PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Stamaril (Yellow Fever Vaccine)

This is a summary of the RMP for Stamaril. The RMP details important risks of Stamaril, how these risks can be minimized, and how more information will be obtained about Stamaril's risks and uncertainties (missing information).

Stamaril's SmPC and its PL give essential information to HCPs and patients on how Stamaril should be used.

I THE MEDICINE AND WHAT IT IS USED FOR

Stamaril is indicated in persons over 9 months of age for active immunization against yellow fever caused by yellow fever virus.

Stamaril is indicated 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,
- and laboratory workers handling potentially infectious materials.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Stamaril, together with measures to minimize such risks and the proposed studies for learning more about Stamaril risks, are outlined below

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Stamaril is not yet available, it is listed under “missing information” outlined in the next section.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Stamaril are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Stamaril. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 32: List of important risks and missing information

Important identified risks	Anaphylactic reactions
	Yellow fever vaccine-associated viscerotropic disease (YEL-AVD)
	Yellow fever vaccine-associated neurotropic disease (YEL-AND)
Important potential risks	Potential transmission of vaccine virus through breast-feeding
Missing information	Use in pregnant women
	Use in immunocompromised individuals

II.B SUMMARY OF IMPORTANT RISKS

Table 33 - Important identified risk with corresponding risk minimization activities: Anaphylactic reactions

Anaphylactic reactions	
Evidence for linking the risk to the medicine	Literature, data from post-marketing individual case safety reports.
Risk factors and risk groups	Hereditary predisposition, history of atopic or allergic conditions. Anaphylactic/allergic reaction following a previous immunization.
Risk minimization measures	**Routine risk minimization measures:** Labelled in Sections 4.3, 4.4 and 4.8 of SmPC. Legal status: Medical product subject to medical prescription. **Additional risk minimization measures:** None

HCP: Healthcare Professional; IHR: International Health Regulation; SmPC: Summary of Product Characteristics.

Table 34 - Important identified risk with corresponding risk minimization activities: Yellow Fever Vaccine-Associated Viscerotropic disease

Yellow Fever Vaccine-Associated Viscerotropic disease (YEL-AVD)	
Evidence for linking the risk to the medicine	Yellow fever vaccine-associated viscerotropic disease was first described in 2001. (57) (58) Source of evidence include literature, data from postmarketing individual case safety reports and Working group review (EU WG, CDC, YF WG).
Risk factors and risk groups	History of thymus disorder, thymectomy. (64) (49) (65) Age ≥60-year-old. (60) Individuals with congenital or acquired immunodeficiency. (66) Among SAEs cases following unapproved use of Stamaril (use in contraindicated population or outside of the indication), only 2 YEL-AVD cases were readily preventable. These 2 cases occurred in UK travelers and lead to fatal outcome. Both were consistent with known risk of YEL-AVD, however investigations concluded on unapproved use in both cases: • one had contraindication to vaccination (past thymectomy) strongly increasing risk of YEL-AVD • one had potential risk factor for YEL-AVD (aged >60) and no indication for vaccination as the patient was traveling into a country in which there is no YF, no certificate of vaccination required as condition of entry to the country, and no recommendation for YF vaccination.
Risk minimization measures	**Routine risk minimization measures:** Labelled in Sections 4.2, 4.3, 4.4 and 4.8 of SmPC (and corresponding PL sections). Legal status: Medical product subject to medical prescription. Restricted medical prescription in designated authorized YFVCs by qualified and trained HCP with experience in benefit risk evaluation of YF vaccine according to IHR 2005. Labelled in Sections 4.1 of SmPC. **Additional risk minimization measures:** None

EU WG: European Union Working Group; HCP: Healthcare Professional; IHR: International Health Regulation; PL: Package Leaflet; SAE: Serious Adverse Event; SmPC: Summary of Product Characteristics; UK: United Kingdom; YEL-AVD: Yellow Fever Vaccine-Associated Viscerotropic Disease; YF: Yellow Fever; YFVC: Yellow Fever Vaccination Centre; YF WG: Yellow Fever Working Group.

