PROPOSED PROFESSIONAL INFORMATION FOR

Tisumor 12,5 mg, 25 mg, 37,5 mg & 50 mg

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Tisumor 12,5 mg Hard Capsules

Tisumor 25 mg Hard Capsules

Tisumor 37,5 mg Hard Capsules

Tisumor 50 mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

12,5 mg hard capsules

Each capsule contains sunitinib malate, equivalent to 12,5 mg of sunitinib.

25 mg hard capsules

Each capsule contains sunitinib malate, equivalent to 25 mg of sunitinib.

37,5 mg hard capsules

Each capsule contains sunitinib malate, equivalent to 37,5 mg of sunitinib.

50 mg hard capsules

Each capsule contains sunitinib malate, equivalent to 50 mg of sunitinib.

Sugar free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules.

Tisumor 12,5 mg hard capsules

Dark brown opaque cap and dark brown opaque body, capsule shell size No. 4 imprinted in white ink with "LP" on the cap and "650" on the body and containing yellow to orange granular powder.

Tisumor 25 mg hard capsules

Light brown opaque cap and dark brown opaque body, capsule

shell size No. 3 imprinted in white ink with "LP" on the cap and "651" on the body and containing yellow to orange granular powder.

Tisumor 37,5 mg hard capsules

Yellow opaque cap and yellow opaque body, capsule shell size No.2 imprinted in black ink with "LP" on the cap and "652" on the body and containing yellow to orange granular powder.

Tisumor 50 mg hard capsules

Light brown opaque cap and light brown opaque body, capsule shell size No. 2 imprinted in white ink with "LP" on the cap and "653" on the body and containing yellow to orange granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Tisumor is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
- Tisumor is indicated for the treatment of treatment- naïve advanced and/or metastatic renal cell carcinoma.
- Tisumor is also indicated for the treatment of metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy (interferon α, interleukin-2).
- Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC.
- Efficacy and safety have not been demonstrated for more than 12 months.

4.2 Posology and method of administration

Therapy with Tisumor should be initiated by a medical practitioner experienced in the administration of anticancer medicines.

Posology

The recommended dose of Tisumor is 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period (Schedule 4/2) to comprise a complete cycle of 6 weeks.

Dose adjustments

Safety and tolerability

Dose modifications in 12,5 mg steps may be applied based on individual safety and tolerability. Daily dose should not exceed 75 mg nor be decreased below 25 mg.

CYP3A4 inhibitors/inducers

In patients receiving Tisumor with a potent CYP3A4 inducer such as rifampin, the dosage of Tisumor may need to be increased in 12.5 mg increments (up to 75 mg per day). Clinical response and tolerability should be carefully monitored.

In patients receiving Tisumor with a CYP3A4 inhibitor such as ketoconazole, the doses of Tisumor may need to be reduced, based on tolerability and/or clinical response. Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP34 should be considered.

Dose modifications in 12.5 mg increments may be applied based on individual safety and tolerability. Daily doses should not exceed 75 mg nor be decreased below 25 mg.

Special populations

Elderly

No significant differences in safety or efficacy were observed between younger and older patients.

Hepatic impairment

No dose adjustment is recommended when administering Tisumor to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment. Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment.

Renal impairment

No clinical studies have been performed in patients with impaired renal function. Studies excluded patients with serum creatinine > 2.0 x ULN. Population pharmacokinetic analyses have shown that Tisumor pharmacokinetics were unaltered in the range of renal function evaluated, as measured by creatinine clearance (42-347 mL/min).

Paediatric population

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

Method of administration

Tisumor is for oral administration. It may be taken with or without food.

If a dose is missed, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

4.3 Contraindications

Tisumor is contraindicated in patients with a hypersensitivity to sunitinib malate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in Tisumor

Cases of cerebrovascular accident, transient ischaemic attack, and ischaemic stroke including fatalities have been reported with the use of Imbruvica, with or without concomitant atrial fibrillation and/or hypertension, although causality with ibrutinib has not been established (see section 4.8, Post marketing Adverse Reactions). Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events, are recommended (see Section 4.4, Cardiac dysrhythmia and hypertension)

Sunitinib neither induces nor inhibits major CYP enzymes, including CYP3A4.The dose of Tisumor may need to be reduced based on tolerability when co-administered with CYP3A4 inhibitors. Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of sunitinib (see sections 4.2 and 4.5). The dose of Tisumor may need to be increased when it is co- administered with potent CYP3A4 inducers. Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration (see sections 4.2 and 4.5).

