PRESCRIBING INFORMATION : For the use of Oncologists only.

℞ Sunitinib Malate Capsules 12.5mg/25mg/50mg

SUNITIGEN

1. **Generic Name**

Sunitinib Malate Capsules 12.5mg/25mg/50mg

2. **Qualitative and Quantitative Composition**

Sunitinib Malate Capsules 12.5mg

Each hard gelatin capsule contains:

Sunitinib Malate	
Equivalent to Sunitinib	12.5 mg
Excipients	q.s.

Approved colours used in capsule shell.

Sunitinib Malate Capsules 25mg

Each hard gelatin capsule contains:

Sunitinib Malate	
Equivalent to Sunitinib	25 mg
Excipients	q.s.

Approved colours used in capsule shell.

Sunitinib Malate Capsules 50mg

Each hard gelatin capsule contains:

Sunitinib Malate	
Equivalent to Sunitinib	50 mg
Excipients	q.s.

Approved colours used in capsule shell.

3. **Dosage Form & Strength**

Hard gelatin capsules for oral use & 12.5, 25 and 50 mg

4. **Clinical Particulars**

4.1 Therapeutic Indications

Sunitinib capsules for the:

- treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma (RCC).
- treatment of unresectable or metastatic well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

4.2 Posology and Method of administration

Posology

For GIST and MRCC, the recommended dose of sunitinib 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.

For pNET, the recommended dose of sunitinib is 37.5 mg taken orally once daily without a scheduled rest period.

Dose adjustments

Safety and tolerability

For GIST and MRCC, 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.

For pNET, dose modification in 12.5 mg steps may be applied based on individual safety and tolerability. The maximum dose administered in the Phase 3 pNET study was 50 mg daily.

Dose interruptions may be required based on individual safety and tolerability.

CYP3A4 inhibitors/inducers

Co-administration of sunitinib with potent CYP3A4 inducers, such as rifampicin, should be avoided. If this is not possible, the dose of sunitinib may need to be increased in 12,5 mg steps (up to 87,5 mg per day for GIST and MRCC or 62,5 mg per day for pNET) based on careful monitoring of tolerability.

Co-administration of sunitinib with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided. If this is not possible, the dose of sunitinib may need to be reduced to a minimum of 37,5 mg daily for GIST and MRCC or 25 mg daily for pNET, based on careful monitoring of tolerability.

Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations

Paediatric population

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

Elderly

Approximately one-third of the patients in clinical studies who received sunitinib were 65 years of age or over. No significant differences in safety or efficacy were observed between younger and older patients.

Hepatic impairment

No starting dose adjustment is recommended when administering sunitinib 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 and therefore its use in patients with severe hepatic impairment cannot be recommended.

Renal impairment

No starting dose adjustment is required when administering sunitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability.

Method of administration

Sunitinib 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

• Hypersensitivity to the active substance or to any of the excipients in this formulation

4.4 Special warnings and precautions for use

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration.

Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of sunitinib.

Skin and tissue disorders

Patients should be advised that depigmentation of the hair or skin may occur during treatment with sunitinib. 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.

The above reactions were not cumulative, were typically reversible, and generally did not result in treatment discontinuation. Cases of pyoderma gangrenosum, generally reversible after discontinuation of sunitinib, have been reported. Severe cutaneous reactions have been reported, including 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, sunitinib 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.

Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported in clinical studies with sunitinib and during post-marketing surveillance have included gastrointestinal, respiratory, urinary tract, and brain haemorrhages.

Routine assessment of bleeding events should include complete blood counts and physical examination.

Epistaxis was the most common haemorrhagic adverse reaction, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. 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, have been observed in clinical trials and have been reported in postmarketing experience in patients treated with sunitinib for MRCC, GIST, and lung cancer. Sunitinib 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.

Gastrointestinal disorders

Diarrhoea, nausea/vomiting, abdominal pain, dyspepsia, and stomatitis/oral pain were the most commonly reported gastrointestinal adverse reactions; oesophagitis events have been also reported.

Supportive care for gastrointestinal adverse reactions requiring treatment may include medicinal products with antiemetic, antidiarrhoeal, or antacid properties.

Serious, sometimes fatal gastrointestinal complications including gastrointestinal perforation were reported in patients with intra-abdominal malignancies treated with sunitinib.

Hypertension

Hypertension has been reported in association with sunitinib, including severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic). Patients should be screened for hypertension and controlled as appropriate.

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.

Haematological disorders

Decreased absolute neutrophil counts and decreased platelet counts were reported in association with sunitinib. The above events were not cumulative, were typically reversible, and generally did not result in treatment discontinuation. None of these events in the Phase 3 studies were fatal, but rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported during post-marketing surveillance.

Anaemia has been observed to occur early as well as late during treatment with sunitinib.

Complete blood counts should be performed at the beginning of each treatment cycle for patients receiving treatment with sunitinib.

Cardiac disorders

Cardiovascular events, including heart failure, cardiomyopathy, left ventricular ejection fraction decline to below the lowe rlimit of normal, myocarditis, myocardial ischaemia and myocardial infarction, some of which were fatal, have been reported in patients treated with sunitinib. These data suggest that sunitinib increases the risk of cardiomyopathy. No specific additional risk factors for sunitinib-induced cardiomyopathy apart from the drug-specific effect have been identified in the treated patients. Use sunitinib with caution in patients who are at risk for, or who have a history of, these events.

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 all sunitinib clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing sunitinib-related left ventricular dysfunction.

Physicians are advised to weigh this risk against the potential benefits of sunitinib. Patients should be carefully monitored for clinical 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.

QT interval prolongation

Prolongation of QT interval and Torsade de pointes have been observed in sunitinib-exposed patients. QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes.

Sunitinib should be used with caution in patients with a known history of QT interval prolongation, patients who are taking anti-arrhythmics or medicinal products 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.

Venous thromboembolic events

Treatment-related venous thromboembolic events were reported in patients who received sunitinib including deep venous thrombosis and pulmonary embolism. Cases of pulmonary embolism with fatal outcome have been observed in postmarketing surveillance.

Arterial thromboembolic events

Cases of arterial thromboembolic events (ATE), sometimes fatal, have been reported in patients treated with sunitinib. The most frequent events included cerebrovascular accident, transient ischaemic attack, and cerebral infarction. Risk factors associated with ATE, in addition to the underlying malignant disease and age ≥ 65 years, included 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.

Thyroid dysfunction

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 standard medical practice.

Hypothyroidism has been observed to occur early as well as late during treatment with sunitinib.

Pancreatitis

Increases in serum lipase and amylase activities were observed 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.

Cases of serious pancreatic events, some with fatal outcome, have been reported. If symptoms of pancreatitis are present, patients should have sunitinib discontinued and be provided with appropriate supportive care.

Hepatotoxicity

Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in < 1% of 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.

Renal function

Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported.

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.

The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Cases of proteinuria and rare cases of nephrotic syndrome have been reported. 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. Limited information is available on the continued use of sunitinib in patients with fistulae.

Impaired wound healing

Cases of impaired wound healing have been reported during sunitinib therapy.

No formal clinical studies of the effect of sunitinib on wound healing have been conducted. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in patients treated with Sunitinib. The majority of cases were reported in patients who had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when Sunitinib and intravenous bisphosphonates are used either simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor. Prior to treatment with Sunitinib, 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.

Hypersensitivity/angioedema

If angioedema due to hypersensitivity occurs, sunitinib treatment should be interrupted and standard medical care provided.

Seizures

In clinical studies of sunitinib and from postmarketing surveillance, seizures have been reported. 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 physician.

Tumour lysis syndrome (TLS)

Cases of TLS, some fatal, have been rarely observed in clinical trials and have been reported in postmarketing surveillance 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 clinically indicated, and prophylactic hydration should be considered.

Infections

Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported. Uncommon cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported.

Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypoglycaemia

Decreases in blood glucose, in some cases clinically symptomatic and requiring hospitalisation due to loss of consciousness, have been reported 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.

4.5 Drug Interactions

Interaction studies have only been performed in adults.

Medicinal products that may increase sunitinib plasma concentrations

Effect of CYP3A4 inhibitors

In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite] maximum concentration (C_{max}) and area under the curve (AUC_{∞}) 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 sunitinib may need to be reduced to a minimum of 37.5 mg daily for GIST and MRCC or25 mg daily for pNET, based on careful monitoring of tolerability.

Effect of Breast Cancer Resistance Protein (BCRP) inhibitors

Limited clinical data are available on the interaction between sunitinib and BCRP inhibitors and the possibility of an interaction between sunitinib and other BCRP inhibitors cannot be excluded.

Medicinal products that may decrease sunitinib plasma concentrations

Effect of CYP3A4 inducers

In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite] C_{max} and AUC_{∞} values of 23% and 46%, respectively.

Administration of sunitinib with potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital 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 sunitinib may need to be increased in 12,5 mg increments (up to 87,5 mg per day for GIST and MRCC or 62,5 mg per day for pNET), based on careful monitoring of tolerability.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Contraception in males and females

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

Pregnant women

There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations. Sunitinib should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus. If sunitinib is used during pregnancy or if the patient becomes pregnant while on treatment with sunitinib, the patient should be apprised of the potential hazard to the foetus.

Lactating women

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. Because active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in breast-feeding infants, women should not breast-feed while taking Sunitinib.

Fertility

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

4.7 Effects on ability to drive and use machines

Sunitinib has minor influence on the ability to drive and use machines. Patients should be advised that they may experience dizziness during treatment with sunitinib.

4.8 Undesirable Effects

The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and haemorrhages (e.g., respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages). The most common adverse reactions of any grade (experienced by patients in RCC, GIST, and pNET registrational trials) included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia, and vomiting), skin discolouration, and palmar-plantar erythrodysaesthesia syndrome. These symptoms may diminish as treatment continues. 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 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

Adverse reactions that were reported in GIST, MRCC, and pNET patients in a pooled dataset of 7,115 patients are listed below, by system organ class, frequency and grade of severity (NCI-CTCAE). Post- marketing adverse reactions identified in clinical studies are also included. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Common: Viral infections,[a] respiratory infections,[b,*] abscess,[c,*] fungal infections,[d] urinary tract infection, skin infections,[e] sepsis[f,*]

Uncommon: Necrotising fasciitis,* bacterial infections[g]

Blood and lymphatic system disorders

Very Common: Neutropoenia, thrombocytopenia, anaemia, leukopoenia,

Common: Lymphopoenia

Uncommon: Pancytopenia

Rare: Thromboticmicroangiopathy [h,*]

Immune system disorders

Uncommon: Hypersensitivity

Rare: Angioedema

Endocrine disorders

Very common: Hypothyroidism

Uncommon: Hyperthyroidism

Rare: Thyroiditis

Metabolism and nutrition disorders

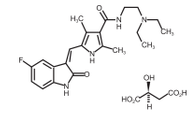
Very Common: Decreased appetite/

Common: Dehydration, hypoglycaemia

Front

Dimension: 200x280 mm,
Colour: Black
Spec: 41 gsm, Bible Paper
Folding size: 50x35 mm
Reason for change: New Brand

