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SUNITINIB MY ALL STRENGTH CAPSULE PIL

lotus PHARMACEUTICAL

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REGULATORY APPROVAL

Glue Point

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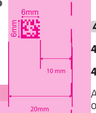
ALSUNI CAPSULES
12.5 mg / 25 mg / 50 mg
SUNITINIB MALATE

ALSUNI CAPSULES
12.5 mg / 25 mg /
50 mg

SUNITINIB MALATE



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Package Insert

ALSUNI CAPSULES
12.5 mg / 25 mg / 50 mg

SUNITINIB MALATE

1. NAME OF THE MEDICINAL PRODUCT

ALSUNI CAPSULES 12.5 MG / 25 MG / 50 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ALSUNI CAPSULES 12.5 MG
Each capsule contains sunitinib malate, equivalent to 12.5 mg of sunitinib.

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ALSUNI CAPSULES 12.5 MG
Hard capsules with dark brown opaque cap and dark brown opaque body, 13.8-14.8 mm, printed with white ink "LP" on the cap, "650" on the body, and containing yellow to orange granular powder.

ALSUNI CAPSULES 25 MG
Hard capsules with light brown opaque cap and dark brown opaque body, 15.4-16.4 mm, printed with white ink "LP" on the cap, "651" on the body, and containing yellow to orange granular powder.

ALSUNI CAPSULES 50 MG
Hard capsules with light brown opaque cap and light brown opaque body, 17.5-18.5 mm, printed with white ink "LP" on the cap, "653" on the body, and containing yellow to orange granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1.1 Gastrointestinal stromal tumour (GIST)

ALSUNI is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

4.1.2 Advanced Renal Cell Carcinoma (RCC)

ALSUNI is indicated for the treatment of advanced renal cell carcinoma.

4.1.3 Pancreatic neuroendocrine tumours (pNET)

ALSUNI is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

4.2 Posology and method of administration

4.2.1 Recommended Dose

For GIST and Advanced RCC, 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.

Sunitinib 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.

4.2.2 Dose Modifications

Safety and tolerability
For GIST and Advanced RCC, dose modifications in 12.5 mg increments or decrements may be applied based on individual safety and tolerability up to 75 mg or down to 25 mg.

For *pNET*, dose modification in 12.5 mg increments or decrements may be applied based on individual safety and tolerability. The maximum dose administered is 50 mg daily.

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

CYP3A4 Inhibition/Induction
Co-administration of sunitinib with strong CYP3A4 inducers such as rifampin, should be avoided. If this is not possible, the dose of sunitinib may need to be increased in 12.5 mg increments to a maximum of 87.5 mg (*GIST* and *RCC*), or 62.5 mg (*pNET*) daily, based on careful monitoring of tolerability.

Co-administration of sunitinib with strong CYP3A4 inhibitors, such as ketoconazole, should be avoided. If this is not possible, the dose of sunitinib may need to be reduced in 12.5 mg decrements to a minimum of 37.5 mg (*GIST* and *RCC*) or 25 mg (*pNET*) daily, based on careful monitoring of tolerability.

Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 is recommended.

Use in Pediatrics
The safety and efficacy of sunitinib in pediatric patients have not been established.

Use in the Elderly
Dose adjustments are not required in elderly patients.

Hepatic Insufficiency
No dose adjustment is necessary when administering sunitinib to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 during postmarketing 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 reported in post marketing experience in patients treated with sunitinib for Advanced RCC, GIST, and lung cancer. ALSUNI 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. Rare fatal haematological events, including haemorrhage associated with thrombocytopenia and neutropenic infections, have been reported during postmarketing 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 lower limit 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.

Conditions like 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 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 antiarrhythmics 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.

Osteonecrosis of the jaw (ONJ)
Cases of ONJ have been reported in patients treated with ALSUNI. 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 ALSUNI and intravenous bisphosphonates are used either simultaneously or sequentially.

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

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that may increase sunitinib plasma concentrations
Effect of CYP3A4 inhibitors
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 ALSUNImay need to be reduced to a minimum of 37.5 mg daily for GIST and Advanced RCC or 25 mg daily for pNET, based on careful monitoring of tolerability.

Effect of Breast Cancer Resistance Protein (BCRP) inhibitors
Due to limited data available on the interaction between sunitinib and BCRP inhibitors, 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
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 ALSUNImay need to be increased in 12.5 mg increments (up to 87.5 mg per day for GIST and Advanced RCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with ALSUNI.

Pregnancy
ALSUNI 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 ALSUNI is used during pregnancy or if the patient becomes pregnant while on treatment with ALSUNI the patient should be apprised of the potential hazard to the foetus.

