PROFESSIONAL INFORMATION FOR SUNITINIB CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SUNITINIB 12,5 CIPLA Hard capsules

SUNITINIB 25 CIPLA Hard capsules

SUNITINIB 37,5 CIPLA Hard capsules

SUNITINIB 50 CIPLA Hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar: Mannitol 35,8 mg.

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

Contains sugar: Mannitol 71,6 mg.

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

Contains sugar: Mannitol 107,4 mg.

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

Contains sugar: Mannitol 143,2 mg.

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Hard capsules

SUNITINIB 12,5 CIPLA: Dark brown opaque cap and dark brown opaque body, capsule shell size no. 4 imprinted in white ink with "LP" on the cap and "650" on the body and containing yellow to orange granular powder.

SUNITINIB 25 CIPLA: Light brown opaque cap and dark brown opaque body, capsule shell size no. 3 imprinted in white ink with "LP" on the cap and "651" on the body and containing yellow to orange granular powder.

SUNITINIB 37,5 CIPLA: Yellow opaque cap and yellow opaque body, capsule shell size no.2 imprinted in black ink with "LP" on the cap and "652" on the body and containing yellow to orange granular powder.

SUNITINIB 50 CIPLA: Light brown opaque cap and light brown opaque body, capsule shell size no. 2 imprinted in white ink with "LP" on the cap and "653" on the body and containing yellow to orange granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastrointestinal stromal tumour (GIST)

SUNITINIB CIPLA is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.

Metastatic renal cell carcinoma (MRCC)

SUNITINIB CIPLA is indicated for the treatment of treatment-naïve advanced and/or metastatic renal cell carcinoma.

SUNITINIB CIPLA is also indicated for the treatment of metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy (interferon α, interleukin-2).

Efficacy is based on time to tumour progression and an increase in survival in GIST and on objective response rates for MRCC.

Efficacy and safety has not been demonstrated for more than 12 months.

Pancreatic neuroendocrine tumours (pNET)

SUNITINIB CIPLA is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

4.2 Posology and method of administration

Therapy with should be initiated by a medical practitioner experienced in the treatment of renal cell carcinoma or GIST.

Posology

For GIST and MRCC, the recommended dose of SUNITINIB CIPLA is one 50 mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (Schedule 4/2) to comprise a complete cycle of 6 weeks.

For pancreatic neuroendocrine tumours (pNET), the recommended dose of SUNITINIB CIPLA is 37,5 mg taken orally once daily without a scheduled rest period.

Dose modifications

Safety and tolerability

For GIST and MRCC, dose modifications in 12,5 mg increments 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

In patients receiving SUNITINIB CIPLA with a potent CYP3A4 inducer such as rifampicin, the dosage of SUNITINIB CIPLA 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). Clinical response and tolerability should be carefully monitored.

In patients receiving SUNITINIB CIPLA with a CYP3A4 inhibitor such as ketoconazole, the doses of SUNITINIB CIPLA 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 tolerability and/or clinical

response. Selection of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 should be considered.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for age, body weight, creatinine clearance, race, gender or ECOG (Eastern Cooperative Oncology Group) score.

Special populations

Elderly patients

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

Hepatic insufficiency

No dosage adjustment is necessary when administering SUNITINIB CIPLA to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. SUNITINIB CIPLA was not studied in patients with severe (Child-Pugh Class C) hepatic impairment.

Renal insufficiency

No starting dose adjustment is required when administering SUNITINIB CIPLA 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.

Paediatric population

The safety and efficacy of SUNITINIB CIPLA in paediatric patients have not been established.

Method of administration

For oral use.

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

- SUNITINIB CIPLA is contraindicated in patients with hypersensitivity to sunitinib malate or to any of the other excipients of SUNITINIB CIPLA (listed in **section 6.1**).
- Pregnancy and lactation (see **section 4.6**).

4.4 Special warnings and precautions for use

Skin and tissues

Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUNITINIB CIPLA. Other possible dermatologic effects may include dryness, thickness or cracking of the skin, blisters or occasional rash on the palms of the hands and soles of the feet**.**

Mouth pain/irritation and dysgeusia (taste disturbance) were reported in studies. These events were not cumulative and were typically reversible and generally did not result in treatment discontinuation.

Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and cases suggestive of Stevens-Johnson syndrome (SJS), some of which were fatal. If signs or symptoms of SJS or EM (e.g., progressive skin rash often with blisters or mucosal lesions) are present, SUNITINIB CIPLA should be discontinued. If the diagnosis of SJS is confirmed, treatment must not be re-started. In some cases of suspected EM, patients tolerated the reintroduction of SUNITINIB CIPLA at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

Haemorrhage

Haemorrhagic events reported through post-marketing experience, some of which were fatal, have included gastrointestinal (GI), respiratory, tumour, urinary tract and brain haemorrhage. In clinical trials, tumour haemorrhage occurred in patients with GIST. These events may occur suddenly, and in the case of pulmonary tumours, may present as severe or life-threatening haemoptysis or pulmonary haemorrhage. Tumour haemorrhage has not been observed in patients with MRCC or other solid tumours. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with

sunitinib as in SUNITINIB CIPLA for MRCC, GIST, and metastatic non-small cell lung cancer (NSCLC). SUNITINIB CIPLA is not approved for use in patients with NSCLC.

Bleeding in patients receiving sunitinib for treatment-naïve MRCC, cytokine-refractory MRCC, and pNET has been reported in clinical studies. Routine assessment of these events should include complete blood counts and physical examination.

Treatment-related epistaxis was reported in patients with solid tumours in clinical trial. Epistaxis was the frequent treatment-related haemorrhagic adverse event, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events.

Gastrointestinal events

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

Nausea, diarrhoea, stomatitis, dyspepsia and vomiting were frequently reported treatment-related gastrointestinal events. Supportive care for gastrointestinal adverse events requiring treatment may include medication with an anti-emetic or anti-diarrhoeal medication.

Pancreatitis

Pancreatitis has been reported in clinical trials of sunitinib. Increases in serum lipase and amylase were observed in patients with various solid tumours who received sunitinib. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumours. If symptoms of pancreatitis are present, patients should have proper medical follow-up.

Hepatotoxicity

Hepatotoxicity has been observed in patients treated with sunitinib. Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be monitored before initiation of treatment, during each cycle of treatment, and additionally as clinically indicated. SUNITINIB CIPLA treatment should be interrupted for Grade 3 or 4 hepatic-related adverse events and discontinued if there is no resolution of the adverse events.

Haematological

Decreased absolute neutrophil counts occurred frequently and decreased platelet counts were reported less frequently in clinical trials. Such events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. In addition, some cases of fatal haemorrhage associated with thrombocytopenia were reported through post-marketing experience.

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

Cardiovascular

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischaemia, angina pectoris and myocardial infarction, some of which were fatal, have been reported in clinical trials and through post-marketing experience.

In the treatment-naïve MRCC study, patients on sunitinib had a left ventricular ejection fraction (LVEF) value below the lower limit of normal.

Cardiac failure that may be fatal, congestive cardiac failure or left ventricular failure were reported in clinical trials.

The relationship between receptor tyrosinase kinase (RTK) inhibition and cardiac function remains unclear but seems to be a class effect. Data from non-clinical *(in vitro* and *in vivo)* studies, at doses higher than the recommended human dose, indicate that sunitinib has the potential to inhibit the cardiac action potential repolarisation process (e.g., prolongation of QT interval). Increases in the QTc interval and changes from baseline that occurred were recognised as potentially significant.

QT interval prolongation

At approximately twice the therapeutic concentrations, sunitinib as in SUNITINIB CIPLA has been shown to prolong the QTcF (Fredericia's correction) interval. QT interval prolongation may lead to an increased risk for ventricular dysrhythmias including torsade de pointes. SUNITINIB CIPLA should be used with caution in patients with a known

history of QT interval prolongation, patients who are taking antidysrhythmics or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances.

Hypertension

Patients treated with SUNITINIB CIPLA should have regular blood pressure assessments.

Hypertension was a frequent adverse event reported in clinical trials in patients with solid tumours, including primarily GIST and cytokine-refractory RCC.

Patients should be screened for hypertension and controlled as appropriate. Temporary suspension of SUNITINIB CIPLA therapy is recommended in patients with severe hypertension that is not controlled with medical management.

Treatment may be resumed once hypertension is appropriately controlled.