Rare: Tumour lysissyndrome*
Psychiatric disorders
Very Common: Insomnia
Common: Depression
Nervous system disorders
Very Common: Dizziness, headache, taste disturbance[i]
Common: Neuropathy peripheral, paraesthesia, hypoaesthesia, hyperaesthesia
Uncommon: Cerebral haemorrhage*, Cerebrovascular accident*, Transient ischaemic attack
Rare: Posterior reversible encephalopathy syndrome*
Eye disorders
Common: Periorbital oedema, eyelid oedema, lacrimation increased
Cardiac disorders
Common: Myocardial ischemia,[k,*] ejection fraction decreased[l],
Uncommon: Cardiac failure congestive, myocardial infarction,[m,*] cardiac failure*, cardiomyopathy*, pericardial effusion, electrocardiogram QT prolonged
Rare: Left ventricular failure*, Torsade de pointes
Vascular disorders
Very Common: Hypertension
Common: Deep vein thrombosis, hot flush, flushing
Uncommon: Tumour haemorrhage*
Not known: Aneurysms and artery dissections*
Respiratory, thoracic and mediastinal disorders
Very Common: Dyspnoea, epistaxis, cough
Common: Pulmonary embolism*, pleural effusion*, haemoptysis, dyspnoea exertional, oropharyngeal pain,[n] nasal congestion, nasal dryness
Uncommon: Pulmonary haemorrhage*, respiratory failure*
Gastrointestinal disorders
Very common: Stomatitis,[o] abdominal pain,[p] vomiting, diarrhoea, dyspepsia, nausea, constipation
Common: Gastro-oesophageal reflux disease, dysphagia, gastrointestinal haemorrhage*, oesophagitis*, abdominal distension, abdominal discomfort, rectal haemorrhage, gingival bleeding, mouth ulceration, proctalgia, cheilitis, haemorrhoids, glossodynia, oral pain, dry mouth, flatulence, oral discomfort, eructation
Uncommon: Gastrointestinal perforation,[q,*] pancreatitis, anal fistula, colitis[r]
Hepatobiliary disorders
Uncommon: Hepatic failure*, Cholecystitis,[s,*] hepatic function abnormal
Rare: Hepatitis
Skin and subcutaneous tissue disorders
Very common: Skin discolouration,[t] palmar-plantar erythrodysaesthesia syndrome, rash,[u] hair colour changes, dry skin
Common: Skin exfoliation, skin reaction,[v] eczema, blister, erythema, alopecia, acne, pruritus, skin hyperpigmentation, skin lesion, hyperkeratosis, dermatitis, nail disorder[w]
Rare: Erythema multiforme*, Stevens-Johnson syndrome*, pyoderma gangrenosum, toxic epidermal necrolysis*
Musculoskeletal and connective tissue disorders
Very common: Pain in extremity, arthralgia, back pain
Common: Musculoskeletal pain, muscle spasms, myalgia, muscular weakness,
Uncommon: Osteonecrosis of the jaw, fistula*
Rare: Rhabdomyolysis*, myopathy
Renal and urinary disorders
Common: Renal failure*, renal failure acute*, chromaturia, proteinuria
Uncommon: Haemorrhage urinary tract
Rare: Nephrotic syndrome
General disorders and administration site conditions
Very common: Mucosal inflammation, fatigue,[x] edema,[y] pyrexia
Common: Chest pain, pain, influenza like illness, chills
Uncommon: Impaired healing
Investigations
Common: 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
Uncommon: Blood creatine 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, rashmaculo-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.
Reporting of suspected adverse reactions
Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form (**form.heteroworld.com**) or by Hetero Helpline No.**1800-120-8689** and for all India safety cases and complaints, please write to **drugsafetyindia@heterodrugs.com.**
4.9 Overdose
There is no specific antidote for overdose with Sunitinib and treatment of overdose should consist of general supportive measures. If indicated, elimination of unabsorbed active substance may be achieved by emesis or gastric lavage. Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known safety profile of sunitinib.
5. Pharmacological Properties
5.1 Mechanism of action
Sunitinib inhibits multiple RTKs that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), VEGF 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). Sunitinib inhibition of the activity of these RTKs 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.
5.2 Pharmacodynamic properties
Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets in vivo and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) in vitro and to inhibit PDGFRβ-and VEGFR2-dependent tumor angiogenesis in vivo.
Cardiac Electrophysiology
Sunitinib can cause QT interval prolongation in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes.
5.3 Pharmacokinetic properties
In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to 4-fold and its primary active 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 PK of sunitinib or the primary active metabolite are observed with repeated daily administration or with repeated cycles in the dosing schedules tested.
Absorption
After oral administration of sunitinib, C_{max} are generally observed from 6 to 12 hours' time to maximum concentration (t_{max}) post administration.
Food has no effect on the bioavailability of sunitinib.
Distribution
In vitro, binding of sunitinib and its primary active metabolite to human plasma protein was 95% and 90%, respectively, with no apparent concentration dependence. The apparent volume of distribution (Vd) for sunitinib was large, 2230 L, indicating distribution into the tissues.
Metabolism
Sunitinib is metabolised primarily by CYP3A4, the CYP isoform which produces its primary active metabolite, desethyl sunitinib, which is then further metabolised by the same isoenzyme. Co-administration of sunitinib with potent CYP3A4 inducers or inhibitors should be avoided because the plasma levels of sunitinib may be altered
Excretion
Excretion is primarily via faeces (61%), with renal elimination of unchanged active substance and metabolites accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major 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/h. 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.
Pharmacokinetics in special population
Renal impairment
Population PK analyses indicated that sunitinib apparent clearance (CL/F) was not affected by creatinine clearance(CLcr) within the range evaluated (42-347 ml/min).
Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr < 30 ml/min) compared to subjects with normal renal function (CLcr > 80 ml/min). Although sunitinib and its primary metabolite were not eliminated through haemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.
Hepatic impairment
Sunitinib and its primary metabolite are mainly metabolised by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment.
Studies in cancer patients have excluded patients with ALT or AST > 2.5 x ULN (upper limit of normal) or > 5.0 x ULN if due to liver metastasis.
Weight, performance status
Population PK analyses of demographic data indicate that no starting dose adjustments are necessary for weight or Eastern Cooperative Oncology Group (ECOG) performance status.
Gender
Available data indicate that females could have about 30% lower apparent clearance (CL/F) of sunitinib than males: this difference, however, does not necessitate starting dose adjustments.
6. Nonclinical Properties
6.1 Animal Toxicology or Pharmacology
In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and diarrhoea in monkeys); adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats); haemo-lymphopoietic system (bone morrow hypocellularity and lymphoid depletion of thymus, spleen, and lymph node); exocrine pancreas (acinar cell degranulation with single cell necrosis); salivary gland (acinar hypertrophy); bone joint (growth plate thickening); uterus (atrophy); and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects observed in other studies included: QTc interval prolongation, LVEF reduction and testicular tubularatrophy, increased mesangial cells in kidney, haemorrhage in gastrointestinal tract and oral mucosa, and hypertrophy of anterior pituitary cells. Changes in the uterus (endometrial atrophy) and bone growth plate (physeal thickening or dysplasia of cartilage) are thought to be related to the pharmacological action of sunitinib. Most of these findings were reversible after 2 to 6 weeks without treatment.
Genotoxicity
The genotoxic potential of sunitinib was assessed in vitro and in vivo. Sunitinib was not mutagenic in bacteria using metabolic activation provided by rat liver. Sunitinib did not induce structural chromosome aberrations in human peripheral blood lymphocyte cells in vitro. Polyploidy (numerical chromosome aberrations) was observed in human peripheral blood lymphocytes in vitro, both in the presence and absence of metabolic activation. Sunitinib was not clastogenic in rat bone marrow in vivo. The major active metabolite was not evaluated for genotoxic potential.
Carcinogenicity
In a 1-month, oral gavage dose-range finding study (0, 10, 25, 75, or 200 mg/kg/day) with continuous daily dosing inrasH2 transgenic mice, carcinoma and hyperplasia of Brunner's glands of the duodenum were observed at the highest dose (200 mg/kg/day) tested.
A 6-month, oral gavage carcinogenicity study (0, 8, 25, 75 [reduced to 50] mg/kg/day), with daily dosing was conducted in rasH2 transgenic mice. Gastroduodenal carcinomas, an increased incidence of background haemangio sarcomas, and/or gastric mucosal hyperplasia were observed at doses of ≥ 25 mg/kg/day following 1- or 6-months duration (≥ 7.3 times the AUC in patients administered the recommended daily dose [RDD]).
In a 2-year rat carcinogenicity study (0, 0.33, 1, or 3 mg/kg/day), administration of sunitinib in 28-day cycles followed by7-day dose-free periods resulted in increases in the incidence of phaeochromocytomas and hyperplasia in the adrenal medulla of male rats given 3 mg/kg/day following > 1 year of dosing (≥ 7.8 times the AUC in patients administered the RDD). Brunner's glands carcinoma occurred in the duodenum at ≥ 1 mg/kg/day in females and at 3 mg/kg/day in males, and mucous cell hyperplasia was evident in the glandular stomach at 3 mg/kg/day in males, which occurred at ≥ 0.9, 7.8, and 7.8 times the AUC in patients administered the RDD, respectively. The relevance to humans of the neoplastic findings observed in the mouse (rasH2 transgenic) and rat carcinogenicity studies with sunitinib treatment is unclear.
Reproductive and developmental toxicity
No effects on male or female fertility were observed in reproductive toxicity studies. However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea, endometrial changes in the uterus, and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididymides, and colloid depletion in prostate and seminal vesicles at plasma exposure levels 25 times the systemic exposure in humans.
In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels5.5 times the systemic exposure in humans. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions, increases in post implantation loss and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3 times the systemic exposure in humans. Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥ 5 mg/kg/day consisting of increased incidence of foetal skeletal malformations, predominantly characterised as retarded ossification of thoracic/lumbar vertebrae and occurred at plasma exposure levels 5.5 times the systemic exposure in humans. In rabbits, developmental effects consisted of increased incidence of cleft lip at plasma exposure levels approximately equal to that observed in clinic, and cleft lip and cleft palate at plasma exposure levels 2.7 times the systemic exposure in humans.
Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre-and postnatal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at ≥ 1 mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimate exposure ≥ 2.3 times the AUC in patients administered the RDD). Reduced offspring body weights were observed during the preweaning and postweaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥ 0.9 times the AUC in patients administered the RDD).
7. Description
Sunitinib is a kinase inhibitor present as the malate salt. Sunitinib malate is described chemically as (2S)-2-hydroxybutanedoic acid with N-[2-(diethylamino) ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$ and the molecular weight is 532.6 Daltons. The chemical structure of sunitinib malate is:



8. Pharmaceutical Particulars
8.1 Incompatibilities
Not Applicable
8.2 Shelf-life
2 years
8.3 Packing Information
HDPE container pack of 28 Capsules
8.4 Storage and handling instructions
Store below 30°C.Protect from moisture.
9. Patient Counselling Information
Advise the patient to read the approved patient labeling.
Hepatotoxicity
Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity.
Cardiovascular Events
Advise patients to contact their healthcare provider if they develop symptoms of heart failure.
QT Prolongation and Torsade de Pointes
Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately in the event of syncope, pre-syncopal symptoms, and cardiac palpitations.
Hypertension
Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.
Hemorrhagic Events
Advise patients that sunitinib can cause severe bleeding. Advise patients to immediately contact their healthcare provider for bleeding or symptoms of bleeding.
Gastrointestinal Disorders
Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during sunitinib treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking sunitinib.
Dermatologic Effects and Toxicities
Advise patients that depigmentation of the hair or skin may occur during treatment with sunitinib due to the drug color (yellow). Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. Severe dermatologic toxicities including Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, erythema multiforme, and necrotizing fasciitis have been reported. Advise patients to immediately inform their healthcare provider if severe dermatologic reactions occur.
Reversible Posterior Leukoencephalopathy Syndrome
Inform patients of the signs and symptoms of reversible posterior leukoencephalopathy syndrome. Advise patients to contact their healthcare provider if they develop symptoms of reversible posterior leukoencephalopathy syndrome.
Thyroid Dysfunction
Advise patients that sunitinib can cause thyroid dysfunction. Advise patient to contact their healthcare provider if symptoms of abnormal thyroid function occur.
Hypoglycemia
Advise patients that sunitinib can cause severe hypoglycemia and may be more severe in patients with diabetes taking antidiabetic medications. Inform patients of the signs, symptoms, and risks associated with hypoglycemia. Advise patients to immediately inform their healthcare provider if severe signs or symptoms of hypoglycemia occur.
Osteonecrosis of the Jaw
Advise patients regarding good oral hygiene practices and to inform their healthcare provider of any planned dental procedures. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.
Impaired Wound Healing
Advise patients that sunitinib impairs wound healing. Advise patients to inform their healthcare provider of any planned surgical procedures.
Concomitant Medications
Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications and dietary supplements.
Embryo-Fetal Toxicity
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy.
Advise females of reproductive potential to use effective contraception during treatment and for 4 weeks after receiving the last dose of sunitinib.
Advise males with female partners of reproductive potential to use effective contraception during treatment and for 7 weeks after receiving the last dose of sunitinib.
Lactation
Advise women not to breastfeed during treatment with sunitinib and for at least 4 weeks after the last dose.
Infertility
Advise patients that sunitinib may impair male and female fertility.
Missed Dose
Advise patients that miss a dose of sunitinib by less than 12 hours to take the missed dose right away. Advise patients that miss a dose of sunitinib by more than 12 hours to take the next scheduled dose at its regular time.
10. Details of Manufacturer
Hetero Labs Limited (Unit-I)
Village: Kalyanpur, Chakkan Road, Tehsil: Baddi, Distt.: Solan, Himachal Pradesh-173 205, India.
11. Details of Permission or Licence number with date
MNB/06/328,
27.01.2021
12. Date of Revision
31-08-2024

Marketed by:
Genygi Life Sciences Private Limited
SS - 29, Second Floor, Aditya Mega Mall,
Plot # 9D, Delhi - 110032

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Back Dimension: 200x280 mm,
Colour: Black
Spec: 41 gsm, Bible Paper
Folding size: 50x35 mm
Reason for change: New Brand