia gravis, thymoma or or thymectomy (for any reasons).

Thymectomy and thymus disease have been identified as potentially influencing the development of yellow fever vaccine-associated viscerotropic disease. Healthcare providers are advised to ask for a history of thymus dysfunction prior to administering yellow fever vaccine. Alternative means of prevention in such individuals are to be considered.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

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

Do not administer by intravascular injection.

In individuals with thrombocytopenia or a bleeding disorder, the vaccine should be administered by subcutaneous route since bleeding may occur following an intramuscular administration to these individuals.

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

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 falling injury and manage syncopal reactions.

Before considering administration of yellow fever vaccine, care should be taken to identify individuals who might be at increased risk of adverse reactions following vaccination.

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 Undesirable effects). Other neurological complications have included Guillain-Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), and bulbar palsy. 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 transmission from nursing mothers to the infants) although cases have been also reported in other age groups. Congenital or acquired immunodeficiency has also been recognised as a predisposing condition (see Section 4.3 Contraindications). 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 after vaccination any symptoms suggestive of YEL-AND 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 yellow fever vaccine (See Section 4.8 Undesirable effects).

Yellow fever vaccine-associated viscerotropic disease

Very rarely, yellow fever vaccine-associated viscerotropic disease (YEL-AVD), which may present as non-specific multi-organ system failure or can be similar to fulminant infection by wild-type virus, with liver failure and internal bleeding leading to death, has been reported following vaccination (see Section 4.8 Undesirable effects). 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, 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. Thymectomy or history of thymus dysfunction have also been recognised as predisposing conditions (see Section 4.3 Contraindications). 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 after vaccination any symptoms suggestive of a YEL-AVD 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 yellow fever vaccine (See Section 4.8 Undesirable effects).

Individuals with altered immune status

Children born to HIV-positive mothers

It is necessary to obtain information of the child's HIV status (See Section 4.3 Contraindications and Section 4.2 Dose and method of administration):

- 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.

Individuals under immunosuppressive treatments

For individuals following an immunosuppressive treatment, it is recommended to delay the vaccination until the immune function has recovered. In individuals taking high doses of systemic corticosteroids, it is advisable to wait for at least one month. Individuals following other immunosuppressive treatments should seek advice from a specialist.

HIV infection

Stamaril must not be administered to individuals 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 individuals 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.

Use in the elderly

Individuals aged 60 years and older may have an increased risk of serious adverse events (systemic or neurological reactions persisting more than 48 hours), including 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. Individuals should not receive the vaccine if they travel to a country without an ongoing risk of yellow fever transmission at the time of travel. Refer to the WHO list of countries with risk of yellow fever transmission or to resources provided by national health authorities.

Paediatric use

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.

Effects on laboratory tests

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

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

To avoid reduction in serological responses, another live vaccine, if not given concurrently with Stamaril, should be given after four weeks have elapsed.

Available data supports concomitant use of Stamaril with polysaccharide typhoid vaccine in separate syringes at separate sites.

Stamaril may be administered in adults at the same time as IMOJEV but with separate syringes, into separate sites.

Data concerning other vaccines is limited. However, no interaction is anticipated when vaccines are given at separate sites using separate syringes.

In the case of immunosuppressive therapies, such as chemotherapy or high doses of systemic corticosteroids, or any other medicinal products including biologicals with known immunosuppressive or immunomodulating properties refer to Section 4.3 Contraindications and Section 4.4 Special Warnings and Precautions for use.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Stamaril has not been evaluated for the effects on fertility.

Use in pregnancy – Pregnancy Category B2

As with all live attenuated vaccines, pregnancy constitutes a contraindication. No animal developmental and reproductive studies have been conducted with Stamaril. Data from post marketing surveillance and literature are not sufficient to demonstrate whether Stamaril can adversely affect pregnancy and embryo-fetal development, parturition and postnatal development. The potential risk is unknown.

Stamaril should be given to pregnant women only when clearly needed, and following an assessment of the risks and benefit.

Use in lactation

No data exists on the use of Stamaril during lactation. As there is a probable risk of transmission of vaccine components to the infants from breast-feeding mothers, Stamaril should not be given to nursing mothers unless when clearly needed and only if the potential benefits to the mother outweigh the potential risks, including those to the breastfed child. In case vaccination is needed, it is recommended to interrupt breastfeeding for at least 2 weeks following vaccination.

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 infants. Following transmission the infants may develop YEL-AND from which the infants recover.

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

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

Very common: ≥ 1/10 (≥ 10%)
Common: < 1/10 and ≥1/100 (< 10% and ≥ 1%)
Uncommon: < 1/100 and ≥1/1000 (< 1% and ≥ 0.1%)
Rare: < 1/1000 and ≥1/10000 (< 0.1% and ≥ 0.01%)
Very rare: < 1/10000 (< 0.01%)

Not known Cannot be estimated from available data

Clinical trial experience

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

General population

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 with a median age of 21 years receiving either 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. Solicited systemic reactions usually occurred within the first 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.

The summary of adverse reactions from this study is available in Table 1.

Table 1: Percentage of Subjects with Adverse Reactions to Stamaril vaccine - Safety Analysis Set (STA05)

Adverse reactions by System Organ Class (SOC)	General population 1-85 year old (N=1,252)
General Disorders and Administration Site Conditions	
Local reactions	
Injection site pain/tenderness	14.0% *(Very common)*
Injection site erythema	1.3% *(Common)*
Injection site haematoma	1.9% *(Common)*
Injection site induration	1.4% *(Common)*
Injection site swelling	1.0% *(Common)*
Systemic complaints	
Asthenia	16.6% *(Very common)*
Pyrexia	8.3% *(Common)*
Nervous system disorders	
Headache	18.0% *(Very common)*
Dizziness‡	0.4% *(Uncommon)*
Musculoskeletal and connective tissue disorders	
Myalgia	12.8% *(Very common)*
Arthralgia	7.5% *(Common)*
Gastrointestinal disorders	
Nausea	5.5% *(Common)*
Vomiting	1.4% *(Common)*
Abdominal pain‡	0.2% *(Uncommon)*
Diarrhoea‡	0.08% *(Rare)*
Skin and subcutaneous tissue disorders	
Rash	1.2% *(Common)*
Pruritus‡	0.2% *(Uncommon)*
Infections and infestations	
Rhinitis‡	0.08% *(Rare)*

N – total number of subjects

‡Unsolicited adverse reaction

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 adverse 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 the 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 not 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.

The summary of adverse reactions to Stamaril from this study is available in Table 2.

Table 2: Percentage of Subjects with Adverse Reactions to Stamaril vaccine (concomitant administration with placebo at different sites) - Safety Analysis Set (CYD29)

Adverse reactions by System Organ Class (SOC)	**Toddlers 12-13 months old (N = 393)**	
General Disorders and Administration Site Conditions		
Local reactions	**Stamaril**	**Placebo**
Injection site pain/tenderness	17.6% *(Very common)*	19.7% *(Very common)*
Injection site erythema	9.8% *(Common)*	10.9% *(Very common)*
Injection site swelling	4.4% *(Common)*	4.9% *(Common)*
Injection site papule‡	0.3% *(Uncommon)*	0.0%
Systemic complaints		
Pyrexia	16.5% *(Very common)*	

Crying	32.1% *(Very common)*
Irritability	34.7% *(Very common)*
Nervous system disorders	
Drowsiness	22.0% *(Very common)*
Gastrointestinal disorders	
Vomiting	17.1% *(Very common)*
Metabolism and nutrition disorders	
Appetite loss	33.7% *(Very common)*

N – total number of subjects

‡Unsolicited adverse reaction

Post-marketing experience

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

Skin and subcutaneous tissue disorders

Urticaria

Blood and lymphatic system disorders

Lymphadenopathy, Transient moderate leucopenia

Immune system disorders

Anaphylactoid reaction including angioedema

Nervous system disorders

Neurotropic disease, described as Yellow Fever Vaccine-Associated Neurotropic Disease (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 neurologic 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 neurologic 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. See Section 4.4 Special Warnings and Precautions for use).

Neurologic disease not meeting the criteria for YEL-AND has been reported. Manifestations may include cases of aseptic meningitis or seizure with no associated

focal neurologic. Those cases are usually of mild or moderate severity and resolve spontaneously.

Syncope and paresthesia

Infections and infestations

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 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.

General disorders and administration site conditions

Influenza-like illness

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration of the medicine is important. It allows continued monitoring of the benefit-risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

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.

For information on the management of overdose, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

Stamaril is a live stabilised vaccine for active immunisation against yellow fever. Immunity appears 10 days after injection, lasts at least 10 years and may be life-long.

5.2 PHARMACOKINETIC PROPERTIES

No pharmacokinetic studies have been performed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Stamaril has not been evaluated for the genotoxic potential.

Carcinogenicity

Stamaril has not been evaluated for the carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Other ingredients:

Stabilising medium:	16.0 mg lactose monohydrate, 8.0 mg sorbitol, 833 micrograms histidine hydrochloride, 362 micrograms alanine, 1.6 mg sodium chloride, 54 micrograms potassium chloride, 298 micrograms dibasic sodium phosphate dihydrate, 63 micrograms monobasic potassium phosphate, 39 micrograms calcium chloride dihydrate, 29 micrograms magnesium sulfate heptahydrate.
Diluent:	0.4% sodium chloride solution.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, Stamaril must not be mixed with other vaccines or medicinal products.

6.3 SHELF LIFE

36 months.

Use immediately after reconstitution.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze.) Protect from light.

For storage conditions after reconstitution of the medicine, see Section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

After use, any remaining vaccine and container must be disposed of safely according to locally agreed procedures.

7 MEDICINE SCHEDULE

S4 – Prescription Only Medicine

8 SPONSOR

Australia:
sanofi-aventis australia pty ltd
12 – 24 Talavera Road
Macquarie Park NSW 2113
Australia
Tel: 1800 818 806

New Zealand:
sanofi-aventis new zealand limited
Level 8
56 Cawley St
Ellerslie
Auckland
New Zealand
Tel: 0800 283 684

9 DATE OF FIRST APPROVAL

6 November 1997

10 DATE OF REVISION OF THE TEXT

20 March 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Minor editorial changes.
4.1 and 4.2	Clarifications on the dose and indication section provided.
4.3	Addition of contraindication thymectomy (for any reasons).
4.4	Addition of YEL-AND and YEL-AVD paragraphs and warning for elderly.
4.5	Immunosuppressive paragraph added and crosslinks to other sections.
4.8	Clarification on adverse event Neurological disease and addition of Skin and subcutaneous tissue disorders.