VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Gastrointestinal stromal tumour (GIST)
GIST, estimated to represent up to 1% of all gastrointestinal tumors, is the most common mesenchymal malignancy of the gastrointestinal tract with a yearly incidence of about 7-15 per million people.

Metastatic renal cell carcinoma (MRCC)
Incidence rates for renal cell carcinoma (RCC) vary by more than 10- to 20-fold around the world, with higher rates in Western countries such as Scandinavia, France, Canada and the US, and the lowest rates in Central and South America and Asia. RCC is nearly twice as common among men than among women: for example, in the US in 2004, it is estimated that there were over 22000 new cases in males (6% of all cancer diagnoses in males) and nearly 8000 deaths (3% of cancer deaths in males), compared to nearly 14000 new cases and nearly 5000 deaths among females.

Pancreatic neuroendocrine tumours (pNET)
Neuroendocrine tumours (NET), including pancreatic islet cell tumour, are uncommon neoplasms. Pancreatic NETs (pNETs) include a group of rare tumours of the endocrine pancreas. In the United States, the age-adjusted annual incidence of pancreatic NET among males is 0.38 per 100000 and among females is 0.27 per 100000; the median age of diagnosis is 60 years. Data from US registries showed that the incidence and prevalence of neuroendocrine tumours, including pNETs, rose over the last three decades. Although similar epidemiology data do not exist in the European patient population, the incidence is likely consistent with that in the United States.

VI.2.2 Summary of treatment benefits

Sunitinib is a protein kinase inhibitor. This means that it blocks some specific enzymes known as protein kinases. These enzymes can be found in some receptors at the surface of cancer cells, where they are involved in the growth and spread of cancer cells and in the blood vessels that supply the tumours, where they are involved in the development of new blood vessels. By blocking these enzymes, sunitinib can reduce the growth and spread of the cancer and cut off the blood supply that keeps cancer cells growing.
Sunitinib was more effective than placebo in treating gastrointestinal stromal tumour and pancreatic neuroendocrine tumours. Patients with gastrointestinal stromal tumour taking sunitinib lived for an average of 26.6 weeks without the disease getting worse, compared with 6.4 weeks in the patients taking placebo. For pancreatic neuroendocrine tumours the figures were 11.4 months in the sunitinib group and 5.5 months in the placebo group.

In metastatic renal cell carcinoma, patients taking sunitinib lived for an average of 47.3 weeks without their disease worsening, compared with 22.0 weeks in the patients receiving interferon alfa.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of sunitinib in patients below 18 years of age have not been established.

There are no studies in pregnant women using sunitinib.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Elevated blood pressure (hypertension)	Sunitinib can raise blood pressure.	Talk to your doctor before taking sunitinib if you have high blood pressure. Your doctor may check your blood pressure during treatment with sunitinib, and you may be treated with medicines to reduce the blood pressure, if needed.
Bleeding (haemorrhagic events)	Treatment with sunitinib may lead to a higher risk of bleeding or lead to changes in the number of certain cells in the blood which may lead to anaemia or affect the ability of your blood to clot. If the patient is taking warfarin or acenocoumarole, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding.	Tell your doctor right away if you have any of these symptoms or a serious bleeding problem during treatment with sunitinib: painful, swollen stomach (abdomen), vomiting blood, black, sticky stools, bloody urine, headache or change in your mental status, coughing up of blood or bloody sputum from the lungs or airway. Talk to your doctor before taking sunitinib if you have or have had blood disease, bleeding problems, or bruising. Tell your doctor if you have any bleeding while on treatment with sunitinib.
Reduction in the number of blood cells (cytopenic events)	Reduction in the number of platelets, red blood cells and/or white blood cells (e.g. neutrophils) is a very common side effect.	Tell your doctor if you have any bleeding while on treatment with sunitinib.
Heart dysfunction or damage (Cardiotoxicity, including Torsade de pointes, Left ventricular dysfunction/Heart Failure, Pericardial events and Cardiac ischemic events)	Sunitinib can cause heart problems. Heart damage was reported in a clinical study with sunitinib.	Talk to your doctor before taking sunitinib if you have heart problems or abnormal heart rhythm changes. Your doctor may obtain electrocardiograms to evaluate for these problems during your treatment with sunitinib. Tell your doctor if you feel very tired or dizzy, faint, are short of breath, have swollen feet and ankles or have abnormal heartbeats while taking sunitinib
Extreme tiredness, loss of strength (fatigue and asthenia)	Extreme tiredness and loss of strength is a very common side effect.	If you experience dizziness or you feel unusually tired, take special care when driving or using machines.
Thyroid dysfunction	Decreased activity of the thyroid gland, overproduction of thyroid hormones and inflammation of the thyroid gland are side effects.	Talk to your doctor before taking sunitinib if you have thyroid glands problems. Tell your doctor if you get tired more easily, generally feel colder than other people or your voice deepens whilst taking sunitinib. Your thyroid

