Optimising Care for Patients on SUTENT® (Sunitinib Malate) in Metastatic Renal Cell Carcinoma

Pocket guide to managing side effects in first-line SUTENT® treatment of patients with metastatic renal cell carcinoma

SUR416
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Prescribing information can be found at the end of the document

For more information on the use of Pfizer products in the treatment of advanced RCC, please visit www.renaloncology.com
This site is intended for UK Healthcare Professionals only
This quick-reference pocket guide has been designed to assist in the therapy management of patients with advanced and/or metastatic renal cell carcinoma (RCC) who are treated with SUTENT®.

Together with patient education, measures to prevent and manage side effects associated with SUTENT® therapy are critical for effective disease management. These measures may reduce the need for dose reductions, delays, interruptions or early treatment discontinuations, and thereby optimise clinical benefit from SUTENT® therapy.

This guide provides advice to support the treating healthcare professional team for the prevention, identification and treatment of key side effects associated with SUTENT®, with the aim of preventing or reducing their severity and improving treatment tolerability.

Please see the Summary of Product Characteristics for full safety information.

### Contents

- **Stomatitis**
- **Hand-foot skin reactions**
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- **Gastrointestinal side effects**
- **Blood disorders/dyscrasias**
- **Fatigue and hypothyroidism**
- **Skin and hair changes**

Stomatitis is an inflammation of the mucous lining of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips, throat, and roof or floor of the mouth.

Hand-foot skin reactions are characterised by red, swollen and painful skin (sometimes with blisters, cracks and/or peeling) and can include palmar-plantar erythema and acral erythema.

Cardiovascular side effects during SUTENT® treatment include decreases in left ventricular ejection fraction, heart failure, prolonged QT interval, arrhythmias and hypertension.

Gastrointestinal side effects associated with SUTENT® therapy include acid indigestion, nausea, bloating, constipation, diarrhoea, sore mouth, vomiting and flatulence.

Blood disorders/dyscrasias are characterised by neutropaenia, thrombocytopaenia, anaemia and leukopaenia.

Fatigue is very common with SUTENT® treatment and can be signalled by changes in patient activities and attention on the phone or in the clinic. Hypothyroidism can be characterised by symptoms of fatigue, swelling around the eyes, dry skin, shortness of breath and feeling cold.

Skin and hair changes include hand-foot skin reactions, rash, dry skin, nail modifications, and skin and hair discolouration.

Select a tab to learn more about the prevention, assessment and treatment of each side effect associated with SUTENT®.
MANAGING STOMATITIS
Stomatitis

**WHAT IS IT?**

• An inflammation of the mucous lining of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips, throat, and roof or floor of the mouth.

• Distinct from chemotherapy-related stomatitis; the signs are less obvious, but the symptoms are pronounced and appear to extend through the gastrointestinal tract.

• 2.7% of patients experienced Grade 3/4 stomatitis in SUTENT® clinical trials.

• Typically manifests early, within days/weeks of initiating treatment.

• Often resolves during the 2-week break between cycles, although tends to recur in subsequent cycles.

**PREVENTION**

• Before starting SUTENT® therapy, help patients to minimise risk/severity of stomatitis by encouraging:
  - Good oral hygiene, including regular visits to the dentist
  - Dietary modifications, such as:
    - Avoid hot foods
    - Avoid spicy foods
    - Avoid acidic foods and alcohol
    - Eat little and often
    - Drink cool liquids, and keep fluid intake high

**SIGNS AND SYMPTOMS**

• Damage to the mouth area, such as bleeding gums and mouth ulcers.

• General sensitivity in the mouth, which feels sore, or alterations to taste.

• Experiencing pain, particularly when eating or brushing teeth.

**ASSESSMENT**

• Confirm the presence of stomatitis.

• Take a full history to check concomitant medications and assess/stabilise co-morbidities.

• Assess the severity of stomatitis and how its impact may differ from patient to patient (see Table 1).

**TREATMENT**

• In addition to preventative measures, encourage patients to:
  - Use baby toothpaste and brushes
  - Use bicarbonate-based mouthwashes, e.g. manuka honey or sodium bicarbonate in water (commercial mouthwashes are often too astringent)
  - Use lip creams/balms
  - Eat soft foods that are at room temperature
  - Consider super-cooled items that may relieve symptoms, such as frozen pineapple chunks
  - Eat with a spoon rather than a fork; drink using a straw

• Patients may also need:
  - Aspirin mouthwash (mucilage) as local analgesic (do not swallow; contraindicated in patients who are haematologically compromised)
  - ‘Magic’ mouthwash containing equal parts of 2% viscous lidocaine, diphenhydramine, and bismuth subsalicylate or aluminum/magnesium hydroxide
  - Anti-inflammatories
  - Nystatin for oral thrush
  - Artificial saliva for dry mouth

**QUESTIONS FOR YOUR PATIENTS**

Do you get more mouth ulcers than usual?