Table 35 - Important identified risk with corresponding risk minimization activities: Yellow Fever Vaccine-Associated Neurotropic disease

Yellow Fever Vaccine-Associated Neurotropic disease (YEL-AND)	
Evidence for linking the risk to the medicine	Literature (47) (50) (53) (56), CDC Publication (67), Working group from EU and CDC YF, and post-marketing setting.
Risk factors and risk groups	Children younger than nine months of age. (81) Adults ≥60 years of age. (81) Individuals with congenital or acquired immunodeficiency. (66) However, in up to 50% of YEL-AND cases there have been no associated risk factors identified [refer to Annex 7], and the occurrence of YEL-AND is unpredictable. Each potential vaccinee should be informed on the risks associated with vaccination or with non-vaccination in the context of the YF epidemiology in the visited area.

Yellow Fever Vaccine-Associated Neurotropic disease (YEL-AND)	
Risk minimization measures	**Routine risk minimization measures:** Labelled in Sections 4.2, 4.3, 4.4 and 4.8 of SmPC (and corresponding PL sections). Legal status: Medical product subject to medical prescription. Restricted medical prescription in designated authorized YFVCs by qualified and trained HCP with experience in benefit risk evaluation of YF vaccine according to IHR 2005. Labelled in Sections 4.1 of SmPC. **Additional risk minimization measures**: None

CDC: Centers for Disease Control and Prevention; EU: European Union; HCP: Healthcare Professional; IHR: International Health Regulation; PL: Package Leaflet; SmPC: Summary of Product Characteristics; YEL-AND: Yellow Fever Vaccine-Associated Neurotropic Disease; YF: Yellow Fever; YEL-AVD: Yellow Fever Vaccine-Associated Viscerotropic Disease; YFVC: Yellow Fever Vaccination Centre.

Table 36 - Important potential risk with corresponding risk minimization activities: Potential transmission of vaccine virus through breast-feeding

Potential transmission of vaccine virus through breast-feeding	
Evidence for linking the risk to the medicine	Aggregate pharmacovigilance data. Public Health Canadian Authorities assessment. Literature publication (82) (83)
Risk factors and risk groups	Children breastfed within 2 week from maternal YF vaccination.
Risk minimization measures	**Routine risk minimization measures:** Labelled in Sections 4.6 of SmPC. Legal status: Medical product subject to medical prescription. Restricted medical prescription in designated authorized YFVC by qualified and trained HCP with experience in benefit risk evaluation of YF vaccine according to IHR 2005. Labelled in Sections 4.1 of SmPC. **Additional risk minimization measures:** None

HCP: Healthcare Professional; IHR: International Health Regulation; SmPC: Summary of Product Characteristics; YF: Yellow Fever; YFVC: Yellow Fever Vaccination Centre.

Table 37 - Missing information with corresponding risk minimization activities: Use in pregnant women

Use in pregnant women	
Risk minimization measures	**Routine risk minimization measures:** Labelled in Sections 4.6 of SmPC. Legal status: Medical product subject to medical prescription. Restricted medical prescription in designated authorized YFVCs by qualified and trained HCP with experience in benefit risk evaluation of YF vaccine according to IHR 2005. Labelled in Sections 4.1 of SmPC. **Additional risk minimization measures:** None

HCP: Healthcare Professional; IHR: International Health Regulation; SmPC: Summary of Product Characteristics; YFVC: Yellow Fever Vaccination Centre.

Table 38 - Missing information with corresponding risk minimization activities: Use in immunocompromised individuals

Use in immunocompromised individuals	
Risk minimization measures	**Routine risk minimization measures:** Labelled in Sections 4.3, 4.4 and 4.8 of SmPC. Legal status: Medical product subject to medical prescription. Restricted medical prescription in designated authorized YFVCs by qualified and trained HCP with experience in benefit risk evaluation of YF vaccine according to IHR 2005. Labelled in Sections 4.1 of SmPC. **Additional risk minimization measures:** None

HCP: Healthcare Professional; IHR: International Health Regulation; SmPC: Summary of Product Characteristics; YF: Yellow Fever; YFVC: Yellow Fever Vaccination Centre.

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Stamaril.

II.C.2 Other studies in post-authorization development plan

Not applicable