Thyroid dysfunction

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical treatment prior to the start of SUNITINIB CIPLA treatment.

All patients should be observed closely for signs and symptoms of thyroid dysfunction whilst on SUNITINIB CIPLA 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.

In studies, acquired hypothyroidism was noted in GIST patients. Hypothyroidism was reported as an adverse event in patients on sunitinib in the treatment-naïve MRCC study and in subjects across 2 cytokine-refractory MRCC studies.

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience.

Seizures

In clinical studies of sunitinib, seizures have been observed in subjects with radiological evidence of brain metastases. Patients with seizures and signs/symptoms consistent with reversible posterior 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 CIPLA therapy is recommended in patients with seizures or RPLS. Following resolution, treatment may be resumed at the discretion of the treating medical practitioner.

Surgical procedures

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

There is limited clinical experience regarding the timing of re-initiation of therapy following major surgical intervention. Therefore, the decision to resume SUNITINIB CIPLA therapy following a major surgical intervention should be based upon clinical judgement of recovery from surgery.

Osteonecrosis of the jaw (ONJ)

ONJ has been less frequently observed in clinical trials and has been reported in post-marketing experience in patients treated with sunitinib. The majority of cases occurred in patients who had received prior or concomitant treatment with intravenous (IV) bisphosphonates, for which ONJ is an identified risk. Caution should therefore be exercised when SUNITINIB CIPLA and IV bisphosphonates are used either simultaneously or sequentially.

Invasive dental procedures are also an identified risk factor for ONJ. Prior to treatment with SUNITINIB CIPLA, a dental examination and appropriate preventative dentistry should be considered. In patients being treated with SUNITINIB CIPLA, who have previously received or are receiving IV bisphosphonates, invasive dental procedures should be avoided, if possible.

Venous thromboembolic event

Some patients on sunitinib in a GIST study experienced venous thromboembolic events and treatment-naïve MRCC had venous thrombolic events reported such as pulmonary embolism.

Pulmonary embolism

Pulmonary embolism was reported in patients with solid tumours who received sunitinib. None of these events resulted in a patient discontinuing treatment with sunitinib; however, a dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these patients after treatment was resumed.

Tumour lysis syndrome (TLS)

Cases of TLS, some fatal, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib. Patients generally at risk of TLS are those with high tumour burden prior to treatment. These patients should be monitored closely and treated as clinically indicated.

Necrotising fasciitis

Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported. SUNITINIB CIPLA therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Thrombotic microangiopathy

Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS), frequently leading to renal failure or a

fatal outcome, has been reported in clinical trials and in post-marketing experience of sunitinib as monotherapy and in combination with bevacizumab.

Discontinue SUNITINIB CIPLA in patients developing TMA.

Proteinuria

Cases of proteinuria and nephrotic syndrome have been reported. Baseline urinalysis is recommended, and patients should be monitored for the development or worsening of proteinuria. The safety of continued sunitinib treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue SUNITINIB CIPLA in patients with nephrotic syndrome.

Hypoglycaemia

Decreases in blood glucose, in some cases clinically symptomatic, have been reported during sunitinib treatment. Blood glucose levels in diabetic patients should be checked regularly in order to assess if antidiabetic medicine dosage needs to be adjusted to minimise the risk of hypoglycaemia.

Cerebrovascular events

Cerebrovascular adverse events identified as class related adverse events have occurred in patients treated with TKI containing medicines. These class-related cerebrovascular adverse events, shared to a variable degree by all TKIs, are cerebrovascular accident (CA), transient ischaemic attack (TIA), ischaemic stroke (IS), and cerebral infarction (CI). These cerebrovascular events may occur in patients on treatment with TKIs with or

without risk factors for these events and may occur at any time during treatment with TKIs. Patients on treatment with TKI containing medicine should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events. Treatment with TKI containing medicines should be discontinued, and alternative treatment options be considered in patients who develop these class-related cerebrovascular adverse events.

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.

4.5 Interaction with other medicines and other forms of interaction

When sunitinib as in SUNITINIB CIPLA is co-administered with other medicines, there is a potential for medicine interaction.

In vitro studies indicate that sunitinib neither induces nor inhibits major CYP enzymes, including CYP3A4. The dose of SUNITINIB CIPLA may need to be reduced based on tolerability when co-administered with CYP3A4 inhibitors.

