To be sold by retail on the prescription of an Oncologist only

MSN

Suntinib

Sunitinib Malate Capsules 12.5 mg, 25 mg And 50 mg

COMPOSITION

SUNITINIB MALATE CAPSULES 12.5 mg
Each hard gelatin capsule Contains
Sunitinib Malate Equivalent to
Sunitinib.....12.5 mg,

SUNITINIB MALATE CAPSULES 25 mg
Each hard gelatin capsule Contains
Sunitinib Malate Equivalent to
Sunitinib.....25 mg,

SUNITINIB MALATE CAPSULES 50 mg
Each hard gelatin capsule Contains
Sunitinib Malate Equivalent to
Sunitinib.....50 mg,
Excipients Q.S&Approved Colors
used in capsule shell,
Colours: Sunset Yellow FCF,
Tartrazine,
Titanium Dioxide-IP.

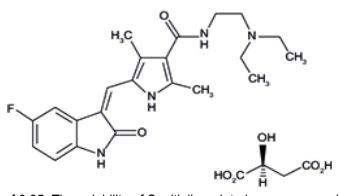
WARNING: EMBRYO-FETAL TOXICITY

Hepatotoxicity has been observed in clinical trials and post marketing experience. Hepatotoxicity may be severe, and in some cases, fatal. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.

DRUG DESCRIPTION

SUNTINIB, an oral multi-kinase inhibitor, is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(diethylamino) ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-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:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of Sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

DOSAGE FORM AND STRENGTHS

Capsules; 12.5 mg, 25 mg and 50 mg

INDICATIONS

Gastrointestinal Stromal Tumor(GIST)
SUNTINIB is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

Advance d Renal Cell Carcinoma (RCC)
SUNTINIB is indicated for the treatment of advanced renal cell carcinoma.

Adjuvant Treatment of Renal Cell Carcinoma (RCC)
SUNTINIB is indicated for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.

Advance d Pancreatic Neuroendocrine Tumors (pNET)
SUNTINIB is indicated for the treatment of progressive, well-differentiated pancreatic neuroendocrine tumors in patients with unresectable locally advanced or metastatic disease.

DOSE AND METHOD OF ADMINISTRATION

Recommended Dose for GIST and Advance d RCC
The recommended dose of SUNTINIB for gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC) is one 50mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). SUNTINIB may be taken with or without food.

Recommended Dose for Adjuvant Treatment of RCC
The recommended dose of SUNTINIB for the adjuvant treatment of RCC is 50 mg taken orally once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2), for nine 6-week cycles. SUNTINIB may be taken with or without food.

Recommended Dose for pNET
The recommended dose of SUNTINIB for pancreatic neuroendocrine tumors (pNET) is 37.5 mg taken orally once daily continuously without a scheduled off-treatment period. SUNTINIB may be taken with or without food.

Dose Modification
Dose interruption and/or dose modification in 12.5 mg increments or decrements is recommended based on individual safety and tolerability. The maximum dose administered in the pNET study was 50 mg daily. In the adjuvant RCC study, the minimum dose administered was 37.5 mg.

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. A dose reduction for SUNTINIB to a minimum of 37.5 mg (GIST and RCC) or 25 mg (pNET) daily should be considered if SUNTINIB must be coadministered with a strong CYP3A4 inhibitor.

CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. A dose increase for SUNTINIB to a maximum of 87.5 mg (GIST and RCC) or 62.5 mg (pNET) daily should be considered if SUNTINIB must be coadministered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.

USE IN SPECIAL POPULATIONS

Pregnancy

Based on animal reproduction studies and its mechanism of action, SUNTINIB can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform a drug-associated risk. In animal developmental and reproductive toxicology studies, oral administration of sunitinib to pregnant rats and rabbits throughout organogenesis resulted in teratogenicity (embryolethality, craniofacial and skeletal malformations). Advise pregnant women or females of reproductive potential of the potential hazard to a fetus.

The background risk of major birth defects and miscarriage for the indicated populations are unknown.

Lactation

There is no information regarding the presence of sunitinib and its metabolites in human milk. Sunitinib and its metabolites were excreted in rat milk at concentrations up to 12-fold higher than in plasma. Because of the potential for serious adverse reactions in breastfed infants from SUNTINIB, advise a lactating woman not to breastfeed during treatment with SUNTINIB and for at least 4 weeks after the last dose.

