SUNitinib 50mg Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.	C26	00325a	CDS
Treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults	C64	00325b	CDS

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

The recommended dose of SUNitinib is 50mg once daily for 4 weeks followed by a 2 week rest period to comprise a complete cycle of 6 weeks.
Treatment is administered continuously until disease progression or unacceptable toxicity occurs.

Day	Drug	Dose	Route
1-28	SUNitinib	50mg daily	PO once daily at the same time every day, consistently either with or without food Swallow whole with a glass of water
29-42	REST PERIOD		

ELIGIBILTY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to SUNitinib, or any of the excipients
- Significant cardiovascular disease and/or LVEF < 55
- Uncontrolled hypertension
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- Thyroid Function tests
- Blood pressure
- MUGA scan or echocardiogram if clinically indicated or history of cardiac problems

Regular tests:

- FBC, renal and liver profile
- Thyroid function tests every 4 weeks
- Blood pressure weekly for first 6 weeks and then every 4 weeks
- MUGA scan or echocardiogram as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- For GIST and MRCC, dose modifications in 12.5 mg steps may be applied based on individual safety and tolerability.
  - Dose level -1 : 37.5mg
  - Dose level -2 : 25mg
- Daily dose should not be decreased below 25 mg.
- A dose increase to a maximum of 87.5 mg (GIST and RCC) should be considered if SUNitinib must be co-administered with a CYP3A4 inducer. If dose is increased, the patient should be monitored carefully for toxicity.
- Co-administration of SUNitinib with potent CYP3A4 inhibitors, should be avoided. If this is not possible, the dose of SUNitinib may need to be reduced to a minimum of 37.5mg daily for GIST and RCC mg based on careful monitoring of tolerability.
- Dose interruptions may be required based on individual safety and tolerability.

Haematological:

Table 1: Dose modification of SUNitinib in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥ 1	and	≥ 75	100%
<1	or	< 75	Delay

Renal and hepatic impairment:

Table 2: Dose modification of SUNitinib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment	
No starting dose adjustment is required when administering SUNitinib to patients with renal impairment (mild-severe) or with end-stage renal disease (ESRD) on haemodialysis. Subsequent dose adjustments should be based on individual safety and tolerability	Child Pugh Class A	No starting dose adjustment required
	Child Pugh Class B	
	Child Pugh Class C	Not recommended

Management of adverse events:

Table 3: Dose Modification of SUNitinib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 1-2 reactions	100%
Grade 3-4 reaction	Delay until Grade 1 Dose reduce by 1 dose level

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Minimal - Low (**Refer to local policy).**

PREMEDICATIONS: None required

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment may be required

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Cardiac Toxicity:** Cardiovascular events, including heart failure, cardiomyopathy, and myocardial ischemia 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. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUNitinib.
- 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 prolongation:** QT interval prolongation may lead to an increased risk of ventricular arrhythmias including Torsade de pointes. Torsade de pointes has been observed in <0.1% of SUNitinib-exposed patients. 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
- **Hypertension:** 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.
- **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.
- **Hypothyroidism:** 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. 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.

- **Skin and tissue disorders:** Skin discolouration, possibly due to the active substance colour (yellow), is a very common adverse reaction occurring in approximately 30% of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with SUNitinib. 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. The above reactions were not cumulative, were typically reversible and generally did not result in treatment discontinuation.
- Cases of pyoderma gangrenosum, generally reversible after drug discontinuation, have been reported. Severe cutaneous reactions have been reported, including cases of erythema multiforme (EM) and 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 re-started. 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.
- **Wound healing:** This treatment may impair wound healing and temporary interruption of treatment is recommended in patients undergoing major surgical procedures.
- **Haemorrhage and tumour bleeding:** Haemorrhagic events, some of which were fatal, reported through post-marketing experience have included gastro-intestinal, respiratory, urinary tract and brain haemorrhages. Patients receiving concomitant treatment with anticoagulants) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR) and physical examination.

DRUG INTERACTIONS:

- Co-administration with potent CYP3A4 inducers should be avoided because it may decrease SUNitinib plasma concentration.
- Limited clinical data are available on the interaction between SUNitinib and BCRP inhibitors and the possibility of an interaction between SUNitinib and other BCRP inhibitors cannot be excluded.
- Co-administration with potent CYP3A4 inhibitors should be avoided because it may increase the plasma concentration of SUNitinib.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

SUNitinib L01XE04

REFERENCES:

1. Demetri, GD., van Oosterom, AT, et al. Efficacy and safety of SUNitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;. 368(9544): 1329-1338.
2. Choueiri TK et al. Efficacy of SUNitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. J Clin Oncol 2008; 26:127
3. Motzer R, et al: Phase III randomized trial of SUNitinib malate (SU11248) versus interferon-alfa (IFN-a) as first-line systemic therapy for patients with metastatic renal cell carcinoma. NEJM 356;2: 115-124, 2007

4. Sunitinib (SUTENT®) Summary of Product Characteristics. Last updated: 27Nov2019. Accessed May 2020 Available at https://www.ema.europa.eu/en/documents/product-information/sutent-epar-product-information_en.pdf
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	30/05/2018	Updated with new NCCP regimen template and drug interations	Prof Maccon Keane
3	23/10/2019	Updated adverse effects/regimen specific events regarding aortic aneurysms and dissections as per SmPC update	Prof Maccon Keane
4	13/05/2020	Update of emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.