Breast-feeding
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 ALSUNI.

Fertility
Male and female fertility may be compromised by treatment with sunitinib.

4.7 Effects on ability to drive and use machines

ALSUNI 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 that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, adrenal insufficiency, pneumothorax, shock, and sudden death.

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[g,*] Bacterial infections[h]		
Blood and lymphatic system disorders	Neutropoenia Thrombocytopoenia Anaemia Leukopoenia	Lymphopoenia	Pancytopenia	Thrombotic microangiopathy[i,*]	
Immune system disorders			Hypersensitivity	Angioedema	
Endocrine disorders	Hypothyroidism		Hyperthyroidism	Thyroiditis	
Metabolism and nutrition disorders	Decreased appetite[j]	Dehydration Hypoglycaemia		Tumour lysis syndrome[k]	
Psychiatric disorders	Insomnia	Depression			
Nervous system disorders	Dizziness Headache Taste disturbance[l]	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[m,*] Ejection fraction decreased	Cardiac failure congestive Myocardial infarction[n,*] 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[o] Nasal congestion Nasal dryness	Pulmonary haemorrhage[*] Respiratory failure[*]		
Gastrointestinal disorders	Stomatitis[p] Abdominal pain[q] Vomiting Diarrhoea Dyspepsia Nausea Constipation	Gastro-oesophageal reflux disease Dysphagia Gastrointestinal haemorrhage[*] Oesophagitis[r] Abdominal distension Abdominal discomfort Rectal haemorrhage Gingival bleeding Mouth ulceration Proctalgia Cheilitis Haemorrhoids Glossodynia Oral pain Dry mouth Flatulence Oral discomfort Eructation	Gastrointestinal perforation[s,*] Pancreatitis Anal fistula Colitis[t]		
Hepatobiliary disorders			Hepatic failure[*] Cholecystitis[u,*] Hepatic function abnormal	Hepatitis	
Skin and subcutaneous tissue disorders	Skin discolouration[v] Palmar-plantar erythrodysaesthesia syndrome Rash[w] Hair colour changes Dry skin	Skin exfoliation Skin reaction[x] 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[y] Oedema[z] 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 aphthous 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.

4.9 Overdose

There is no specific antidote for overdose with ALSUNI 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors; ATC code: L01XE04

Mechanism of action
Sunitinib inhibits multiple RTKs that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Sunitinib 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 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

5.2 Pharmacokinetic properties

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 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. 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.

Metabolic interactions
The calculated *in vitro* Ki values for all cytochrome P450 (CYP) isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11) indicated that sunitinib and its primary active metabolite are unlikely to induce metabolism, to any clinically relevant extent, of other actives substances that may be metabolised by these enzymes.

Biotransformation
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.

Elimination
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ALSUNI CAPSULES 12.5 MG
Capsule content
Povidone (K-25)
Mannitol (E421) (Ph. Eur.)
Croscamellose sodium
Magnesium stearate (Ph. Eur.) [vegetable]

Capsule shell
Gelatin
Red Iron Oxide (E172)
Titanium Dioxide (E171)
Black Iron Oxide (E172)

Printing ink
Shellac
Propylene Glycol
Sodium Hydroxide
Povidone
Titanium Dioxide (E171)

ALSUNI CAPSULES 25 MG
Capsule content
Povidone (K-25)
Mannitol (E421) (Ph. Eur.)
Croscamellose sodium
Magnesium stearate (Ph. Eur.) [vegetable]

Capsule shell
Gelatin
Titanium dioxide (E171)
Red Iron Oxide (E172)
Black Iron Oxide (E172)
Yellow Iron Oxide (E172)

Printing ink
Shellac
Propylene Glycol
Sodium Hydroxide
Povidone
Titanium Dioxide (E171)

ALSUNI CAPSULES 50 MG
Capsule content
Povidone
Mannitol (E421)
Croscamellose sodium
Magnesium stearate

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
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to the outer carton.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Capsules are packed in:
Blister: White PVC/Aclar-Aluminium blister pack containing 4x7 hard capsules

7. MANUFACTURER

Lotus Pharmaceutical Co., Ltd. Nantou Plant
No. 30, Chenggong 1st Rd., Sinsing Village, Nantou City, Nantou County 540033, Taiwan

8. PRODUCT REGISTRATION HOLDER

Lotus Healthcare Malaysia Sdn. Bhd.
UOA Business Park Tower 3, 9th Floor, K03-09-11, 1 Jalan Pengaturcara U1/51A Section U1, 40150 Shah Alam, Malaysia

9. DATE OF REVISION OF THE TEXT

15/04/2026

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