Inflammation of the oral cavity and mouth ulcers can be an indication of stomatitis or other oral changes.

In your mouth sore or painful?

Patients may experience pain, but lack physical signs of functional stomatitis.

Does it hurt when you eat certain foods?

Encourage your patients to avoid hot, spicy foods and alcohol.

Do your gums bleed when you brush your teeth?

Encourage your patients to use gentle toothbrushes and sodium bicarbonate-based mouthwashes.

**TABLE 1: GRADING STOMATITIS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
</tr>
<tr>
<td>2</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
</tr>
<tr>
<td>3</td>
<td>Severe pain; interfering with oral intake</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

**TABLE 2: PATIENT MANAGEMENT STRATEGIES FOR STOMATITIS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue at same dose level</td>
</tr>
<tr>
<td>2</td>
<td>Reduce dose or interrupt treatment</td>
</tr>
<tr>
<td>3</td>
<td>Reduce dose or interrupt treatment</td>
</tr>
<tr>
<td>4</td>
<td>Reduce dose or interrupt treatment</td>
</tr>
</tbody>
</table>

**DOESAGE**

• Oral changes are reversible and do not usually require treatment discontinuation.

• However, progression to Grade 3/4 stomatitis requires dose reduction or treatment interruption.

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**SIDE EFFECTS**

- Oral changes are reversible and do not usually require treatment discontinuation.
- However, progression to Grade 3/4 stomatitis requires dose reduction or treatment interruption.
MANAGING HAND–FOOT SKIN REACTIONS
WHAT ARE THEY?

- Include palmar–plantar erythema or acral erythema
- Very common with SUTENT® therapy, typically occurs early (Cycle 1/2) and is distinct from chemotherapy-related hand–foot skin reactions; lesions are more localized and hyperkeratotic
- Often mild to moderate, but can be debilitating (7.7% Grade 3/4 in SUTENT® clinical trials)
- More pronounced on the feet of active people and in hot climates
- Uncomfortable and can impair daily activities
- Preventable if patients are adequately educated and easily treated if reported early

PREVENTION

- Before starting SUTENT® therapy, help patients to minimize risk/severity of hand–foot skin reactions; encourage them to:
  - Take good care of their skin; wash gently with baby soaps and shampoos, and regularly apply moisturising emollients (available from chemists)
  - Wear cotton or rubber gloves for housework, washing up, etc
  - Keep skin cool
  - Keep feet bare or wear cotton socks and comfortable shoes
  - Visit a chiropodist prior to beginning SUTENT® therapy for a podiatry review and to remove calluses

SIGNS AND SYMPTOMS

- Hand–foot skin reactions usually occur on the palms of hands and soles of feet, but may affect other areas
- Typically feet are more affected than hands
- Skin can become red, swollen and painful— sometimes with blisters, cracks and/or peeling
- Hand–foot skin reactions are commonly preceded or accompanied by paraesthesia, tingling or numbness

ASSESSMENT

- Confirm the presence of hand–foot skin reactions
- Hand–foot skin reactions often occur in the first 2–4 weeks of SUTENT® therapy
- Take a full history to check concomitant medications and assess/stabilise co-morbidities
- Assess severity of hand–foot skin reactions; its impact may differ from patient to patient. Use the grading table to assess severity (see Table 3)

QUESTIONS FOR YOUR PATIENTS

- Have you felt any tingling sensations?
- Skin changes are often preceded by a tingling sensation in the hands and feet
- Can you hold a cup of tea? Is wearing shoes unbearable?
- What are your hand–foot skin reactions preventing you from doing?
- It is important to assess the severity of hand–foot skin reactions for each individual
- Are you noticing any skin changes, such as change in colour, feel or sensation?
- Encourage your patients to examine their skin regularly and discuss any changes or concerns that they have with you at clinic and phone in between visits
- Do you have any skin changes in other areas?
- Remember that skin changes may occur in areas of the body that patients may not want to immediately disclose
- How does your hand–foot skin reaction affect your everyday life?
- The severity and impact of hand–foot skin reactions may differ from patient to patient

TABLE 3: GRADING HAND–FOOT SKIN REACTIONS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal skin changes (e.g. erythema, oedema or hyperkeratosis) without pain</td>
</tr>
<tr>
<td>2</td>
<td>Skin changes (e.g. peeling, blisters, bleeding, oedema or hyperkeratosis) with pain, limiting instrumental activities of daily living</td>
</tr>
<tr>
<td>3</td>
<td>Severe skin changes (e.g. peeling, blisters, bleeding, oedema or hyperkeratosis) with pain, limiting self-care activities of daily living</td>
</tr>
</tbody>
</table>

TREATMENT

- Provide supportive advice to patients if they suffer hand–foot skin reactions. Reinforce preventative advice (see prevention) and further encourage patients to:
  - Avoid/reduce activities that put a lot of pressure on the affected areas
  - Wear loose, comfortable clothes and shoes, and use gel/soft insoles
  - Avoid strong sunlight or extreme heat (including very hot baths)
  - Protect tender areas, pressure points with padding, foam absorbents and shock absorbers
- Relief from symptoms can be found using:
  - Topical painkillers (e.g. ibuprofen) combined with a petrolatum jelly-based ointment for patients experiencing severe pain
  - Moisturising emollients and urea-based creams, especially for the feet
  - Topical skin adhesives (medical superglue) applied to cracks and painful areas
- Daily foot soaks in lukewarm water with Epsom salts for 20–30 minutes
DOSAGE

- **SUTENT®** dose interruptions/reductions from the recommended 50 mg daily dosing can be avoided or minimised using therapy management, helping patients to gain optimal benefit.