The dose of SUNITINIB CIPLA may need to be increased when it is co-administered with potent CYP3A4 inducers.

Medicines that may increase SUNITINIB CIPLA plasma concentrations

Concurrent administration of SUNITINIB CIPLA with the CYP3A4 inhibitor, ketoconazole, increases sunitinib C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in clinical studies.

Administration of SUNITINIB CIPLA with other inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase SUNITINIB CIPLA concentrations. Concomitant administration with inhibitors should therefore be avoided, or the selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4, should be considered. If this is not possible, the dosage of SUNITINIB CIPLA may need to be reduced (see **section 4.2**, Dose modifications).

Medicines that may decrease SUNITINIB CIPLA plasma concentrations

Concomitant use of sunitinib as in SUNITINIB CIPLA with the CYP3A4 inducer, rifampicin, resulted in reduction in sunitinib C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib in healthy volunteers.

Administration of SUNITINIB CIPLA with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbitone or *Hypericum perforatum* known also as St. John's Wort) may decrease SUNITINIB CIPLA concentrations. To maintain SUNITINIB CIPLA target concentrations, dose adjustment of SUNITINIB CIPLA, or selection of co-medications with less enzyme induction potential, should be considered.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Teratogenicity has been observed in animal studies. Women of childbearing potential should use effective contraceptive measures during SUNITINIB CIPLA treatment and 4 weeks after the last dose of SUNITINIB CIPLA.

Pregnancy

SUNITINIB CIPLA is contraindicated in pregnancy as safety has not been demonstrated.

Breastfeeding

SUNITINIB CIPLA is secreted in breast milk. Women using SUNITINIB CIPLA should not breastfeed their infants, because of the potential for serious adverse reactions in nursing infants.

Fertility

Based on the findings of pre-clinical studies, fertility in males and females may be compromised by treatment with SUNITINIB CIPLA**.**

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or operate machinery have been performed. Patients should be advised that they may experience dizziness during treatment with SUNITINIB CIPLA.

4.8 Undesirable effects

Summary of the safety profile

The most important serious adverse events associated with sunitinib treatment of solid tumour patients were pulmonary embolism, thrombocytopenia, tumour haemorrhage, febrile neutropenia, and hypertension.

Frequent adverse events included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; rash; hand-foot syndrome (palmarplantar erythrodysaesthesia); dry skin; hair colour changes; mucosal inflammation; asthenia; dysgeusia; anorexia and hypertension.

Fatigue, hypertension and neutropenia were the frequent adverse events of Grade 3 maximum severity; and increased lipase was the frequently occurring adverse event of Grade 4 maximum severity in patients with solid tumours.

Infections and infestations

Frequent:	Infections*, viral infections[a], respiratory infections[b,**], abscess[c,**], fungal infections[d], urinary tract infection, skin infections[e], sepsis[f,**].
Less frequent:	Necrotising fasciitis**, bacterial infections[g].

Blood and lymphatic system disorders

Frequent:	Neutropenia, leukopenia, thrombocytopenia, anaemia, lymphopenia.
Less frequent:	Pancytopenia, thrombotic microangiopathy[h]**.

Immune system disorders

Less frequent:	Hypersensitivity, angioedema.

Endocrine disorders

Frequent:	Hypothyroidism.
Less frequent:	Hyperthyroidism, thyroiditis.

Metabolism and nutrition disorders

Frequent: Decreased appetite[i], dehydration, hypoglycaemia.

Less frequent: Tumour lysis syndrome**.

Psychiatric disorders

Frequent: Insomnia, depression.

Nervous system disorders

Frequent: Dysgeusia[j], headache, dizziness, paraesthesia, peripheral neuropathy, hypoaesthesia, hyperaesthesia.

Less frequent: Cerebral haemorrhage**, cerebrovascular accident**, transient ischaemic attack, cerebral infarction, reversible posterior encephalopathy syndrome**, ageusia.

Eye disorders

Frequent: Periorbital oedema, eyelid oedema, increased lacrimation.

Cardiac disorders

Frequent: Myocardial ischaemia[k, **], decreased ejection fraction[l].