Females and Males of Re productive Potential
Based on animal reproduction studies and its mechanism of action, SUNTINIB can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing
Females of reproductive potential should have a pregnancy test before treatment with SUNTINIB is started.

Contraception
Females
Advise females of reproductive potential to use effective contraception during treatment with SUNTINIB and for at least 4 weeks after the last dose.
Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment with SUNTINIB and for 7 weeks after the last dose.
Infertility
Based on findings in animals, male and female fertility may be compromised by treatment with SUNTINIB.

Pediatric Use
The safety and efficacy of SUNTINIB in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between younger and older patients.

Hepatic Impairment
No dose adjustment to the starting dose is required when administering SUNTINIB to patients with Child-Pugh Class A or B hepatic impairment. Sunitinib and its primary metabolite are primarily metabolized by the liver. Systemic exposures after a single dose of SUNTINIB were similar in patients with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to patients with normal hepatic function. SUNTINIB was not studied in patients with severe (Child-Pugh Class C) hepatic impairment.

Renal Impairment
No adjustment to the starting dose is required when administering SUNTINIB to patients with mild (CLcr 50–80 mL/min), moderate (CLcr 30–<50 mL/min), or severe (CLcr <30 mL/min) renal impairment who are not on dialysis. In patients with end-stage renal disease (ESRD) on hemodialysis, no adjustment to the starting dose is required. However, compared to patients with normal renal function, the sunitinib exposure is 47% lower in patients with ESRD on hemodialysis. Therefore, the subsequent doses may be increased gradually up to 2-fold based on safety and tolerability.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients used in formulation

WARNINGS AND PRECAUTIONS

Hepatotoxicity
SUNTINIB can cause severe hepatotoxicity, resulting in liver failure or death. Liver failure signs include jaundice, elevated transaminases and/or hyperbilirubinemia in conjunction with encephalopathy, coagulopathy, and/or renal failure. Monitor liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) before initiation of treatment, during each cycle of treatment, and as clinically indicated. Interrupt SUNTINIB for Grade 3 or 4 drug-related hepatic adverse reactions and discontinue if there is no resolution. Do not restart SUNTINIB if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure.

Safety in patients with ALT or AST >2.5 x upper limit of normal (ULN) or, if due to liver metastases, >5.0 x ULN has not been established.

Cardiovascular Events
Discontinue SUNTINIB in the presence of clinical manifestations of congestive heart failure (CHF). Interrupt SUNTINIB and/or reduce the dose in patients without clinical evidence of CHF who have an ejection fraction of >20% but <50% below baseline or below the lower limit of normal if baseline ejection fraction is not obtained.

In patients without cardiac risk factors a baseline evaluation of ejection fraction should be considered. Carefully monitor patients for clinical signs and symptoms of CHF while receiving SUNTINIB. Baseline and periodic evaluations of left ventricular ejection fraction (LVEF) should also be considered while these patients are receiving SUNTINIB.

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia, and myocardial infarction, some of which were fatal, have been reported.

QT Interval Prolongation and Torsade de Pointes
SUNTINIB can cause QT interval prolongation in a dose-dependent manner, which may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes. Torsade de Pointes has been observed in <0.1% of Sunitinib - exposed patients.

Monitor patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using SUNTINIB, periodic monitoring with on-treatment electrocardiograms and electrolytes (magnesium, potassium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors may increase sunitinib plasma concentrations and dose reduction of SUNTINIB should be considered.

Hypertension
Monitor patients for hypertension and treat as needed with standard antihypertensive therapy. In cases of severe hypertension, temporary suspension of SUNTINIB is recommended until hypertension is controlled.

Hemorrhagic Events and Viscus Perforation
Hemorrhagic events reported through post marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract, and brain hemorrhages. In patients treated with Sunitinib for GIST, advanced RCC, adjuvant treatment of RCC and pNET, 30% of patients experienced hemorrhagic events, and 4.2% of patients experienced a Grade 3 or 4 event. Epistaxis was the most common hemorrhagic adverse reaction and gastrointestinal hemorrhage was the most common Grade≥3 event.

Tumor-related hemorrhage has been observed in patients treated with SUNTINIB. These events may occur suddenly, and in the case of pulmonary tumors, may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Cases of pulmonary hemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post marketing experience in patients treated with SUNTINIB for metastatic RCC, GIST, and metastatic lung cancer. SUNTINIB is not approved for use in patients with lung cancer. Clinical assessment of hemorrhagic events should include serial complete blood counts (CBCs) and physical examinations.

