Summary of the Risk Management Plan for STIVARGA®

Active substance: Regorafenib

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Based on the EU-RMP v6.1 dated 26-Oct-2022 for STIVARGA®

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of STIVARGA® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of STIVARGA® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of STIVARGA®.

Summary of risk management plan for Stivarga (Regorafenib)

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

Stivarga's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Stivarga should be used.

This summary of the RMP for Stivarga should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Stivarga's RMP.

I. The medicine and what it is used for

Stivarga is authorised for

- the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies.
- Unresectable or metastatic gastrointestinal stromal Tumours (GIST) who have progressed on or are intolerant to prior treatment with imatinib and sunitinib.
- the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. (see SmPC for the full indication)

It contains Regorafenib as the active substance and it is given by oral route of administration.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Stivarga, together with measures to minimise such risks and the proposed studies for learning more about Stivarga's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER/PSUR 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 Stivarga is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Stivarga are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Stivarga. 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 (e.g., on the long-term use of the medicine).

Table Part VI-1: Summary of safety concerns

Important identified risks	• Severe drug-induced liver injury (DILI) • Cardiac ischemic events • Hypertension and hypertensive crisis • Haemorrhage • Hand-foot skin reaction (HFSR) • Posterior reversible encephalopathy syndrome (PRES) • Gastrointestinal perforation and fistulae • Stevens-Johnson syndrome (SJS) /Toxic epidermal necrolysis (TEN) • Infection
Important potential risks	• Wound healing complications • Interstitial lung disease (ILD) • Atrial fibrillation • Reproductive and developmental toxicity • Thrombotic microangiopathies (TMA)
Missing information	• Safety in severe hepatic impairment • Safety in children • Safety in patients with a cardiac history • Activity in biomarker-defined tumour subtypes

II.B Summary of important risks

Table Part VI-2: Important identified risks, potential risks and missing information

Important identified risk: Severe drug-induced liver injury (DILI)	
Evidence for linking the risk to the medicine	Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)-EU: Table 3/9, 3/10, 3/11, 3/12, 4/1, 4/2, 4/3, 4/4, and 4/6 Tables for Risk Management Plan Monotherapy safety set (MSAF)-EU: Table 3/3, 4/1, 4/3 Tables for Risk Management Plan Monotherapy safety set (MSAF)-EU-CONSIGN (15967): Table 3/3 Global Integrated Analysis 20150317_bay734506_japan_cmsaf, Tables 1/1 + 2 Additional tables for Risk Management Plan Monotherapy safety set (MSAF)-CONSIGN (15967): Table 3/12 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/1
Risk factors and risk groups	Age over 50 years, nutritional deficiencies, pregnancy, pre-existing liver diseases, concurrent acute infections, chronic alcohol abuse and drug interactions
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 Dosage and method of administration-Table 2 for the recommended measures and dose modifications in case of drug-related liver function test abnormalities • SmPC Section 4.4 Special warnings and precautions for use • Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Cardiac ischemic events	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)-EU: Table 3/13, 3/14, 3/15, 3/16, 5/9, 5/10, and 5/11 Tables for Risk Management Plan Monotherapy safety set (MSAF)-EU: Table 2/3, 3/4, 3/19, 3/20, and 5/3 Tables for Risk Management Plan Monotherapy safety set (MSAF)-EU-CONSIGN (15967): Table 3/4 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/2.
Risk factors and risk groups	Established risk factors for cardiovascular disease include hypertension, hypercholesterolemia, type II diabetes mellitus and hypertriglyceridemia.

Table Part VI-2: Important identified risks, potential risks and missing information

Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Hypertension and hypertensive crisis	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–EU: Table 3/17, 3/18, 3/19, 3/20, 3/21, 3/22, 3/24, 5/1, 5/2, 5/3, 5/4, 5/5, 5/6, 5/7, and 5/8 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/5, 3/6, 5/1 and 5/2 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/3.
Risk factors and risk groups	Patients with pre-existing hypertension.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Haemorrhage	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–EU: Table 3/25, 3/26, 3/27, 3/28, and 3/81 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/7, 3/21 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU-CONSIGN (15967): Table 3/7 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/5.
Risk factors and risk groups	Patients with conditions that increase the risk of bleeding, such as severe thrombocytopenia or coagulopathy of any aetiology, and those on concomitant anti-coagulation therapy.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None

Table Part VI-2: Important identified risks, potential risks and missing information

Additional pharmacovigilance activities	None
Important identified risk: Hand-foot skin reaction	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.4 and Module 5, Section 5.3.5.3. Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–EU: Table 3/29, 3/30, and 3/31 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/8 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU-CONSIGN (15967): Table 3/8 Module 5.3.5.1, A59137 (14874) _ 16.1.9.2 14874_ema_03, Tables 16.1.9.2/7+8, 15+16, 23+24, 31+32, 39+40, 47+48 Global Integrated Analysis 20150317_bay734506_japan_cmsaf, Tables 2/2, 2/3, 2/4, 2/5 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/6.
Risk factors and risk groups	Factors like pre-existing corns and calluses and excessive pressure or sheer stress on the skin of the palms and soles such as may be caused by vigorous exercise or ill-fitting shoe ware.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 Posology and method of administration-Table 1 for recommended dose modifications and measures for HFSR • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Posterior reversible encephalopathy syndrome	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.4 and Module 5, Section 5.3.5.3. Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/19, 3/20, and 3/21, 3/22, 3/23, and 3/24 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/9, 3/10 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU-CONSIGN (15967): Table 3/9, 3/10 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/7.
Risk factors and risk groups	Hypertension, immunosuppressive/cytotoxic drugs and acute or chronic renal failure.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for