Skin and tissues disorders

Skin discolouration due to medicine colour(yellow) is a common treatment-related adverse event occurring in approximately 30 % of patients. Patients should be advised that depigmentation of the hair or skin may occur during treatment with Tisumor. Other possible dermatological effects may include dryness, thickness or cracking of the skin, blisters, or rash on the palms of the hands and soles of the feet. Mouth pain/irritation and Dysgeusia (taste disturbance) may also occur. The above reactions were not cumulative, were typically

reversible, and generally, did not result in treatment discontinuation. Pyoderma gangrenosum are generally reversible after discontinuation of Tisumor.

Severe cutaneous reactions

Cases of erythema multiforme (EM), cases suggestive of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of SJS, TEN, or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, Tisumor treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be restarted. In some cases of suspected EM, patients tolerated the reintroduction of sunitinib therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines (see section 4.8).

Haemorrhage and tumour bleeding

Haemorrhagic events, that may be fatal, may occur with sunitinib and may include gastrointestinal, respiratory, urinary tract and brain haemorrhages (see section 4.8). Treatment-related tumour haemorrhage occurred in approximately 2 % of patients with GIST. Tumour haemorrhage has not been observed in patients with MRCC or other solid tumours. Routine assessment of bleeding events should include complete blood counts and physical examination. Epistaxis was the most common haemorrhagic adverse reaction. Some of the epistaxis events were severe, but very rarely fatal. Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal. Tumour haemorrhage may occur suddenly, and in the case of pulmonary tumours, may present as severe and life-threatening haemoptysis or pulmonary haemorrhage. Cases of pulmonary haemorrhage, some with a fatal outcome, may occur in patients treated with Tisumor for MRCC, GIST, and lung cancer. Tisumor is not approved for use in patients with lung cancer. Patients receiving concomitant treatment with

anticoagulants (e.g. warfarin, acenocoumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR), and physical examination. In patients receiving Tisumor for treatment-naïve MRCC, patients had bleeding events. Of patients receiving Tisumor for cytokine-refractory.

Gastrointestinal disorders

Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia, and stomatitis/oral pain are common gastrointestinal adverse reactions; oesophagitis events are not common (see section 4.8). Supportive care for gastrointestinal adverse reactions requiring treatment may include medicines with antiemetic, anti-diarrhoeal, or antacid properties. Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation, is known to be in patients with intra-abdominal malignancies treated with sunitinib.

Hypertension

Treatment-related hypertension may be common in 16 % of patients with solid tumours. Hypertension in association with sunitinib, includes severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic). Patients should be screened for hypertension and controlled as appropriate. Treatment-related hypertension may occur in patients receiving Tisumor for treatment-naïve MRCC. Temporary suspension is recommended in patients with severe hypertension that is not controlled with medical management. Treatment may be resumed once hypertension is appropriately controlled (see section 4.8).

Haematological disorders

Decreased absolute neutrophil counts and decreased platelet counts may occur in association with the use of sunitinib (see section 4.8).

Tisumor has the potential to inhibit the cardiac action potential repolarization process (e.g. prolongation of QT interval). Increases in the QTc interval to over 500 msec may occur and changes from baseline in excess of 60 msec. May occur in solid tumour patients; both these parameters are recognised as potentially significant changes.

Cardiovascular events, including heart failure, cardiomyopathy, left ventricular ejection fraction decline to below the lower limit of normal, myocarditis, myocardial ischaemia and myocardial infarction, some of which may be fatal, may occur in patients treated with sunitinib. Sunitinib increases the risk of cardiomyopathy. Use sunitinib with caution in patients who are at risk for, or who have a history of, these events (see section 4.8). Patients who presented with cardiac events within 12 months prior to sunitinib administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischaemic attack, or pulmonary embolism were excluded from sunitinib. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing sunitinib- related left ventricular dysfunction. Medical practitioners are advised to weigh this risk against the potential benefits of sunitinib. Patients should be carefully monitored for signs and symptoms of CHF while receiving sunitinib especially patients with cardiac risk factors and/or history of coronary artery disease. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving sunitinib. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered. In the presence of clinical manifestations of CHF, discontinuation of sunitinib is recommended. The administration of sunitinib should be interrupted and/or the dose reduced in patients without clinical evidence of CHF but with an ejection fraction < 50 % and > 20 % below baseline.