- Some patients may require a **SUTENT®** dose adjustment or treatment break based on severity of hand–foot skin reactions (see Table 4).

- The severity of hand–foot skin reactions needs to be weighed up against the benefits of maintaining the recommended **SUTENT®** dosing schedule.

- Once hand–foot skin reactions have resolved, consider re-initiating or re-establishing **SUTENT®** treatment at 50 mg daily.

- If a patient believed to have hand–foot skin reactions does not respond to dose interruption or dose reduction, then other diagnoses must be considered.

**TABLE 4: MANAGEMENT STRATEGIES FOR HAND–FOOT SKIN REACTIONS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue at same dose level</td>
</tr>
<tr>
<td></td>
<td>Treat with emollient creams and encourage measures to avoid skin irritation</td>
</tr>
<tr>
<td>2</td>
<td>Treat with emollient creams and encourage measures to avoid skin irritation</td>
</tr>
<tr>
<td></td>
<td>Consider a <strong>SUTENT®</strong> dose reduction</td>
</tr>
<tr>
<td>3</td>
<td>Consider a <strong>SUTENT®</strong> dose reduction or treatment break until Grade ≤1</td>
</tr>
<tr>
<td></td>
<td>Resume treatment at reduced dose</td>
</tr>
</tbody>
</table>

HAND–FOOT SKIN REACTIONS

MANAGING CARDIOVASCULAR SIDE EFFECTS AND HYPERTENSION
 WHAT ARE THEY?

CARDIOVASCULAR SIDE EFFECTS

• Decreases in left ventricular ejection fraction (LVEF) of greater than or equal to 20% and below the lower limit of normal – 2.1% of patients at all grades
• Heart failure has been reported in mRCC clinical trials and in post-marketing experience
• SUTENT® has the potential to prolong the QT interval
• Arrhythmias – incidence <1% (e.g. bradycardia and torsades de pointes)
• Cardiovascular side effects associated with SUTENT® are generally reversible on stopping treatment

HYPERTENSION

• Associated with SUTENT®, typically manifests early (within days/weeks of initiating treatment) and is usually mild to moderate (Grade 2/3)
• Occurred in 28% of patients at all grades, 7.1% of patients at Grade 3 and 0.2% of patients at Grade 4 in clinical trials with SUTENT®
• Exact aetiology unknown when caused by SUTENT® treatment

PREVENTION

• Normalise pre-existing hypertension prior to starting SUTENT® therapy
• Close monitoring is recommended for patients with cardiac risk factors and/or history of coronary artery disease
• Encourage patients to keep a diary of their blood pressure and report any signs of hypertension to staff
• Before starting SUTENT® treatment, help patients to minimise risk/severity of cardiovascular side effects/hypertension – encourage them to:
  – Exercise regularly
  – Control their weight
  – Consider a Mediterranean diet
  – Moderate their alcohol consumption
  – Reduce their salt intake to less than 2 g/day

QUESTIONS FOR YOUR PATIENTS

Have you taken your blood pressure this week?
Encourage your patients to monitor their blood pressure and keep a diary of their blood pressure readings
Have you felt short of breath, very tired or any swelling of the hands and feet since taking SUTENT®?
These symptoms may indicate a cardiovascular side effect and will require urgent attention
Have you had a persistent headache or felt any dizziness since taking SUTENT®?
These symptoms may indicate a cardiovascular side effect and will require urgent attention

SIGNS AND SYMPTOMS

CARDIOVASCULAR SIDE EFFECTS

• Shortness of breath
• Extreme fatigue
• Swelling of the hands or feet

HYPERTENSION

• Persistent headache
• Dizziness
• Usually asymptomatic

Advertise your patients to report any of the above signs and symptoms to you immediately. They should ring the clinic and not wait for their next hospital appointment.