Table Part VI-2: Important identified risks, potential risks and missing information

	use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Gastrointestinal perforation and fistulae	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Sections 2.1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/41, 3/42, 3/43, and 3/44 Tables for Risk Management Plan Monotherapy safety set (MSAF)-EU: Table 3/11 Tables for Risk Management Plan Monotherapy safety set (MSAF)-EU - CONSIGN (15967): Table 3/11 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/9.
Risk factors and risk groups	Intra-abdominal tumour lesions are the main risk factor for GI perforation and fistula formation.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Stevens-Johnson syndrome (SJS) /Toxic epidermal necrolysis)	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/45, 3/46, 3/47, and 3/48 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/12, Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU - CONSIGN (15967): Table 3/12 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/10.
Risk factors and risk groups	Patient-related risk factors for the development of SJS/TEN include genetic predisposition, slow acetylator genotype, and pre-existing immune compromise. Factors associated with poorer outcomes in patients with SJS/TEN include advanced age, pre-existing malignancy, metabolic disorders and organ dysfunction
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for

Table Part VI-2: Important identified risks, potential risks and missing information

	use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important identified risk: Infection	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.5.12 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–CS: Table 1.1/5, 1.1/6, 1.1/7, and 1.1/8 Tables for Risk Management Plan Monotherapy safety set (MSAF)–CS: Table 1.2/2 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/11.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects Additional risk minimisation measures: None
Important potential risk: Wound healing complications	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/49, 3/50, 3/51, and 3/52 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/13, 3/18 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU - CONSIGN (15967): Table 3/13 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/12.
Risk factors and risk groups	Diabetes mellitus and chronic inflammatory diseases predispose to wound healing complications
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None
Important potential risk: Interstitial lung disease	
Evidence for linking the risk to the medicine	CTD Module 2.7.4, Section 2.1.5 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/53, 3/54, 3/55, 3/56, and 3/69 Tables for Risk Management Plan Monotherapy safety set

Table Part VI-2: Important identified risks, potential risks and missing information

	(MSAF)–EU: Table 3/14, 3/18 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU - CONSIGN (15967): Table 3/14 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/13.
Risk factors and risk groups	Smoking is thought to be a risk factor, as are pre-existing pulmonary pathologies including lung cancer. The incidence also seems to be higher in Japanese patients probably due to ethnic, environmental or clinical practice differences
Risk minimisation measures	None
Important potential risk: Atrial fibrillation	
Evidence for linking the risk to the medicine	Regorafenib study reports PH-33963, PH-35619, PH-34500 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF) – EU: Table 3/65, 3/66, 3/67, and 3/68 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/17 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/14
Risk factors and risk groups	Risk factors for AF that are well established include advancing age, male sex, diabetes mellitus, hypertension, valvular, disease, myocardial infarction, heart failure, obesity, elevated inflammatory marker concentrations, and PR interval prolongation (119).
Risk minimisation measures	None
Important potential risk: Reproductive and developmental toxicity	
Evidence for linking the risk to the medicine	Regorafenib study report PH-36036 Tables for Risk Management Plan Controlled monotherapy safety set (CMSAF)–EU: Table 3/61, 3/62, 3/63, and 3/64 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/16, and 3/18 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU-CONSIGN (15967): Table 3/16 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/15.
Risk factors and risk groups	Women of child-bearing potential, their male partners, and the unborn child (if exposed via parent) are the risk groups
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.6 Fertility, pregnancy and lactation Additional risk minimisation measures: None
Important potential risk: Thrombotic microangiopathies	
Evidence for linking the risk to the medicine	Tables for Risk Management Plan Controlled monotherapy safety

Table Part VI-2: Important identified risks, potential risks and missing information

	set (CMSAF)–EU: Table 3/57, 3/58, 3/59, and 3/60 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU: Table 3/15 and 3/18 Tables for Risk Management Plan Monotherapy safety set (MSAF)–EU - CONSIGN (15967): Table 3/15 REFINE safety analysis set, patients who did not tolerate sorafenib: Table 14.2.1/16.
Risk factors and risk groups	Drugs appear to be responsible for up to 15% of all TTP cases. A small number of TMA cases have been reported for targeted cancer therapies including VEGF(R) inhibitors, mainly for bevacizumab (Avastin) and sunitinib (Sutent).
Risk minimisation measures	None
Missing information: Safety in severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • Section 5.2. Pharmacokinetic properties Additional risk minimisation measures: None
Missing information: Safety in children	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.2 Posology and method of administration Additional risk minimisation measures: None
Missing information: Safety in patients with a cardiac history	
Risk minimisation measures	Routine risk minimisation measures: • SmPC Section 4.4 Special warnings and precautions for use Additional risk minimisation measures: None
Missing information: Activity in biomarker-defined tumour subtypes	
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None

DILI: Drug-Induced Liver Injury, HFSR: Hand-Foot Skin Reaction, SJS: Stevens-Johnson Syndrome, SmPC: Summary of Product Characteristics, TEN: Toxic Epidermal Necrolysis, TMA: Thrombotic Microangiopathy, TTP: Thrombocytopenic Purpura, VEGF: Vascular Endothelial Growth Factor.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Stivarga.

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

Not applicable.