Pulmonary Embolism

Treatment-related pulmonary embolism may occur in patients with solid tumours who have received Tisumor. There were no further occurrences of pulmonary embolism in patients after treatment was resumed.

QT interval prolongation

Approximately twice, the therapeutic concentrations, Tisumor is known to show prolongation to QTcF (Fredericia's correction) interval. Prolongation of QT interval and Torsade de pointes may be observed in <0,1 % of sunitinib-exposed patients. QT interval prolongation may lead to an increased risk of ventricular dysrhythmias including Torsade de pointes. Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking antidysrhythmics or medicines that can prolong QT interval, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant administration of sunitinib with potent CYP3A4 inhibitors should be limited because of the possible increase in sunitinib plasma concentrations (see sections 4.2, 4.5 and 4.8).

Venous thromboembolic events

Treatment-related venous thromboembolic events may occur in patients who received sunitinib including deep venous thrombosis and pulmonary embolism (see section 4.8). Cases of pulmonary embolism with fatal outcome may occur.

Arterial thromboembolic events

Arterial thromboembolic events (ATE), sometimes fatal, may occur in patients treated with sunitinib. The most frequent events include cerebrovascular accident, transient ischaemic attack, and cerebral infarction. Risk factors associated with ATE, in addition to the underlying malignant disease and age ≥ 65 years, include hypertension, diabetes mellitus, and prior thromboembolic disease.

Aneurysms and artery dissections

The use of vascular endothelial growth factor (VEGF) pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating sunitinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Thrombotic microangiopathy (TMA)

The diagnosis of TMA, including thrombotic thrombocytopaenic purpura (TTP) and haemolytic uraemic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, should be considered in the occurrence of haemolytic anaemia, thrombocytopenia, fatigue, fluctuating neurological manifestation, renal impairment, and fever. Sunitinib therapy should be discontinued in patients who develop TMA and prompt treatment is required. Reversal of the effects of TMA has been observed after treatment discontinuation (see section 4.8).

Thyroid dysfunction

Treatment-emergent acquired hypothyroidism may occur in patients with GIST. Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. In addition, patients should be observed closely for signs and symptoms of thyroid dysfunction during treatment, and patients who develop any signs and/or symptoms suggestive of thyroid dysfunction should have laboratory testing of thyroid function performed as clinically indicated. Patients who develop thyroid dysfunction should be treated as per the standard medical practice. Hypothyroidism may occur early as well as late during treatment with sunitinib (see section 4.8).

Pancreatitis

Increases in serum lipase and amylase activities may occur in patients with various solid tumours who received sunitinib. Increases in lipase activities were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours (see section 4.8). Pancreatitis may occur in patients with solid tumours. Hepatic failure may occur in solid tumour patients treated with Tisumor. Cases of serious pancreatic events, some with fatal outcome, may occur. If symptoms of pancreatitis are present, patients should discontinue sunitinib and be provided with appropriate supportive care.

Hepatotoxicity

Hepatotoxicity may occur in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, may occur in solid tumour patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. If signs or symptoms of hepatic failure are present, sunitinib should be discontinued and appropriate supportive care should be provided (see section 4.8).

Renal function

Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, may occur (see section 4.8). Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying RCC, older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolaemia, and rhabdomyolysis. Cases of proteinuria and rare cases of nephrotic syndrome may occur. Baseline urinalysis is recommended, and patients should be

monitored for the development or worsening of proteinuria. Discontinue sunitinib in patients with nephrotic syndrome.

Fistula

If fistula formation occurs, sunitinib treatment should be interrupted.

Impaired wound healing

Cases of impaired wound healing have been reported during sunitinib therapy. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ may occur in patients treated with Tisumor. Caution should therefore be exercised when Tisumor and intravenous bisphosphonates are used either simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. Prior to treatment with Tisumor, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving intravenous bisphosphonates, invasive dental procedures should be avoided if possible (see section 4.8).

Hypersensitivity/angioedema

If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided (see section 4.8).