Risk	What is known	Preventability
		function should be checked before you take sunitinib and regularly while you are taking it. If your thyroid gland is not producing enough thyroid hormone, you may be treated with thyroid hormone replacement.
Serious infection (necrotising fasciitis)	Serious infections including "necrotising fasciitis" (rapidly spreading infection of the skin/soft tissue that may be life-threatening) may occur.	Talk to your doctor before taking sunitinib if you have or have had skin and subcutaneous tissue disorders. Contact your doctor immediately if symptoms of infection occur around a skin injury, including fever, pain, redness, swelling, or drainage of pus or blood.
Damage to the smallest blood vessels (thrombotic microangiopathy)	Damage to the smallest blood vessels known as thrombotic microangiopathy is a rare side effect.	Talk to your doctor before taking sunitinib if you have or have had damage to the smallest blood vessels known as thrombotic microangiopathy (TMA). Tell your doctor if you develop fever, fatigue, tiredness, bruising, bleeding, swelling, confusion, vision loss and seizures.
Loss of protein in the urine / kidney disease (proteinuria / nephrotic syndrome)	Loss of protein in the urine sometime resulting in swelling is a common side effect.	Talk to your doctor before taking sunitinib if you have or have had kidney problems. Your doctor will monitor your kidney function. Tell your doctor if you experience altered frequency or absence of urination which may be symptoms of kidney failure
Abnormal changes in the brain (reversible posterior leukoencephalopathy syndrome)	Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss (reversible posterior leukoencephalopathy syndrome) is a rare side effect.	Talk to your doctor before taking sunitinib if you have or have had seizures. Notify your doctor as soon as possible if you have high blood pressure, headache and loss of sight.
Abnormal tube like passage from one normal body cavity to another body cavity or the skin (Fistula formation)	An abnormal tube like passage from one normal body cavity to another body cavity or the skin is an uncommon side effect.	If fistula formation occurs, sunitinib treatment should be interrupted.
Hepatic failure	Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumour patients treated with sunitinib.	Talk to your doctor before taking sunitinib if you have or have had liver problems. Tell your doctor if you develop any of the following signs and symptoms of liver problems during sunitinib treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor should do blood

Risk	What is known	Preventability
		tests to check your liver function before and during treatment with sunitinib, and as clinically indicated.
Blood clots in the blood vessels (embolic and thrombotic/embolism and thrombosis)	Blood clots in the blood vessels were reported in clinical trials with sunitinib.	Talk to your doctor before taking sunitinib if you have had a recent problem with blood clots in your veins and/or arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis. Call your doctor immediately if you get symptoms such as chest pain or pressure, pain in your arms, back, neck or jaw, shortness of breath, numbness or weakness on one side of your body, trouble talking, headache, or dizziness while on treatment with sunitinib.
Tumour destruction leading to hole in the intestine (gastrointestinal perforation)	Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation have occurred in patients with intra-abdominal malignancies treated with sunitinib.	Tell your doctor if you have severe abdominal pain, fever, nausea, vomiting, blood in your stool, or changes in bowel habits.
Inflammation of the pancreas (pancreatitis)	Cases of serious pancreatic events, some with fatal outcome, have been reported.	Talk to your doctor before taking sunitinib if you have or have had pancreatic disorders.
Muscle dysfunction or damage (myopathy/ rhabdomyolysis)	Musculoskeletal pain (pain in muscles and bones), muscular weakness, muscular fatigue, muscle pain, muscle spasms have been commonly reported. Abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis) have been rarely reported.	If you get any side effects, talk to your doctor or pharmacist.
Bone damage in the jaw (osteonecrosis of the jaw)	Cases of osteonecrosis of the jaw have been reported in patients treated with sunitinib.	Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them. If you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with sunitinib.
Inflammation of the oesophagus (oesophagitis)	Oesophagitis events have been reported in patients treated with sunitinib.	Unknown.

