STAMARIL

POWDER AND SOLVENT FOR SUSPENSION FOR INJECTION, YELLOW FEVER VACCINE (LIVE)

1. NAME OF THE MEDICINAL PRODUCT

STAMARIL, powder and solvent for suspension for injection in prefilled syringe, Yellow fever vaccine (Live).

STAMARIL, powder and solvent for suspension for injection in multidose container, Yellow fever vaccine (Live).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, 1 dose (0.5 ml) contains:
Yellow fever virus[1] 17 D-204 strain (live, attenuated) . . . . . not less than 1000 IU
[1] produced in specific pathogen-free chick embryos.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Before reconstitution, the powder is beige to orange beige; the solvent is clear and colourless.

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 centre and registered on an International Certificate of Vaccination. This certificate is valid for 10 years from the 10th day after vaccination and immediately after re-vaccination.

4.2 Posology and method of administration

Posology:

Primary vaccination

Adults and children aged 9 months and over: A single dose of 0.5 ml of reconstituted vaccine.

Children under 9 months of age: The vaccine must not be given to children less than 6 months old (see section 4.3). Vaccination against yellow fever is not usually 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.

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.

Elderly

The dose is the same as for adults. However due to a 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 considerable and unavoidable risk of acquiring yellow fever infection (see sections 4.4 and 4.8).

Re-vaccination

Re-vaccination with one dose of 0.5 ml is recommended every 10 years in persons considered to be at risk of exposure.

International Health Regulations require re-vaccination, using the same dose as for primary vaccination, at intervals of 10 years in order to retain a valid certificate.

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 the infants and toddlers (6 months up to 2 years of age) and the deltoid muscle in older children and adults.

DO NOT INJECT INTRAVASCULARLY.

See section 6.6 for instructions on reconstitution.

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 (YEL-AND)

Very rarely, yellow fever vaccine-associated neurotopic 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 (YEL-AVD)

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 recognized 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 any 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.

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 yellow fever vaccine associated neurotropic disease (YEL-AND) from which the infants recover (see section 4.6).

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).

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

STAMARIL may be administered at the same time as vaccines containing typhoid Vi capsular polysaccharide and/or inactivated hepatitis A virus.

STAMARIL 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.

4.6 Pregnancy and lactation

Pregnancy

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

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).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Data from clinical studies

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

The following adverse events are from one clinical study in which 106 healthy adult subjects received STAMARIL.

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

- Very common: ≥ 10%
- Common: ≥ 1% and < 10%
- Uncommon: ≥ 0.1% and < 1%

Nervous system disorders
Very common: Headache

Gastro-intestinal system disorders
Common: Nausea, diarrhoea, vomiting
Uncommon: Abdominal pain

Musculo-skeletal and connective tissue disorders
Common: Myalgia
Uncommon: Arthralgia

General disorders and administration site conditions
Very common: Local reactions (including pain, redness, haematoma, induration, swelling)
Common: Pyrexia, Asthenia

Data from post-marketing experience

The following additional adverse events have been reported during post marketing experience with STAMARIL. They are based on spontaneous reporting therefore the frequencies are unknown.

Blood and lymphatic system disorders
Lymphadenopathy.

Immune system disorders
Anaphylaxis, angioedema.

Nervous system disorders
Cases of neurotropic disease (known as YEL-AND), some of which resulted in death, have been reported following yellow fever vaccination (see section 4.4). The neutropic disease may manifest as high fever with headache that may progress to confusion, lethargy, encephalitis, encephalopathy and meningitis (see section 4.4).

Other neurological signs and symptoms have been reported and include convulsion, Guillain-Barré syndrome and focal neurological deficits.

Skin and subcutaneous tissue disorders
Rash, urticaria.

General disorders and administration site conditions
Cases of viscerotropic disease (known as YEL-AVD and formerly described as "Febrile Multiple Organ-System Failure"), some of which resulted in death, have been reported following yellow fever vaccination, (see section 4.4). The viscerotropic disease may manifest as fever, fatigue, myalgia, headache and hypotension progressing to metabolic acidosis, muscle and liver cytolysis, lymphocytopenia and thrombocytopenia, and renal or respiratory failure.

Additional information on special population

Congenital or acquired immunodeficiency has been identified as a risk factor for neurotropic disease (See section 4.3 and 4.4).

Age of more than 60 years has been identified as a risk factor for neurotropic and viscerotropic diseases associated with yellow fever vaccination (see section 4.4). A medical history of thymic disease has also been identified as a risk factor for viscerotropic disease (see sections 4.3 and 4.4).

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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic propertics

Pharmacotherapeutic group: Yellow Fever Vaccine (Live)
ATC code: J07B L1

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.

Protective immunity appears from about 10 days after injection. Although International Health Regulations require re-vaccination at intervals of 10 years in order to retain a valid certificate, some degree of immunity likely persists for more than 10 years.

5.2 Pharmacokinetic properties
No pharmacokinetic studies have been performed.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Lactose
Sorbitol E420
L-histidine hydrochloride
L-alanine
Sodium chloride
Potassium chloride
Disodium phosphate
Monopotassium phosphate
Calcium chloride
Magnesium sulphate

Solvent:

Sodium chloride
Water for injections

6.2 Incompatibilities

The vaccine must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

STAMARIL, powder and solvent for suspension for injection in prefilled syringe, Yellow fever vaccine (Live)

After reconstitution, the medicinal product must be used immediately.

STAMARIL, powder and solvent for suspension for injection in multidose container, Yellow fever vaccine (Live)

After reconstitution, the product must be kept in a refrigerator (2°C - 8°C) and must be used within 6 hours.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

STAMARIL, powder and solvent for suspension for injection in prefilled syringe, Yellow fever vaccine (Live)

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

Powder in vial (type I glass), with a stopper (chlorobutyl) and flip-off cap (aluminium) + 0.5 ml of solvent in prefilled syringe (type I glass), with a plunger-stopper (halobutyl) and a tip cap (chlorobromobutyl or butadiene styrene) - box of 1 or 10.

Powder in vial (type I glass), with stopper (chlorobutyl) and flip-off cap (aluminium) + 0.5 ml of solvent in prefilled syringe (type I glass), with a plunger-stopper (halobutyl) and a tip cap (chlorobromobutyl or butadiene styrene) with 1 or 2 separate needles provided in the blister - box of 1 or 10.

STAMARIL, powder and solvent for suspension for injection in multidose container, Yellow fever vaccine (Live)

Powder (10 doses) in vial (type I glass) with a stopper (bromobutyl) + 5 ml of solvent in vial (type I glass) with a stopper (chlorobutyl) – Pack size of 10.

Powder (10 doses) in vial (type I glass) with a stopper (bromobutyl) + 5 ml of solvent in ampoule (polypropylene) – Pack size of 10.

Not all pack sizes or presentations may be marketed.

6.6 Special precautions for disposal and other handling

STAMARIL, powder and solvent for suspension for injection in prefilled syringe, Yellow fever vaccine (Live)

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

The powder is reconstituted by adding the solvent provided in the prefilled syringe to the vial. The vial is shaken and, after complete dissolution, the suspension obtained is withdrawn into this same syringe for injection.

Before administration, the reconstituted vaccine should be shaken vigorously.

Use immediately after reconstitution.

After reconstitution the suspension is beige to pink beige.

STAMARIL, powder and solvent for suspension for injection in multidose container, Yellow fever vaccine (Live)

The vaccine is reconstituted as follows:

- Inject a small quantity 9 mg/ml (0.9%) sodium chloride solution for injection into the vial of powder.
- Shake the vial until the powder turns into a homogenous suspension.
- Add the remaining sodium chloride solution for injection into the vial.

Before administration, the reconstituted vaccine is vigorously shaken.

For each vaccination 0.5 ml is withdrawn.

The reconstitution and withdrawal of vaccine should be performed under aseptic conditions.

After reconstitution, STAMARIL is a beige to pink beige suspension for injection.

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

Any unused product or waste material should be disposed of, preferably by heat inactivation or incineration, in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. DATE OF REVISION OF TEXT

October 2014