Less frequent: Myocardial infarction[m, **], cardiac failure**, congestive cardiac failure, prolonged electrocardiogram QT, pericardial effusion cardiomyopathy**, left ventricular failure**, torsade de pointes.

Vascular disorders

Frequent:	Hypertension, deep vein thrombosis, hot flush, flushing.
Less frequent:	Tumour haemorrhage**.
Frequency unknown:	Aneurysms and artery dissections**.

Respiratory, thoracic and mediastinal disorders

Frequent:	Dyspnoea, epistaxis, cough, oropharyngeal pain[n], haemoptysis[o**], pulmonary embolism**, pleural effusion**, exertional dyspnoea, nasal congestion, nasal dryness.
Less frequent:	Pulmonary haemorrhage**, respiratory failure**.

Gastrointestinal disorders

Frequent:	Diarrhoea, nausea, vomiting, abdominal pain[p], stomatitis[q], constipation, dyspepsia, gastrointestinal haemorrhage**, oesophagitis**, gastro-oesophageal reflux disease, oral pain, glossodynia, abdominal distension, gingival bleeding, dry mouth, flatulence, dysphagia, abdominal discomfort, rectal haemorrhage, mouth ulceration, proctalgia, cheilitis, haemorrhoids, oral discomfort, eructation.
Less frequent:	Pancreatitis, gastrointestinal perforation[r]**, anal fistula, colitis[s]

Hepato-biliary disorders

Less frequent: Cholecystitis[t]**, hepatic failure**, abnormal hepatic function, hepatitis.

Skin and subcutaneous tissue disorders

Frequent: Hand-foot syndrome (Palmar-plantar erythrodysaesthesia syndrome), skin discolouration[u], rash[v], hair colour changes, dry skin, alopecia, erythema, pruritus, skin exfoliation, blister, skin lesion, skin reaction[w], nail disorder[x], eczema, acne, skin hyperpigmentation, hyperkeratosis, dermatitis.

Less frequent: Exfoliative dermatitis, erythema multiforme**, Stevens-Johnson Syndrome**, pyoderma gangrenosum, toxic epidermal necrolysis**.

Musculoskeletal and connective tissue disorders

Frequent: Pain in extremity, arthralgia, back pain, musculoskeletal pain, muscle spasms, myalgia, muscular weakness.

Less frequent: Osteonecrosis of jaw, fistula formation**, rhabdomyolysis**, myopathy.

Renal and urinary disorders

Frequent: Renal failure**, acute renal failure**, chromaturia, proteinuria.

Less frequent: Renal impairment, urinary tract, haemorrhage, nephrotic syndrome.

General disorders and administration site conditions

Frequent:	Fatigue[y], mucosal inflammation, oedema[z], pyrexia, chills, influenza like illness, chest pain, pain.
Less frequent:	Impaired healing.

Investigations

Frequent:	Increased lipase, increased amylase[za], increased blood uric acid, decreased white blood cell count, decreased platelet count, decreased haemoglobin, decreased weight, increased aspartate aminotransferase, increased alanine aminotransferase, increased blood creatinine, increased blood pressure.
Less frequent:	Increased blood creatine phosphokinase, increased blood thyroid stimulating hormone.

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, haemolytic uraemic syndrome.

[i] Decreased appetite and anorexia.

[j] Dysgeusia, ageusia, and taste disturbance.

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

[l] Decreased ejection fraction and abnormal ejection fraction.

[m] Acute myocardial infarction, myocardial infarction, silent myocardial infarction.

[n] Pharyngolaryngeal pain and oropharyngeal pain.

[o] Haemoptysis and pulmonary haemorrrhage.

[p] Abdominal pain, lower abdominal pain, upper abdominal pain

[q] Stomatitis and aphthous stomatitis

[r] Gastrointestinal perforation and intestinal perforation

[s] Colitis and colitis ischaemic.

[t] Cholecystitis and acalculous cholecystitis.

[u] Skin discolouration, yellow skin, pigmentation disorder.

[v] Dermatitis psoriasiform, exfoliative rash, rash, erythematous rash, follicular rash, generalised rash, macular rash, maculo-papular rash, rash papular, pruritic rash.

[w] Skin reaction and skin disorder.

[x] Nail disorder and discolouration.

[y] Fatigue and asthenia.

[z] Face oedema, oedema, peripheral oedema.

[za] Amylase, increased amylase.

* Infections and infestations are described in the post-marketing experience section.

** Event may be fatal.

Post-marketing experience

The following adverse events have been identified during post-approval use of sunitinib.

Description of selected adverse reactions

Infections and infestations

Cases of serious infection (with or without neutropenia) in some cases with fatal outcome have been reported.

The infections frequently observed with sunitinib treatment were respiratory infections (e.g., pneumonia, bronchitis), urinary tract infections, skin infections (e.g., cellulitis) sepsis/septic shock and abscess (e.g., oral, genital, anorectal, skin, limb, visceral). Infections may be bacterial or fungal. Cases of necrotising fasciitis, including of the perineum, sometimes fatal, have been reported (see **section 4.4**).

Blood and lymphatic system disorders

Cases of thrombotic microangiopathy, in some cases with fatal outcome and haemolytic uraemic syndrome have been reported. Temporary suspension of SUNITINIB CIPLA is

recommended. Following resolution, treatment may be resumed at the discretion of the treating medical practitioner.

Immune system disorders

Hypersensitivity reactions, including angioedema.

Endocrine disorders

Cases of hyperthyroidism, some followed by hypothyroidism, have been reported in clinical trials and through post-marketing experience (see **section 4.4**). Cases of thyroiditis have been reported.

Metabolism and nutrition disorders

Cases of Tumour Lysis Syndrome, some fatal, have been reported in patients treated with sunitinib. Decreases in blood glucose, in some cases clinically symptomatic, have been reported during sunitinib treatment.

Nervous system disorders

Taste disturbance, including ageusia.

Cardiac disorders

Cardiac failure, congestive cardiac failure, prolonged QT interval and torsade de pointes have been reported. Cardiomyopathy, myocardial ischaemia, left ventricular failure and myocardial infarction, in some cases with fatal outcome, have been observed.

Vascular disorders

Cases of arterial thromboembolic events, sometimes fatal, have been reported in patients treated with sunitinib. Frequent events included cerebrovascular accident, transient ischaemic attack and cerebral infarction. Risk factors associated with arterial thromboembolic events, in addition to the underlying malignant disease and age ≥ 65 years, included hypertension, diabetes mellitus and prior thromboembolic disease.

Respiratory, thoracic and mediastinal disorders

Pulmonary embolism, in some cases with fatal outcome.

Gastrointestinal disorders

Pancreatitis, gastrointestinal perforation, oesophagitis.

Hepato-biliary disorders

Hepatic failure and cholecystitis, particularly acalculous cholecystitis have been reported.

Skin and subcutaneous tissue disorders

Cases of pyoderma gangrenosum, erythema multiforme and Stevens-Johnson syndrome have been reported.

Musculoskeletal and connective tissue disorders

Cases of myopathy and/or rhabdomyolysis, with or without acute renal failure, in some cases with fatal outcome have been reported. Most of these patients had pre-existing risk factors and/or were receiving concomitant medicines known to be associated with these adverse reactions. Patients with signs or symptoms of muscle toxicity should be managed as per standard medical practice.

Cases of fistula formation, sometimes associated with tumour necrosis and/or regression, in some cases with fatal outcome.

Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with sunitinib, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to IV bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see **section 4.4**).

Renal and urinary disorders

Cases of renal impairment and/or failure, in some cases with fatal outcome. Cases of proteinuria and cases of nephrotic syndrome have been reported (see **section 4.4**).

Investigations

Increased TSH and increased blood uric acid have been reported.

Haemorrhagic events

Cases of pulmonary, gastrointestinal, tumour, urinary tract, and brain haemorrhage, some fatal, have been reported in patients treated with sunitinib.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

There is no specific antidote for overdosage with sunitinib as in SUNITINIB CIPLA.

Treatment of overdose is symptomatic and supportive. Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known adverse effects profile of sunitinib (see **section 4.8**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic Agents

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors.