Risk	What is known	Preventability
Severe skin rashes (Toxic epidermal necrolysis, Stevens-Johnson Syndrome, Erythema multiforme)	Severe skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) have been reported with the use of sunitinib, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. The rash may progress to widespread blistering or peeling of the skin and may be life-threatening.	If you develop a rash or these skin symptoms, seek immediate advice from a doctor.
Renal failure	Cases of renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.	Talk to your doctor before taking sunitinib if you have or have had kidney problems. Your doctor will monitor your kidney function.
Adrenal gland dysfunction	Fatal events that were considered possibly related to sunitinib included adrenal insufficiency.	Unknown
Inflammation of the gallbladder (cholecystitis)	Sunitinib treatment may be associated with cholecystitis.	Talk to your doctor before taking sunitinib if you have or have had gallbladder disorders.
A group of metabolic complications that can occur during treatment of cancer (tumour lysis syndrome)	These complications are caused by the break-down products of dying cancer cells and may include the following: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness associated with abnormal laboratory test results (high potassium, uric acid and phosphorous levels and low calcium levels in the blood) that can lead to changes in kidney function and acute renal failure. Cases of tumour lysis syndrome, some fatal, have been rarely observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib.	Talk to your doctor before taking sunitinib if you have or have had kidney problems. Your doctor will monitor your kidney function.
Swelling of the lips and face, neck,	Angioedema has been reported rarely.	If angioedema occurs, sunitinib treatment should be interrupted.

Risk	What is known	Preventability
possibly also hands and feet, difficulty to swallow, difficulties to breath (angioedema)		
Decreased blood sugar level (hypoglycaemia)	Decreased blood sugar level may affect up to1 in 10 people taking sunitinib,	Talk to your doctor before taking sunitinib if you have diabetes. Blood sugar levels in diabetic patients should be checked regularly in order to assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of low blood sugar. If you experience any signs and symptoms of low blood sugar: Notify your doctor as soon as possible if you experience fatigue, palpitations, sweating, hunger and loss of consciousness.

Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
Carcinogenicity	The relevance to humans of the neoplastic findings observed in the mouse and rat carcinogenicity studies with sunitinib treatment is unclear.
Other potential cardiac effects o Conduction defect events o Tachycardia events	Sunitinib treatment may be associated with changes in the electrical activity or abnormal rhythm of the heart. Talk to your doctor before taking sunitinib if you have heart problems or abnormal heart rhythm changes. Your doctor may obtain electrocardiograms to evaluate for these problems during your treatment with sunitinib.
Retinal detachment	In the absence of specific safety signals the applicant does not propose any risk minimisation activities at this time.
Reproductive and developmental toxicity	Based on findings in animal studies, male and female fertility may be compromised by treatment with sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations. If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. If you might get pregnant, you should use reliable method of contraception during treatment with sunitinib.

Identified and potential interactions

Interaction	What is known
Drug interaction with CYP3A4 inhibitor or inducer	Some medicines can affect the levels of sunitinib in your body. You should inform your doctor if you are taking medicines containing the following active substances: • ketoconazole, itraconazole – used to treat fungal infections • erythromycin, clarithromycin, rifampicin –used to treat infections • ritonavir –used to treat HIV • dexamethasone – a corticosteroid used for various conditions • phenytoin, carbamazepine, phenobarbital – used to treat epilepsy and other neurological conditions • herbal preparations containing St. John's Wort (Hypericum perforatum)

Missing information

Risk	What is known
Use in paediatric patients	The safety and efficacy of sunitinib in patients below 18 years of age have not been established. This product is approved for use in adults only.
Use in patients with severe hepatic impairment	Sunitinib has not been studied in patients with severe hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended.
Use in patients with cardiac impairment	Patients who had cardiac events within 12 months prior to sunitinib administration were excluded from sunitinib clinical studies. It is unknown whether patients with cardiac impairment may be at a higher risk of developing further cardiac dysfunction.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable.