PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Sutent (Sunitinib malate)

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

Sutent's SmPC and its PL give essential information to healthcare professionals and patients on how Sutent should be used.

This summary of the RMP for Sutent 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 Sutent's RMP.

I. The Medicine and What It Is Used For

Sutent is authorised for the treatment of unresectable and/or metastatic malignant GIST, advanced RCC/mRCC and unresectable or metastatic, well-differentiated pNET with disease progression in adults (see SmPC for the full indication). It contains sunitinib malate as the active substance and it is given by oral route of administration.

Further information about the evaluation of Sutent's benefits can be found in Sutent's EPAR, including in its plain-language summary, available on the EMA website under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000687/human_med_001069.jsp&mid=WC0b01ac058001d124 (accessed September 2018).

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of sunitinib together with measures to minimise such risks and the proposed studies for learning more about sunitinib'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 public (e.g. with or without prescription) can help to minimise its risks.

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

If important information that may affect the safe use of sunitinib is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of sunitinib are risks that need special risk management activities to further investigate or minimise 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 sunitinib. 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.

Table 1. List of Important Risks and Missing Information

Important identified risks	Cardiotoxicity • Torsade de pointes • Left ventricular dysfunction/heart failure • Pericardial events • Cardiac ischemic events
	Reversible posterior leukoencephalopathy syndrome
	Hepatic failure
	Osteonecrosis of the jaw
	Severe cutaneous adverse reactions
	Renal failure
Important potential risks	Carcinogenicity
Missing information	Severe hepatic impairment

II.B. Summary of Important Risks

Table 2. Summary of Important Identified Risks

Important Identified Risk: Cardiotoxicity	
Torsade de pointes	
Evidence for linking the risk to the medicine	Evidence Source: Non-clinical and company-sponsored clinical studies, Spontaneous reports Strength of Evidence: In non-clinical studies QT prolongation was noted with dose levels corresponding to greater than the recommended doses used in humans. QT prolongation may lead to arrhythmias such as Torsade de pointes.

Table 2. Summary of Important Identified Risks

Risk factors and risk groups	No risk factors have been identified. Theoretically patients who have baseline QT interval prolongation, cardiac disease, or receive other medicines that cause QT interval prolongation or inhibit the metabolism of sunitinib may be at increased risk. There are many factors that can increase the QT interval, such as metabolic and cardiac disease and gender (women tend to have a longer QT interval). A life-threatening complication of QT interval prolongation is torsade de pointes, a ventricular tachycardia that is characterised by QRS complexes of changing amplitude that appear to twist around the isoelectric line and occur at rates of 200 to 250/min.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Left ventricular dysfunction/Heart failure	
Evidence for linking the risk to the medicine	Evidence Source: Non-clinical and company-sponsored clinical studies, Spontaneous reports Strength of Evidence: Left ventricular dysfunction/Heart failure has been reported with other TKIs and has been reported in sunitinib clinical trials and in the post-marketing setting.
Risk factors and risk groups	No risk factors have been identified. It is theoretically possible that patients with a history of cardiac disease, cardiac risk factors, or prior therapy with cardiotoxic drugs have a higher risk developing ventricular dysfunction while receiving sunitinib.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Pericardial events	
Evidence for linking the risk to the medicine	Evidence Source: Non-clinical and company-sponsored clinical studies, Spontaneous reports Strength of Evidence: Pericardial events have been reported in clinical trials and in the post-marketing setting.
Risk factors and risk groups	No risk factors have been identified for pericardial effusion associated with sunitinib treatment. Patients with pericardial metastases are likely to have a higher risk of developing pericardial effusion.

Table 2. Summary of Important Identified Risks

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Cardiac ischaemic events	
Evidence for linking the risk to the medicine	Evidence Source: Non-clinical and company-sponsored clinical studies, Spontaneous reports Strength of Evidence: Cardiac ischemic events have been reported with other TKIs, and can be of significant consequence to the patient. Cardiac ischaemic events have been reported in clinical trials and in the post-marketing setting.
Risk factors and risk groups	Increasing age, smoking, hypertension, hypercholesterolemia, diabetes, obesity, family history of coronary artery disease, polycythemia, and a history of coronary artery disease are other recognised predisposing risk factors for cardiac ischaemic events.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Important Identified Risk: Reversible Posterior Leukoencephalopathy Syndrome	
Evidence for linking the risk to the medicine	Evidence Source: Company-sponsored clinical studies, Spontaneous reports Strength of Evidence: RPLS has been reported in clinical trials and in the post-marketing setting and may be related to the recognised risk of hypertension with sunitinib.
Risk factors and risk groups	RPLS occurrence is usually associated with hypertension.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.

Table 2. Summary of Important Identified Risks

Important Identified Risk: Hepatic Failure	
Evidence for linking the risk to the medicine	Evidence Source: Non-clinical and company-sponsored clinical studies, Spontaneous reports Strength of Evidence: Hepatic failure some with a fatal outcome has been reported in clinical trials and in the post-marketing setting.
Risk factors and risk groups	It is not known which patients may be at increased risk of developing hepatic failure following exposure to sunitinib.
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 SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Important Identified Risk: Osteonecrosis of the jaw	
Evidence for linking the risk to the medicine	Evidence Source: Company-sponsored clinical studies, Spontaneous reports Strength of Evidence: The majority of patients who developed ONJ during sunitinib treatment had received prior or concomitant treatment with IV bisphosphonates, for which ONJ is an identified risk.
Risk factors and risk groups	Risk factors for ONJ in the general population include bisphosphonates, diabetes, alcoholism, cigarette smoking, obesity, hyperlipidemia, pancreatitis, chemotherapy with L-asparaginase, radiotherapy, receipt of parenteral steroids, jaw trauma, and dental procedures.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Important Identified Risk: Severe Cutaneous Adverse Reactions	
Evidence for linking the risk to the medicine	Evidence Source: Company-sponsored clinical studies, Spontaneous reports Strength of Evidence: SCARs (SJS and EM) are listed adverse drug reactions of sorafenib, a tyrosine kinase inhibitor that inhibits some of the same tyrosine kinases as sunitinib. It is unknown whether inhibition of tyrosine kinases expressed in the skin could result in these effects.

Table 2. Summary of Important Identified Risks

Risk factors and risk groups	Triggering causes of EM in the general population may include viral illness, other infections, or drug use. When the cause of SJS or TEN is identified, it is most frequently use of a drug; other causes or contributory factors include infections, eg, HIV, sepsis, also lymphoma, graft-versus-host disease, vaccination and radiation therapy.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.
Important Identified Risk: Renal failure	
Evidence for linking the risk to the medicine	Evidence Source: Company-sponsored clinical studies, Spontaneous reports Strength of Evidence: Most cases of renal failure in the clinical trierroral and safety database involved known risk factors which may have contributed to the development of renal failure.
Risk factors and risk groups	Risk factors identified for renal failure in the general population include advanced age; chronic infection; diabetes; hypertension; heart failure; immune disorders, such as lupus, IgA nephropathy and scleroderma; hepatic disease; prostate gland enlargement; and bladder outlet obstruction. Risk factors for prerenal acute renal failure include dehydration, heart failure, sepsis, and severe blood loss. Most cases in the clinical trial and safety database involved dehydration events such as nausea and vomiting, diarrhoea, and poor oral intake.
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 SmPC Section 4.8 Undesirable effects PL Section 2 What you need to know before you use Sutent: Warnings and precautions PL Section 4 Possible side effects Additional risk minimisation measures: None.

Table 3. Summary of Important Potential Risks

Important Potential Risk: Carcinogenicity	
Evidence for linking the risk to the medicine	Evidence Source: Spontaneous reports Strength of Evidence: Pre-clinical carcinogenicity study and spontaneous reports of second primary malignancy. However, the relationship between sunitinib administration and carcinogenicity in humans is not yet established.

Table 3. Summary of Important Potential Risks

Risk factors and risk groups	There is accumulating evidence that survivors of a primary malignancy are at an increased risk of developing a second primary malignancy. The risk of developing subsequent multiple primary cancers varies from 1% for an initial liver cancer primary diagnosis to 16% for initial bladder cancer primaries. The observed documented association between the renal cell carcinoma (RCC) and development of second primary malignancies in the epidemiologic literature dates back to the 1980s. Second primary malignancies that have been most frequently associated with RCC include cancers of the bladder, prostate, colon, rectum, lung, and non-Hodgkin lymphoma and melanoma. There are numerous explanations for these associations including the shared risk factors (genetic and/or environmental), antecedent cancer therapy and detection bias following the diagnosis of the primary cancer.
Risk minimisation measures	SmPC Section 5.3 Pre-clinical safety data

Table 4. Summary of Missing Information

Missing Information: 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 SmPC Section 5.2 Pharmacokinetic properties PL Section 2 What you need to know before you use Sutent: Children and adolescents Additional risk minimisation measures: None.

II.C. Post-Authorisation 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 sunitinib.

II.C.2. Other Studies in Post-Authorisation Development Plan

None