ASSESSMENT

• Conduct a full cardiovascular assessment, including baseline ECG and LVEF evaluation, and monitor throughout treatment
• Screen for hypertension, stabilise blood pressure and monitor throughout treatment
• Blood pressure should be monitored weekly for the first 4 weeks and monthly thereafter, ideally by patients themselves or in primary care
• Perform risk/benefit analysis based on cardiovascular risk factors/ coronary artery disease history
• Take a full history to check concomitant medications and assess or stabilise co-morbidities
• Assess severity of hypertension – its impact may differ from patient to patient (see Table 5 for the grading criteria for hypertension)

BP=blood pressure; ULN=upper limit of normal

TABLE 5: GRADING HYPERTENSION

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg)</td>
</tr>
<tr>
<td>2</td>
<td>Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg; medical intervention indicated; occur/occurred in &lt;1% races); asymptomatic increase in systolic BP &gt;20 mmHg (diastolic) or to &gt;140/90 mmHg if previously within normal limits; monotherapy indicated</td>
</tr>
<tr>
<td>3</td>
<td>Stage 2 hypertension (systolic BP &gt;160 mmHg or diastolic BP &gt;100 mmHg; medical intervention indicated; more than one drug or more intensive therapy than previously used/indicated)</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; urgent intervention indicated)</td>
</tr>
</tbody>
</table>

CONTINUE
TREATMENT

- Reinforce preventative advice and further encourage patients to consider non-pharmacological measures in the first instance (see prevention)12
- SUTENT® dose interruptions/reductions from the recommended 50 mg daily dosing can be avoided or minimised through careful SUTENT® therapy management thereby helping patients to gain optimal benefit7
- Some patients may require SUTENT® dose adjustment or treatment break based on severity of their cardiovascular side effects/hypertension (see Table 6)2,5
- The severity of the cardiovascular side effects/hypertension needs to be weighed up against the benefits of maintaining the recommended SUTENT® dosing schedule

CARDIOVASCULAR SIDE EFFECTS

- Interrupt/reduce SUTENT® dose in patients with clinical evidence of chronic heart failure if LVEF <50% and >20% below baseline1,2

HYPERTENSION

- Temporarily suspend SUTENT® in patients with severe uncontrolled hypertension that is not controlled with medical management; treatment may resume once hypertension is controlled2,7
- If prescribed, antihypertensive treatment may need to be reduced during off-treatment periods and stopped altogether when not taking SUTENT®, to prevent postural hypotension4

MANAGING GASTROINTESTINAL SIDE EFFECTS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue at same dose level</td>
</tr>
</tbody>
</table>
| 2     | Continue at same dose level, except in the event of:  
  - Asymptomatic decreases in LVEF to an absolute value of 20% and below lower limit of normal OR  
  - Non-urgent paroxysmal ventricular dysrythmia requiring intervention suspend SUTENT® therapy until Grade ≤1 THEN resume at –1 dose level |
| 3     | Interrupt SUTENT® therapy until Grade ≤1 or return to baseline  
  Resume at –1 dose level |
| 4     | Discontinue |

TABLE 6: MANAGEMENT STRATEGIES FOR CARDIAC TOXICITY
GASTROINTESTINAL SIDE EFFECTS

• Gastrointestinal side effects include: nausea, diarrhoea, flatulence, constipation, vomiting, dyspepsia, abdominal pain.

PREVENTION

• Before starting SUTENT™ therapy, help patients to minimise the risk and severity of gastrointestinal side effects by encouraging them to:
  - Adjust their diet – bananas, rice, grated apple and toast can increase stool consistency
  - Take a full history to check concomitant medications and reinforce preventative advice
  - Avoid grapefruit or its juice since these will increase plasma concentrations of SUTENT

SIGNS AND SYMPTOMS

• Loss of appetite, generally caused by altered taste, tends to manifest during the first few treatment cycles

ASSESSMENT

• Confirm the presence of gastrointestinal symptoms
• Take a full history to check concomitant medications and assess/stabilise co-morbidities
• Assess severity of gastrointestinal symptoms since their impact may differ from patient to patient (see Table 7)

QUESTIONS FOR YOUR PATIENTS

Have you suffered from a loss of appetite since starting treatment?

This may be due to a variety of reasons, such as nausea, taste changes and pain while eating

Have you had constipation since starting treatment?

Changes in bowel movements are very common with SUTENT®, but symptoms are usually mild to moderate

Have you felt nauseous or been sick since starting treatment?

Nausea is not usually experienced after the first few treatment cycles

TREATMENT

• Patients should be made aware that both diarrhoea and constipation are associated with SUTENT®
• Patient education regarding nutrition and consultation with a dietician can be recommended
• SUTENT® dose interruptions/reductions from the recommended 50 mg daily dosing can be avoided or minimised using therapy management, helping patients to gain optimal benefit (see Table 8 for advice on diarrhoea)
• Provide supporting advice to patients if they suffer gastrointestinal side effects and reinforce preventative advice

NAUSEA AND VOMITING

• 34.6% of patients experience nausea at all Grades, 4% experience Grade 3, 0.2% experience Grade 4

• Any grade diarrhoea, stomatitis and painful tongue sensation (glossitis) occurred in 23.3% and 6.0% of patients, respectively

• Any grade dryness, abdominal pain and constipation occurred in 22.0, 30.4 and 23.2% of patients, respectively

• Grade 4 was observed in 0.2% of cases – Grade 3 was observed in 6.0% of cases and Grade 2 in 32.6% of cases

• 22.0, 30.4 and 23.2% of patients experience nausea at all Grades, 4% experience Grade 3; 0.2% experience Grade 4

• Changes in bowel movements are very common with SUTENT®, but symptoms are usually mild to moderate

• Any grade diarrhoea, stomatitis and painful tongue sensation (glossitis) occurred in 23.3% and 6.0% of patients, respectively

• Any grade dryness, abdominal pain and constipation occurred in 22.0, 30.4 and 23.2% of patients, respectively
DIARRHOEA

• Encourage patients to:
  – Temporarily discontinue the use of stool softeners or fibre supplements, as required
  – Eat and drink often in small amounts
  – Drink plenty of liquids (approx. 2–2.5 L/day, in small amounts at a time) and avoid drinking fluids with meals and for 1 hour after meals
  – Avoid spicy, high-fibre and fatty foods, and caffeine
  – Use anti-diarrhoeal treatments (e.g. loperamide), as required
  – Eat live yoghurt and other acidophilus products
  – Keep a diary to help monitor their bowel movements and highlight any factors that may make symptoms worse
  – Apply barrier creams (e.g. Sudocrem, Drapolene, Vaseline, aloe vera)
  – Use local anaesthesia (e.g. lignocaine gel)
  – Resolves quickly in the 2-week treatment break

OTHER GASTROINTESTINAL DISORDER

• Oral mucositis/stomatitis and burning tongue sensation:
  – Take plenty of fluids; use children’s or cheap toothpaste with no additives; and avoid salty, spicy, too hot or too cold foods and drinks

• Dysgeusia:
  – Peppermint and antacids, according to local prescribing policy

• Abdominal pain:
  – Analgesia and antispasmodics

• Constipation:
  – Fluids, diet, exercise and mild laxatives

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>Continue at same dose level; Oral hydration in small amounts at a time + anti-diarrhoeal medications</td>
</tr>
<tr>
<td>2*</td>
<td>Continue at same dose level; Oral hydration in small amounts at a time + anti-diarrhoeal medications</td>
</tr>
<tr>
<td>3</td>
<td>Interrupt SUTENT® therapy until Grade ≤1; Resume SUTENT® dose at –1 dose level (12.5 mg) in subsequent cycles in cases of Grade 3 or 4 diarrhoea</td>
</tr>
<tr>
<td>4</td>
<td>Interrupt SUTENT® therapy until Grade ≤1; Resume SUTENT® dose at –1 dose level (12.5 mg) in subsequent cycles in cases of Grade 3 or 4 diarrhoea</td>
</tr>
</tbody>
</table>

* Dose reductions are rarely necessary for Grade 1 and 2 toxicities.
**WHAT ARE THEY?**

- Blood disorders/dyscrasias such as neutropaenia, thrombocytopaenia, anaemia and leukopaenia have been associated with SUTENT® treatment.

**NEUTROPAENIA AND THROMBOCYTOPAENIA**

- Occurred at all grades in 17.2% (neutropaenia) and 22.0% (thrombocytopaenia) of patients receiving SUTENT® clinical trials.
  - Grade 4 neutropaenia and thrombocytopaenia occurred in 0.6 and 1.6% of patients, respectively.
  - Typically manifested early, during the first treatment cycle, without progression during later cycles.
  - SUTENT®-induced neutropaenia and thrombocytopaenia usually resolve during the 2-week treatment break.

**ANAEMIA**

- Anaemia occurred at all grades in 23.9% of patients receiving SUTENT® in clinical trials.
  - Grade 4 anaemia occurred in 1.4% of patients.

**LEUKOPAENIA**

- Leukopaenia occurred at all grades in 10.2% of patients receiving SUTENT® in clinical trials.
  - Grade 4 leukopaenia was seen in 0.1% of patients.

**PREVENTION**

- Before starting SUTENT®, advise patients on:
  - The importance of good hygiene and diet.
  - Basic guidelines to minimise the risk of infection (e.g. washing hands).

**SIGNS AND SYMPTOMS**

- Signs of infection/edematous skin.
- Bruising (thrombocytopaenia).
- Fatigue, pale skin (anaemia).

**ASSESSMENT**

- Carry out a complete blood count to assess for blood disorders and abnormal blood counts.
  - This should be performed before initiating SUTENT® and at the start of each treatment cycle.
  - Full blood count monitoring is recommended every 3 weeks, work up to carry out blood counts locally.
  - Take a full history to check concomitant medications (such as NSAIDs) that may increase bleeding risk and assess or stabilise co-morbidities.
  - Assess severity of blood disorders – the impact may differ from patient to patient (see Table 9 and 10 for grading and management recommendations).