Seizures

Seizures may occur with Sunitinib. Patients with seizures and signs/symptoms consistent with posterior reversible leukoencephalopathy syndrome (RPLS), such as hypertension,

headache, decreased alertness, altered mental functioning and visual loss, including cortical blindness, should be controlled with medical management including control of hypertension. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating medical practitioner (see section 4.8).

Tumour lysis syndrome (TLS)

Cases of TLS, some fatal, may occur in patients treated with sunitinib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated as indicated, and prophylactic hydration should be considered.

Infections

Serious infections, with or without neutropenia, including some with a fatal outcome, may occur. Uncommon cases of necrotising fasciitis, including of the perineum, sometimes fatal, may occur (see section 4.8). Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypoglycaemia

Decreases in blood glucose, which may be symptomatic and requiring hospitalisation due to loss of consciousness, may occur during sunitinib treatment. In case of symptomatic hypoglycaemia, sunitinib should be temporarily interrupted. Blood glucose levels in diabetic patients should be checked regularly in order to assess if antidiabetic medicinal product's dosage needs to be adjusted to minimise the risk of hypoglycaemia (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

When Tisumor is co-administered with other medications, there is a potential for medicine interaction.

Medicine that may increase sunitinib plasma concentrations

Effect of CYP3A4 inhibitors

Concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole results in an increase of the combined [sunitinib + primary metabolite] maximum concentration (Cmax)and area under the curve (AUC0-∞) values of 49 % and 51 %, respectively. Administration of sunitinib with potent CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations. Combination with CYP3A4 inhibitors should therefore be avoided, or the selection of an alternate concomitant medicinal product with no or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dose of Tisumor may need to be reduced to a minimum of 37,5 mg daily for GIST and MRCC based on careful monitoring of tolerability (see section 4.2).

Effect of Breast Cancer Resistance Protein (BCRP) inhibitors

An interaction between sunitinib and other BCRP inhibitors cannot be excluded (see section 5.2).

Medicine that may decrease sunitinib plasma concentrations

Effect of CYP3A4 inducers

Concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin results in a reduction of the combined [sunitinib + primary metabolite] Cmax and AUC0-∞ values of 23 % and 46 %, respectively. Administration of sunitinib with potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbitone or herbal preparations containing St. John's Wort (Hypericum perforatum) may decrease sunitinib concentrations. Combination with CYP3A4 inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dose of Tisumor may need to be increased in 12,5 mg increments (up to 75 mg per day for GIST and per MRCC),

based on careful monitoring of tolerability (see section 4.2). The calculated in vitro Ki values for all CYP isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 AND CYP4A9/11) indicated that Tisumor and its primary active metabolite are unlikely to have any relevant interactions with medicine that may be metabolised by these enzymes.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with Tisumor.

Pregnancy

There are no studies in pregnant women using Tisumor. Studies in animals have shown reproductive toxicity including foetal malformations. Tisumor should not be used during pregnancy. If the patient becomes pregnant while on treatment with Tisumor, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite is excreted in human milk. Active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in breastfeeding infants, women should not breastfeed while taking Tisumor.

Fertility

Based on nonclinical findings, male and female fertility may be compromised by treatment with Tisumor.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or operate machinery have been performed. Patients should be advised that they may experience dizziness during treatment with sunitinib (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, thrombocytopenia, gastrointestinal perforation, and haemorrhages (e.g., respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages), febrile neutropenia, and hypertension. The most common adverse reactions of any grade (experienced by patients in MRCC and GIST) include a decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia, and vomiting), skin discolouration, dysgeusia, anorexia and palmar-plantar erythrodysaesthesia syndrome. These symptoms may diminish as treatment continues. Fatigue, hypertension and neutropenia are the most common treatment-related adverse events.

Increased lipase was the most frequently occurring treatment-related adverse event with maximum severity in patients with solid tumours.
Hypothyroidism may develop during treatment. Haematological disorders (e.g., neutropenia, thrombocytopenia, and anaemia) are amongst the most common adverse drug reactions.

Fatal events other than those listed in section 4.4 above or in section 4.8 below that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, adrenal insufficiency, pneumothorax, shock, and sudden death.