Serious, sometimes fatal, gastrointestinal complications including gastrointestinal perforation have been reported in patients with intra-abdominal malignancies treated with SUNTINIB.

Tumor Lysis Syndrome (TLS)
Cases of TLS, some fatal, occurred in clinical trials and have been reported in postmarketing experience, primarily in patients with RCC or GIST treated with SUNTINIB. Patients generally at risk of TLS are those with high tumor burden prior to treatment. Monitor these patients closely and treat as clinically indicated.

Thrombotic Microangiopathy
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, sometimes leading to renal failure or a fatal outcome, occurred in clinical trials and in post marketing experience of SUNTINIB as monotherapy and administered in combination with bevacizumab. Discontinue SUNTINIB in patients developing TMA. Reversal of the effects of TMA has been observed after treatment was discontinued.

Proteinuria
Proteinuria and nephrotic syndrome have been reported. Some of these cases have resulted in renal failure and fatal outcomes. Monitor patients for the development or worsening of proteinuria. Perform baseline and periodic urinalyses during treatment, with follow up measurement of 24-hour urine protein as clinically indicated. Interrupt Sunitinib and dose reduce for 24-hour urine protein ≥3 grams. Discontinue SUNTINIB for patients with nephrotic syndrome or repeat episodes of urine protein ≥3 grams despite dose reductions. The safety of continued SUNTINIB treatment in patients with moderate to severe proteinuria has not been systematically evaluated.

Dermatologic Toxicities
Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), some of which were fatal. If signs or symptoms of EM, SJS, or TEN (e.g., progressive skin rash often with blisters or mucosal lesions) are present, discontinue SUNTINIB treatment. If a diagnosis of SJS or TEN is suspected, SUNTINIB treatment must not be re-started.

Necrotizing fasciitis, including fatal cases, has been reported in patients treated with SUNTINIB, including of the perineum and secondary to fistula formation. Discontinue SUNTINIB in patients who develop necrotizing fasciitis.

Thyroid Dysfunction
Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of SUNTINIB treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction, including hypothyroidism, hyperthyroidism, and thyroiditis, while on SUNTINIB treatment. Patients with signs and/or symptoms suggestive of thyroid dysfunction should have laboratory monitoring of thyroid function performed and be treated as per standard medical practice.
Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post marketing experience.

Hypoglycemia
SUNITINIB can result in symptomatic hypoglycemia, which may lead to loss of consciousness, or require hospitalization. For patients being treated with SUNTINIB for pNET, pre-existing abnormalities in glucose homeostasis were not present in all patients who experienced hypoglycemia. Reductions in blood glucose levels may be worse in diabetic patients. Check blood glucose levels regularly during and after discontinuation of treatment with SUNTINIB. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Osteonecrosis of the Jaw (ONJ)
ONJ has been observed in clinical trials and has been reported in post marketing experience in patients treated with SUNTINIB. Concomitant exposure to other risk factors, such as bisphosphonates or dental disease, may increase the risk of osteonecrosis of the jaw. Consider preventive dentistry prior to treatment with SUNTINIB. If possible, avoid invasive dental procedures while on SUNTINIB treatment, particularly in patients receiving intravenous bisphosphonate therapy.

Wound Healing
Cases of impaired wound healing have been reported during SUNTINIB therapy. Temporary interruption of SUNTINIB 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 SUNTINIB therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Embryo-Fetal Toxicity
Based on findings from animal studies and its mechanism of action, SUNTINIB can cause fetal harm when administered to pregnant woman. Administration of SUNTINIB to pregnant rats and rabbits during the period of organogenesis resulted in teratogenicity at approximately 5.5 and 0.3 times the clinical systemic exposure (AUC) at the recommended daily doses (RDD) of 50 mg/day, respectively.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with SUNTINIB and for 4 weeks following the final dose.

DRUG INTERACTIONS

CYP3A4 Inhibitors

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of sunitinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) C_{max} and AUC 0-∞ values, respectively, after a single dose of sunitinib in healthy volunteers. Coadministration of SUNTINIB with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma concentrations of sunitinib. A dose reduction for SUNTINIB should be considered when it must be coadministered with strong CYP3A4 inhibitors.

CYP3A4 Inducers

CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of SUNTINIB with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (Sunitinib + primary active metabolite) Cmax and AUC 0-∞ values, respectively, after a single dose of SUNTINIB in healthy volunteers. Coadministration of SUNTINIB with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving sunitinib should not take St. John's Wort concomitantly. A dose increase for SUNTINIB should be considered when it must be coadministered with CYP3A4 inducers.