**QUESTIONS FOR YOUR PATIENTS**

- Have you felt ill or had a temperature recently?
- Any incidence of temperature over 38°C and other signs of infection may indicate neutropaenia.
- Are you bruising more easily or having more nosebleeds than normal? This may indicate thrombocytopaenia.
- Have you been very tired recently, any breathlessness, faster heart rate than normal, rushing sounds in the ears, feeling faint, headaches or pallor? These symptoms may indicate anaemia.
- How do the blood disorders affect your everyday life?
  - The severity of symptoms and the impact may differ from patient to patient.

**TREATMENT**

- Provide supporting advice to patients with blood disorders.

**NEUTROPAENIA**

- Typically, the neutropaenia associated with SUTENT® treatment requires no intervention – blood counts tend to recover during the 2-week treatment break between cycles.

**ANAEMIA**

- Grade 3/4 anaemia usually does not require dose modification.
- Anaemia can be treated with iron supplementation or blood transfusions if severe or life threatening; however, erythropoietin-stimulating agents should be used with caution owing to potential risks and toxicities associated with these drugs.

**TABLE 9: GRADING NEUTROPAENIA AND ANAEMIA**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Neutropaenia</th>
<th>Anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ANC ≥1.5 to &lt;2 x 10^9/L</td>
<td>Hb &lt;10.0 g/dL</td>
</tr>
<tr>
<td>2</td>
<td>ANC ≥1.0 to &lt;1.5 x 10^9/L</td>
<td>Hb &lt;10.0–8.0 g/dL</td>
</tr>
<tr>
<td>3</td>
<td>ANC ≥0.5 to &lt;1.0 x 10^9/L</td>
<td>Hb &lt;8.0 g/dL</td>
</tr>
<tr>
<td>4</td>
<td>ANC &lt;0.5 x 10^9/L</td>
<td>Life-threatening consequences, urgent intervention indicated</td>
</tr>
</tbody>
</table>

**TABLE 10: MANAGEMENT STRATEGIES FOR BLOOD DISORDERS/DYSCRASIAS**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue at same dose level</td>
</tr>
<tr>
<td>2</td>
<td>Continue at same dose level</td>
</tr>
<tr>
<td>3</td>
<td>Withhold dose</td>
</tr>
<tr>
<td>4</td>
<td>Withhold dose</td>
</tr>
</tbody>
</table>

**ANC**=absolute neutrophil count; **Hb**=haemoglobin; **LLN**=lower limit of normal

*Recurring Grade 3/4 neutropaenia or thrombocytopaenia persisting for at least 5 days and/or neutropaenia; following signs may require dose/schedule changes.*

**QUESTIONS FOR YOUR PATIENTS**

- Have you felt ill or had a temperature recently? An incidence of temperature over 38°C and other signs of infection may indicate neutropaenia.
- Are you bruising more easily or having more nosebleeds than normal? This may indicate thrombocytopaenia.
- Have you been very tired recently, any breathlessness, faster heart rate than normal, rushing sounds in the ears, feeling faint, headaches or pallor? These symptoms may indicate anaemia.
- How do the blood disorders affect your everyday life? The severity of symptoms and the impact may differ from patient to patient.

**QUESTIONS FOR YOUR PATIENTS**

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MANAGING FATIGUE AND HYPOTHYROIDISM
FATIGUE AND HYPOTHYROIDISM

WHAT ARE THEY?

FATIGUE
• Very common with SUTENT® treatment, affecting 62.7% of patients in SUTENT® clinical trials
• Is usually unrelated to patients, but it can reduce their quality of life
• 18.2% Grade 3/4 treatment-related fatigue in SUTENT® clinical trials
• Typically manifests early, within days or weeks of SUTENT® treatment initiation
• May be transient, resolving as the patient responds to treatment
• Is often related to both the disease and psychosomatic factors related to disease, as well as SUTENT®
• Can be a treatment effect since SUTENT® can cause hypothyroidism or anaemia, which results in fatigue

HYPOTHYROIDISM
• Is also very common with SUTENT® treatment, affecting 18.2% Grade 3/4 treatment-related fatigue in SUTENT® clinical trials
• Typically manifests early, within days or weeks of SUTENT® treatment initiation
• Abn or patients that they may feel tired once SUTENT® therapy begins
• In order to minimise the impact of fatigue, advice on lifestyle modification can help patients
• - Take short naps or breaks when necessary
• - Accept help from others
• - Take regular light exercise
• - Try to maintain a normal sleep pattern
• - Accept help from others
• - Use relaxation techniques, read a book or listen to music
• - Make use of treatment breaks

PREVENTION
• Identify and resolve underlying factors that may affect the level of fatigue:
  - Haemoglobin levels
  - Thyroid function
  - Pain control
• Access baseline thyroid function/manage before treatment initiation
• Abn or patients that they may feel tired once SUTENT® therapy begins

ASSESSMENT
• Confirm the presence of fatigue and/or hypothyroidism
• Take a full history to check concomitant medications and assess stabilise co-morbidities
• In Cycles 1–3, monitor for impact of fatigue on quality of life
• Every 2–3 cycles check for anaemia, depression and hypothyroidism; treat as appropriate
• Encourage patients to rate their fatigue on a numeric scale, where 0=not at all fatigued and 10=worst fatigue imaginable
• Thyroid profiles should be measured at baseline on Day 1 of each cycle, for 4 cycles, and every 3 months thereafter (see Figure)

QUESTIONS FOR YOUR PATIENTS
Have you been feeling more tired than usual since you started taking SUTENT®?
It is important to have excluded your symptoms as a side effect, if the fatigue, becomes troublesome so that the most appropriate supportive care can be provided before you stop your SUTENT®

Light physical exercise may reduce fatigue levels and help your patient get a better night’s sleep
At what time of the day do you take SUTENT®?
Some patients cope better if they take SUTENT® in the evening, while others have difficulty sleeping after a night-time dose. There is no ‘correct’ time, but once a pattern has been established, medication should be taken at roughly the same time every day
How does your fatigue and/or hypothyroidism affect your everyday life?
The severity and impact of fatigue/hypothyroidism may differ from patient to patient

SIGNS AND SYMPTOMS

FATIGUE
• Changes in your patient’s activities and attention on the phone or in the clinic
• Check for underlying factors that may affect the level of fatigue, for example, hypothyroidism, anaemia, depression, diabetes, poor diet, lack of exercise, pain, insomnia, chronic illness and appetite

HYPOTHYROIDISM
• Symptoms of hypothyroidism include:
  - Fatigue
  - Swelling around the eyes
  - Dry skin
  - Shortness of breath
  - Feeling cold
• Several of these symptoms can also be independent side effects of SUTENT® therapy

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FIGURE: RECOMMENDATIONS FOR THYROID DYSFUNCTION MANAGEMENT

<table>
<thead>
<tr>
<th>Thyroid Profile</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Monitor for anaemia, depression and hypothyroidism; treat as appropriate</td>
</tr>
<tr>
<td>During treatment</td>
<td>Measure thyroid profile on Day 1 of each cycle for 4 cycles. After Cycle 4, measure every 3 months</td>
</tr>
</tbody>
</table>

ASSESSMENT
• Confirms the presence of fatigue and/or hypothyroidism
• Takes a full history to check concomitant medications and assess stabilises co-morbidities
• In Cycles 1–3, monitor for impact of fatigue on quality of life
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• Thyroid profiles should be measured at baseline on Day 1 of each cycle, for 4 cycles, and every 3 months thereafter (see Figure)
**TREATMENT**

- **SUTENT®** dose interruptions/reductions from the recommended 50 mg daily dosing can be avoided or minimised using therapy management, helping patients to gain optimal benefit.

- Patients may require **SUTENT®** dose adjustment or treatment break based on severity of fatigue/hypothyroidism (see Table 11).

- Severity of the symptoms need to be weighed up against the benefits of maintaining the recommended **SUTENT®** dosing schedule.

**FATIGUE**

- Determine if fatigue is disease- or drug-related.

- Alternative causes for fatigue should be ruled out; fatigue may be exacerbated by dehydration, hypercalcaemia, anaemia or depression.

- Reinforce preventative advice (see prevention for more tips) and further encourage patients to:
  - Maintain normal work and social schedules, but to take breaks where necessary,
  - Carry out light physical exercise in order to reduce fatigue levels and help to get to sleep.

- Identify and treat all fatigue-inducible factors to optimise quality of life (daily activities, comfort, associated pain, emotional distress, depression, and nutrition disorders).

- Treat anaemia with iron supplementation or blood transfusions if severe or life threatening; use of erythropoietin-stimulating agents is cautioned due to potential risks and side effects.

- Incidence of fatigue has been shown to reduce following subsequent treatment cycles.

**HYPOTHYROIDISM**

- Thyroid-stimulating hormone levels tend to improve during the 2-week treatment break.

- Hypothyroidism can be managed with thyroid hormone replacement therapy.

**MANAGING SKIN AND HAIR CHANGES**

**FATIGUE AND HYPOTHYROIDISM**

**TABLE 11: MANAGEMENT STRATEGIES FOR FATIGUE AND HYPOTHYROIDISM**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Continue at same dose level</td>
</tr>
<tr>
<td>2</td>
<td>Continue at same dose level</td>
</tr>
<tr>
<td>3</td>
<td>Interrupt <strong>SUTENT®</strong> therapy until Grade ≤1 or return to baseline. Resume at same or –1 dose level</td>
</tr>
<tr>
<td>4</td>
<td>Interrupt <strong>SUTENT®</strong> therapy until Grade ≤1 or return to baseline. Resume at same or –1 dose level or discontinue.</td>
</tr>
</tbody>
</table>
SKIN AND HAIR CHANGES

WHAT ARE THEY?

- Have been commonly reported in patients receiving SUTENT®
- Are reversible and generally mild or moderate in severity; however, they can also have a physical and psychological impact on patients
- Include the following conditions (see Table 12 for more side effects and incidence):
  - Hand-foot skin reactions (the most clinically significant)
  - Rash
  - Dry skin
  - Nail modifications
  - Skin and hair discolouration/depigmentation
- Often occur within the first 6 weeks of treatment (typically in Weeks 3 and 4)
- Are not physically harmful; the benefits of maintaining the optimal SUTENT® dosing schedule generally outweigh the inconvenience of these side effects

PREVENTION

- Inform patients of the potential for reversible depigmentation of the hair and skin
- Patients should avoid hot showers, use sun protection and wear loose-fitting cotton clothes
- Before starting SUTENT® therapy, help patients to minimise risk/severity of skin and hair changes – encourage them to:
  - Reduce pressure on skin areas
  - Take good care of their skin – wash gently with baby soaps and shampoos, and regularly apply moisturising emollients (available from chemists)
  - Use anti-itch and anti-dandruff shampoos, hydrocolloidal bandages, thick-soled shoes, local corticoid cream, vitamin A and urea creams

SIGNS AND SYMPTOMS

- Skin colour changes – a yellowish, reversible discolouration
- Hair depigmentation – growing hair may become grey or white during the course of treatment
- Genital dermatitis – an erythematous, desquamative rash that can become erosive
- Small subungual haemorrhages – small linear brown or black lines located under the distal portion of the nails

ASSESSMENT

- Take a full history to check concomitant medications and assess/stabilise co-morbidities
- Assess severity of the skin and hair changes since their impact may differ from patient to patient
- A bilirubin level may be required to distinguish between SUTENT®-induced skin discolouration and jaundice due to liver disease or biliary obstruction
- Use a grading table to assess and make management recommendations – see Table 13 for grading rash

QUESTIONS FOR YOUR PATIENTS

- Have you felt any tingling sensations? Skin changes are often preceded by a tingling sensation in the hands and feet
- Are you noticing any skin or hair changes, such as change in colour, feel or sensation?
- Are you concerned about any change in skin texture or appearance, and are you aware of any changes they have with you at clinic and by telephone in between visits?

The severity of the symptoms, and their physical and psychological impact may differ from patient to patient

$TABLE 12$: KEY TREATMENT-RELATED DERMATOLOGICAL ADVERSE EVENTS WITH SUTENT® IN CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades, %</th>
<th>Grade 3, %</th>
<th>Grade 4, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand-foot skin reactions</td>
<td>27.9</td>
<td>7.7</td>
<td>0</td>
</tr>
<tr>
<td>Skin discolouration</td>
<td>24.8</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>22.4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hair colour changes</td>
<td>12.1</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>11.1</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>8.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>6.3</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin oedema</td>
<td>5.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Periorbital oedema</td>
<td>4.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3.6</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Skin lesion</td>
<td>2.7</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>2.5</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>2.5</td>
<td>0.2</td>
<td>0</td>
</tr>
</tbody>
</table>

$TABLE 13$: GRADING FOR RASH

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>1</td>
<td>Macules/papules covering &lt;10% body surface area with or without symptoms (e.g. pruritus, burning, tightness)</td>
</tr>
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<td>2</td>
<td>Macules/papules covering 10–30% body surface area with or without symptoms (e.g. pruritus, burning, tightness; limiting instrumental active daily living)</td>
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<tr>
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<td>Macules/papules covering &gt;30% body surface area with or without associated symptoms; limiting self care active daily living</td>
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</tr>
</tbody>
</table>

CONTINUE
TREATMENT

• There are no known treatments for hair or skin discoloration and no treatment is known or needed for subungual haemorrhages.
• Provide supporting advice to patients if they suffer from skin and hair changes.
• Patients with dry skin/rash

– Can benefit from moisturising creams andointments, which are usually sufficient to alleviate skin dryness.
– Should change to an odour-free soap or liquid shower gel.
– Should reduce friction from clothes by wearing loose-fitting clothing.
– If it worsens, prescription-strength emollients may be needed.
– If affecting the scalp, should use an anti-dandruff shampoo to help relieve discomfort.
• Patients with severe genital rash should be referred to a dermatologist who can prescribe an appropriate treatment after ruling out a yeast or bacterial infection.
• The severity of the skin and hair changes need to be weighed up against the benefits of maintaining the recommended SUTENT® dosing schedule.
REFERENCES

SUNITINIB® (sunitinib malate) - GIST, MRCC, PNET
Presentation: Capsules (sunitinib malate) - GIST, MRCC, PNET
Capsules (sunitinib malate) - GIST, MRCC, PNET
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<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 28</td>
<td>Son’s 30th birthday</td>
</tr>
<tr>
<td>December 15</td>
<td>Family reunion</td>
</tr>
<tr>
<td>April 30</td>
<td>Spring holiday</td>
</tr>
<tr>
<td>August 30</td>
<td>Start cooking class</td>
</tr>
</tbody>
</table>

Prescribing information can be found within this document