Tabulated list of adverse reactions

Frequencies are defined as: Frequent, less Frequent, frequency not known

Table 1. Adverse reactions reported

System organ class	Frequent	Less Frequent	Frequency not known
Infections and infestations	Viral infections[a] Respiratory infections[b.*] Abscess[c.*] Fungal infections[d] Urinary tract infections Skin infections[e] Sepsis[f.*]	Necrotising fasciitis* Bacterial infections[g.*]	
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Anaemia Leukopenia Lymphopenia	Pancytopenia Thrombotic microangiopathyh.*	
Immune system disorders		Hypersensitivity Angioedema	
Endocrine disorders	Hypothyroidism	Hyperthyroidism Thyroiditis	
Metabolism and nutrition disorders	Decreased appetite[i] Dehydration Hypoglycaemia	Tumour lysis syndrome*	

Psychiatric disorders	Insomnia Depression		
Nervous system disorders	Dizziness Headache Taste disturbance[j] Neuropathy peripheral Paraesthesia Hypoaesthesia Hyperaesthesia	Cerebral haemorrhage* Cerebrovascular accident* Transient ischaemic attack Posterior reversible encephalopathy syndrome *	Ischaemic stroke
Eye disorders	Periorbital oedema Eyelid oedema Lacrimation increased		
Cardiac disorders	Myocardial ischemia[k.*] Ejection fraction decreased	Cardiac failure congestive Myocardial infarction[m.*] Cardiac failure* Cardiomyopathy* Pericardial effusion Electrocardiogram QT prolonged Left ventricular failure* Torsade de pointes	

Vascular disorders	Hypertension Deep vein thrombosis Hot flush Flushing	Tumour haemorrhage*	Aneurysms and artery dissections*
Respiratory, thoracic and mediastinal disorders	Dyspnoea Epistaxis Cough Pulmonary embolism* Pleural effusion* Haemoptysis Dyspnoea exertional Oropharyngeal pain[n] Nasal congestion Nasal dryness	Pulmonary haemorrhage* Respiratory failure*	
Gastrointestinal disorders	Stomatitis[o] Abdominal pain[p] Vomiting Diarrhoea Dyspepsia Nausea Constipation Gastro-oesophageal reflux disease Dysphagia Gastrointestinal haemorrhage* Oesophagitis*	Gastrointestinal perforation[q,*] Pancreatitis Anal fistula Colitis[r]	

	Abdominal distension Abdominal discomfort Rectal haemorrhage Gingival bleeding Mouth ulceration Proctalgia Cheilitis Haemorrhoids Glossodynia Oral pain Dry mouth Flatulence Oral discomfort Eructation		
Hepatobiliary disorders		Hepatic failure* Cholecystitis[s,*] Hepatic function abnormal Hepatitis	
Skin and subcutaneous tissue disorders	Skin discolouration[t] Palmar-plantar erythrodysaesthesia syndrome Rash[u] Hair colour changes Dry skin Skin exfoliation	Erythema multiforme* Stevens-Johnson syndrome* Pyoderma gangrenosum Toxic epidermal necrolysis*	

	Skin reaction[v] Eczema Blister Erythema Alopecia Acne Pruritus Skin hyperpigmentation Skin lesion Hyperkeratosis Dermatitis Nail disorder[w]		
Musculoskeletal and connective tissue disorders	Pain in extremity Arthralgia Back pain Musculoskeletal pain Muscle spasms Myalgia Muscle weakness	Osteonecrosis of the jaw Fistula* Rhabdomyolysis* Myopathy	
Renal and urinary disorders	Renal failure* Renal failure acute* Chromaturia Proteinuria	Haemorrhage urinary tract Nephrotic syndrome	
General disorders	Mucosal inflammation Fatigue[x] Oedema[y]	Impaired healing	

	Pyrexia Chest pain Pain Influenza like illness Chills		
Investigations	Weight decreased White blood cell count decreased Lipase increased Platelet count decreased Haemoglobin decreased Amylase increased[z] Aspartate aminotransferase increased Alanine aminotransferase increased Blood creatinine increased Blood pressure increased Blood uric acid increased	Blood creatinine phosphokinase increased Blood thyroid stimulating hormone increased	

* Including fatal events.