In Vitro Studies of CYP Inhibition and Induction
In vitro studies indicated that Sunitinib does not induce or inhibit major CYP enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.

UNDESIRABLE EFFECTS
The following serious adverse reactions are discussed in greater detail in other sections of the labeling.

- Hepatotoxicity
- Cardiovascular Events
- QT Interval Prolongation and Torsade de Pointes
- Hypertension
- Hemorrhagic Events
- Tumor Lysis Syndrome (TLS)
- Thrombotic Microangiopathy
- Proteinuria
- Dermatologic Toxicities
- Thyroid Dysfunction
- Hypoglycemia
- Osteonecrosis of the Jaw (ONJ)
- Wound Healing

System organ class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations		Viral infections[a] Respiratory infections[b,*] Abscess[c,*] Fungal infections[d] Urinary tract infection Skin infections[e] Sepsis[f,*]	Necrotising fasciitis* Bacterial infections[g]		
Blood and lymphatic system disorders	Neutropoenia Thrombocytopoenia Anaemia Leukopoenia	Lymphopoenia	Pancytopenia	Thrombotic microangiopathy[h,*]	
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*	
Eye disorders		Periorbital oedema Eyelid oedema Lacrimation increased			
Cardiac disorders		Myocardial ischemia[k,*] Ejection fraction decreased[l]	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*		Aortic aneurysms and 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* Abdominal distension Abdominal discomfort Rectal haemorrhage Gingival bleeding Mouth ulceration Proctalgia Cheilitis Haemorrhoids Glossodynia Oral pain Dry mouth Flatulence Oral discomfort Eructation	Gastrointestinal perforation[q,*] Pancreatitis Anal fistula Colitis[r]		
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 Skin reaction[v] Eczema Blister Erythema Alopecia Acne Pruritus Skin hyperpigmentation Skin lesion Hyperkeratosis Dermatitis Nail disorder[w]		Erythema multiforme* Stevens-Johnson syndrome* Pyoderma gangrenosum Toxic epidermal necrolysis*	
Musculoskeletal and connective tissue disorders	Pain in extremity Arthralgia Back pain	Musculoskeletal pain Muscle spasms Myalgia Muscular 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 and administration site conditions	Mucosal inflammation Fatigue[x] Oedema[y] Pyrexia	Chest pain Pain Influenza like illness Chills	Impaired healing		
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 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, 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/To report a side effect.

OVERDOSE
Treatment of overdose with Sunitinib should consist of general supportive measures. There is no specific antidote for overdosage with Sunitinib. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of accidental overdose have been reported; these cases were associated with adverse reactions consistent with the known safety profile of Sunitinib, or without adverse reactions. A case of intentional overdose involving the ingestion of 1500 mg of Sunitinib in an attempted suicide was reported without adverse reaction. In nonclinical studies, mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection, and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Antihypertensives for pulmonary arterial hypertension,

ATC code: L01XE04

Mechanism of action
Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor 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 an 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 Type 1 (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.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFR β, VEGFR2, KIT) in tumor xenografts expressing RTK targets *Invivo* 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 PDGFR β - and VEGFR2-dependent tumor angiogenesis *Invivo*.

PHARMACOKINETIC PROPERTIES

Absorption
Maximum plasma concentrations (Cmax) of Sunitinib are generally observed between 6 and 12 hours (time to maximum plasma concentration [T_{max}]) following oral administration. Food has no effect on the bioavailability of Sunitinib. Sunitinib may be taken with or without food.

Distribution
Binding of Sunitinib and its primary active metabolite to human plasma protein in vitro was 95% and 90%, respectively, with no concentration dependence in the range of 100–4000 ng/mL. The apparent volume of distribution (V_d/F) for Sunitinib was 2230 L. In the dosing range of 25-100 mg, the AUC and Cmax increase proportionately with dose.

Biotransformation
Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23% to 37% of the total exposure. Elimination is primarily via feces. In a human mass balance study of [^{14}C] Sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose.

Elimination
Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4%, and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (C_L/F) ranged from 34 to 62 L/h with an interpatient variability of 40%.

INCOMPATIBILITIES
Not applicable.

PACKING INFORMATION
28's Count Bottle pack
7's Count blister pack

STORAGE
Do not store above 30°C.

KEEP AWAY FROM INFANTS AND SMALL CHILDREN

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division, Unit-II,
Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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