Sunitinib malate is a small molecule that simultaneously inhibits multiple receptor tyrosine kinases (RTKs) that are implicated in tumour growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (> 80 kinases) and was identified as a potent inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Inhibition of the tyrosine kinase activity of these RTKs by sunitinib has been demonstrated in biochemical and cellular assays, and inhibition of function has been demonstrated in cell proliferation assays.
The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib malate demonstrated inhibition of activity of target RTKs (PDGFR β, VEGFR2, KIT) in tumours *in vivo* and demonstrated the ability to inhibit tumour growth, cause tumour regression, and/or inhibit metastatic progression in a variety of rodent cancer models. Consistent with its multi-targeted profile, sunitinib malate demonstrated the ability to directly inhibit growth of tumour cells expressing dysregulated RTK targets (PDGFR, RET, or KIT) and to inhibit PDGFR β- and VEGFR2-dependent tumour angiogenesis.

5.2 Pharmacokinetic properties

Absorption

Sunitinib is absorbed after oral administration with maximum concentrations (C_{max}) generally observed from 6 - 12 hours (T_{max}) post-dose. Food has no effect on the bioavailability of sunitinib.

Distribution

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

Biotransformation

The calculated *in vitro* Ki values for all CYP isoforms tested (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 and CYP4A9/11) indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant interactions with medicines that may be metabolised by these enzymes.

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

Elimination

Excretion is primarily via faeces (61 %) with renal elimination of sunitinib and metabolites accounting for 16 % of the administered dose. Sunitinib and its primary active metabolite were the major sunitinib-related compounds identified in plasma, urine and faeces, representing 91,5 %, 86,4 % and 73,8 % of radioactivity in pooled samples, respectively.

Minor metabolites were identified in urine and faeces, but generally were not found in plasma. Total oral clearance (CL/F) was 34 - 62 L/hr.

Pharmacokinetics in special patient groups

Hepatic insufficiency

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 (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to subjects with normal hepatic function. Sunitinib has not been studied in patients with severe (Child-Pugh Class C) hepatic impairment.

Renal insufficiency

Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CL_{cr} < 30 mL/min) compared to subjects with normal renal function (CL_{cr} > 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.

The elimination half-lives of sunitinib and its primary active desethyl metabolite are approximately 40 - 60 hours, and 80 - 110 hours, respectively. In the dosing ranges of 25 to 100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionally with dose. With repeated daily administration, sunitinib accumulates 3- to

4-fold and its primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and is active metabolite are 62,9 - 101 ng/mL which are target concentrations predicted from preclinical data to inhibit receptor phosphorylation *in vitro* and result in tumour stasis/growth reduction *in vivo*. The primary active metabolite comprises 23 % to 37 % of the total exposure. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite are observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

Population pharmacokinetic analyses of demographic data indicate that no dose adjustments are necessary for weight, creatinine clearance, gender, race or ECOG score.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Croscarmellose sodium

Magnesium stearate

Mannitol

Povidone

Capsule shell

SUNITINIB 12,5 CIPLA: capsule shell size no.4 for LP650

SUNITINIB 25 CIPLA: capsule shell size no.3 for LP651

SUNITINIB 50 CIPLA: capsule shell size no.2 for LP653

Black iron oxide (E172)

Gelatin

Red iron oxide (E172)

Titanium dioxide (E171)

Yellow iron oxide (E172) (for SUNITINIB 25 CIPLA and SUNITINIB 50 CIPLA)

SUNITINIB 37,5 CIPLA: capsule shell size No. 2 for LP652

Gelatin

Titanium dioxide (E171)

FD&C yellow #6 (E110)

FD&C yellow #5 (E102)

Printing ink

SUNITINIB 12,5, 25, 50 CIPLA:

Shellac

Propylene glycol

Sodium hydroxide

Povidone

Titanium dioxide

SUNITINIB 37,5 CIPLA:

Shellac

Propylene glycol

Strong ammonia solution

Black iron oxide

Potassium hydroxide

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

The capsules are packed in:

- White PVC/Aclar-aluminium blisters. The blisters are packed in carton boxes containing 7 capsules per blister, packed in 28 capsules.
- HDPE bottles with PP caps containing 30 capsules per bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street,

Bellville, 7530,

RSA

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

SUNITINIB 12,5 Cipla: 56/26/0151

SUNITINIB 25 Cipla: 56/26/0152

SUNITINIB 37,5 Cipla: 56/26/0153

SUNITINIB 50 Cipla: 56/26/0154

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2023

Date of latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

Not applicable.