The following terms have been combined:

a Nasopharyngitis and oral herpes.

b Bronchitis, lower respiratory tract infection, pneumonia, and respiratory tract infection.

c Abscess, abscess limb, anal abscess, gingival abscess, liver abscess, pancreatic abscess, perineal abscess, perirectal abscess, rectal abscess, subcutaneous abscess, and tooth abscess.

d Oesophageal candidiasis and oral candidiasis.

e Cellulitis and skin infection.

f Sepsis and sepsis shock.

g Abdominal abscess, abdominal sepsis, diverticulitis, and osteomyelitis.

h Thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome.

i Decreased appetite and anorexia

j Dysgeusia, ageusia, and taste disturbance.

k Acute coronary syndrome, angina pectoris, angina unstable, coronary artery occlusion, and myocardial ischaemia.

l Ejection fraction decreased/abnormal.

m Acute myocardial infarction, myocardial infarction, and silent myocardial infarction.

n Oropharyngeal and pharyngolaryngeal pain.

o Stomatitis and aphtous stomatitis.

p Abdominal pain, abdominal pain lower, and abdominal pain upper.

q Gastrointestinal perforation and intestinal perforation.

r Colitis and colitis ischaemic.

s Cholecystitis and acalculous cholecystitis.

t Yellow skin, skin discolouration, and pigmentation disorder.

u Dermatitis psoriasiform, exfoliative rash, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, and rash pruritic.

v Skin reaction and skin disorder.

w Nail disorder and discolouration.

x Fatigue and asthenia.

y Face oedema, oedema, and oedema peripheral.

z Amylase and amylase increased.

Description of selected adverse reactions

Infections and infestations

Cases of serious infection (with or without neutropenia), including cases with fatal outcome, may occur. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, may occur (see also section 4.4).

Blood and lymphatic system disorders

Cases of thrombotic microangiopathy and haemolytic uraemic syndrome may occur. Temporary suspension of Tisumor is recommended; following resolution, treatment may be resumed at the discretion of the treating medical practitioner.

The following are known to occur:

- Decreased absolute neutrophil counts of Grade 3 and 4 severities,
- Decreased platelet counts of Grade 3 and 4 severities
- Bleeding events
- Tumour haemorrhage

Renal and urinary disorders

Cases of proteinuria and cases of nephrotic syndrome may occur. Baseline urinalysis may occur and patients should be monitored for the development or worsening of proteinuria. The

safety of continued Tisumor treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue patients with nephrotic syndrome.

Immune system disorders

Hypersensitivity reactions, including angioedema, have been reported (see section 4.4).

Endocrine disorders

Hypothyroidism may occur as an adverse reaction in patients receiving sunitinib across the 2 cytokine-refractory MRCC's. Additionally, thyroid-stimulating hormone (TSH) elevations were reported in 4 cytokine-refractory MRCC patients.

Metabolism and nutrition disorders

Hypoglycaemia events may occur in patients with MRCC and GIST.

Nervous system disorders

Seizures may occur in patients with or without radiological evidence of brain metastases (see section 4.4).

Cardiac disorders

A decrease in left ventricular ejection fraction (LVEF) may occur in sunitinib-treated GIST patients and cytokine-refractory MRCC patients. These LVEF declines do not appear to have been progressive and often improved as treatment continued.

Vascular disorders

Hypertension

Hypertension is a very common adverse reaction which may reported.

Venous thromboembolic events

Treatment-related venous thromboembolic events may occur in patients with solid tumours who received sunitinib, including GIST and RCC.

Gastrointestinal disorders

Pancreatitis may uncommonly occur in patients receiving sunitinib for GIST or MRCC.

Hepatobiliary disorders

Hepatic dysfunction may occur and may include Liver Function Test abnormalities, hepatitis, or liver failure (see section 4.4).

Skin and subcutaneous tissue disorders

Cases of pyoderma gangrenosum, generally reversible after discontinuation of sunitinib, may occur (see also section 4.4).

Musculoskeletal and connective tissue disorders

Cases of myopathy and/or rhabdomyolysis, some with acute renal failure, may occur. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice (see section 4.4). Cases of fistula formation, sometimes associated with tumour necrosis and regression, in some cases with fatal outcomes, may occur (see section 4.4). Cases of ONJ may occur in patients treated with Tisumor, most of which may occur in patients who have an identified risk factor for ONJ, in particular, exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4).

Long-term safety in MRCC

Most treatment related adverse events (TRAEs) are expected to occur initially in the first 6 months–1 year of treatment and then should stabilise or decrease in frequency over time, with the exception of hypothyroidism, which may gradually increase over time. Prolonged treatment with sunitinib may not be associated with new types of TRAEs.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no experience of acute overdosage with Tisumor. There is no specific antidote for overdose with Tisumor and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis. Cases of overdose may occur, some cases which were associated with adverse reactions consistent with the known safety profile of sunitinib. (See section 4.8)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic Agents

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01XE04 Sunitinib malate is a small molecule that simultaneously inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as a potent inhibitor of platelet-derived

growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Inhibition of the tyrosine kinase activity of these RTKs by sunitinib has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays. Sunitinib malate demonstrated inhibition of activity of target RTKs (PDGFRβ, VEGFR2, KIT) in tumours in vivo and demonstrated the ability to inhibit tumour growth, cause tumour regression, and/or inhibit metastatic progression in a variety of rodent cancer models. Consistent with its multi-targeted profile, sunitinib malate demonstrated the ability to directly inhibit growth of tumour cells expressing dysregulated RTK targets (PDGFR, RET, or KIT) and to inhibit PDGFRβ- and VEGFR2-dependent tumour angiogenesis.

5.2 Pharmacokinetic properties

Absorption

Sunitinib is absorbed after oral administration with maximum concentrations (Cmax) generally observed from 6 – 12 hours (Tmax) post-dose. Food has no effect on the bioavailability of sunitinib.

Distribution

Binding of sunitinib and its primary active metabolite to human plasma protein in in vitro assays was 95 % and 90 %, respectively, with no apparent concentration dependence.

Biotransformation

Sunitinib is metabolised primarily by CYP3A4, the cytochrome P450 enzyme, which produces its primary active metabolite, which is then further metabolised by CYP3A4.

Elimination

Excretion is primarily via faeces (61 %) with renal elimination of drug and metabolites accounting for 16 % of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine and faeces, representing 91.5 %, 86.4 % and 73.8 % of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (CL/F) was 34-62 l/hr.

Plasma Pharmacokinetics

Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and Cmax increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and its active metabolite are 62.9 – 101 ng/ml which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation in vitro and result in tumour stasis/growth reduction in vivo. The primary active metabolite comprises 23 to 37 % of the total exposure. No significant changes in the pharmacokinetics of sunitinib or the primary, active metabolite is observed with repeated daily administration or with repeated cycles in the dosing regimens tested. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers. Population pharmacokinetic analyses indicated that no dose adjustments are necessary for weight, creatinine clearance, gender, race or ECOG score.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium, magnesium stearate, mannitol, povidone (K-25)

12,5 mg hard capsules

Capsule shell: Gelatin, Red iron oxide (E172), Titanium dioxide (E171), Black iron oxide (E172)

Printing ink: Shellac, Propylene glycol, Sodium hydroxide, Povidone and Titanium dioxide

25 mg hard capsules

Capsule shell: Gelatin, Red iron oxide (E172), Titanium dioxide (E171) Yellow iron oxide (E172), Black iron oxide (E172)

Printing ink: Shellac, Propylene glycol, Sodium hydroxide, Povidone and Titanium dioxide

37,5 mg hard capsules

Capsule shell: Gelatin, Titanium dioxide (E171), FD&C Yellow #6 (E110) FD&C Yellow #5 (E102)

Printing ink: Shellac, Propylene glycol, Strong Ammonia Solution, Potassium hydroxide, Black iron oxide (E172)

50 mg hard capsules

Capsule shell: Gelatin, Titanium dioxide (E171), Yellow iron oxide (E172) Red iron oxide (E172), Black iron oxide (E172)

Printing ink: Shellac, Propylene glycol, Sodium hydroxide, Povidone and Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC. Keep in the original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

The capsules are packed in:

- White PVC/ACLAR-Aluminum blisters. The blisters are packed in carton boxes.
- HDPE bottles with PP caps

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park, 3 Stirrup Lane

Van Reenens Avenue

Woodmead

8 REGISTRATION NUMBER(S)

Tisumor 12,5: To be allocated

Tisumor 25: To be allocated

Tisumor 37,5: To be allocated

Tisumor 50: To be allocated

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Tisumor: To be allocated

10 DATE OF REVISION OF THE TEXT

Tisumor: To be allocated