PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TINSUNEB 12,5 capsules

TINSUNEB 25 capsules

TINSUNEB 50 capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TINSUNEB 12,5:

Each capsule contains sunitinib malate equivalent to sunitinib 12,5 mg

Contains sugar alcohol: mannitol 57,669 per capsule

TINSUNEB 25: Each capsule contains sunitinib malate equivalent to sunitinib 25 mg

Contains sugar alcohol: mannitol 115,338 per capsule

TINSUNEB 50: Each capsule contains sunitinib malate equivalent to sunitinib 50 mg

Contains sugar alcohol: mannitol 230,675 per capsule

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsules

TINSUNEB 12,5:

Hard gelatin capsule with opaque reddish brown cap and opaque reddish brown body, self lock capsule, imprinted with 'RM53' on cap and 'RM53' on body in white ink, containing yellow to orange coloured powder.

TINSUNEB 25:

Hard gelatin capsule with opaque caramel cap and opaque reddish brown body, self lock capsule, imprinted with 'RM54' on cap and 'RM54' on body in white ink, containing yellow to orange coloured powder.

TINSUNEB 50:

Hard gelatin capsule with opaque caramel cap and opaque caramel body, self lock capsule, imprinted with 'RM56' on cap and 'RM56' on body in white ink, containing yellow to orange coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gastrointestinal stromal tumour (GIST)

TINSUNEB 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)

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

TINSUNEB 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 reported for more than 12 months.

Pancreatic neuroendocrine tumours (pNET)

TINSUNEB 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 should be initiated by a medical practitioner experienced in the treatment of renal cell carcinoma, GIST or pNET.

Posology

For GIST and MRCC, the recommended dose of TINSUNEB 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 pNET, the recommended dose of TINSUNEB 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 reported 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 TINSUNEB with a potent CYP3A4 inducer such as rifampicin, its use should be avoided (see section 4.5). If this is not possible, the dosage of TINSUNEB 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 TINSUNEB with a CYP3A4 inhibitor such as ketoconazole, its use should be avoided (see section 4.5). If this is not possible, the doses of TINSUNEB 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 CYP34 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 has been reported between younger and older patients.

Hepatic insufficiency

No dosage adjustment is necessary when administering TINSUNEB to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Sunitinib as contained in TINSUNEB was not studied in patients with severe (Child-Pugh Class C) hepatic impairment (see section 5.2).

Renal insufficiency

No starting dose adjustment is required when administering TINSUNEB 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 TINSUNEB in paediatric patients have not been established.

Method of administration

For oral use.

TINSUNEB may be taken with or without food.

If a dose is missed, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Cerebrovascular adverse events identified as class related adverse events have occurred in patients treated with TKI (Tyrosine Kinase Inhibitor) containing medicines such as TINSUNEB. These adverse events include cerebrovascular accident (CA), transient ischaemic attack (TIA), ischaemic stroke (IS), and cerebral infarct (CI). These events may occur in patients on treatment, with or without risk factors and may occur at any time during treatment. Patients on treatment should be carefully monitored and relevant risk factors managed to reduce the risk of these cerebrovascular adverse events. Treatment with TINSUNEB should be discontinued, and alternative treatment options be considered in patients who develop these class related adverse events.

Co-administration with potent CYP3A4 inducers should be avoided because it may decrease sunitinib plasma concentration.

Co-administration with potent CYP3A4 inhibitors should be avoided because it ma y increase the plasma concentration of sunitinib.

Skin and tissues

Skin discolouration due to the active substance colour (yellow) has been reported to be a very common adverse event occurring in approximately 30 % of patients. Patients should be advised that depigmentation of the hair or skin may also occur during treatment with TINSUNEB. 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 has been reported in approximately 14 % of patients. Dysgeusia (taste disturbance) has been reported in approximately 28 % of patients.

The above events were not cumulative, 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, TINSUNEB 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 TINSUNEB 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 reported in approximately 2 % of 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 reported in patients with MRCC or other solid tumours. Cases of pulmonary haemorrhage some with a fatal outcome, have been reported in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST, and metastatic non-small cell lung cancer (NSCLC). TINSUNEB is not approved for use in patients with NSCLC.

In patients receiving sunitinib as contained in TINSUNEB for treatment-naïve MRCC, 39 % had bleeding events. Of patients receiving sunitinib as contained in TINSUNEB for cytokine-refractory MRCC, 26 % reported to have experienced bleeding. Bleeding events, excluding epistaxis, reported in 21,7 % of patients receiving sunitinib as contained in TINSUNEB in a Phase 3 pNET study compared to 9,85 % of subjects receiving placebo. Routine assessment of these events should include complete blood counts and physical examination.

Patients receiving concomitant treatment with anticoagulants (e.g., warfarin, acenocoumarole) may be periodically monitored by complete blood counts (platelets), coagulation factors (PT/INR), and physical examination.

Treatment-related epistaxis was reported in 8 % of patients with solid tumours. Epistaxis was the most common 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 been reported in patients with intra-abdominal malignancies treated with sunitinib as contained in TINSUNEB.

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

Pancreatitis

Pancreatitis has been reported in clinical trials of sunitinib as contained in TINSUNEB. Increases in serum lipase and amylase has been reported in patients with various solid tumours who received sunitinib as contained in TINSUNEB. 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 reported in patients treated with sunitinib as contained in TINSUNEB. Cases of hepatic failure, some with a fatal outcome, were reported in < 1 % of solid tumour patients treated with sunitinib as contained in TINSUNEB. 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. TINSUNEB 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 reported commonly and decreased platelet counts were reported less commonly. 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.

Anaemia has been reported to occur early as well as late during treatment with sunitinib as contained in TINSUNEB.

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

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 reported post-marketing experience. Decreases in left ventricular ejection fraction (LVEF) of ≥ 20 % and below the lower limit of normal reported in approximately 2 % of GIST patients treated with sunitinib as contained in TINSUNEB, 4 % of MRCC patients and 2 % of placebo-treated patients.

In the reported treatment-naïve MRCC study, 27 % patients on sunitinib as contained in TINSUNEB, had an LVEF value below the lower limit of normal. Less than 1 % of the study patients who received sunitinib as contained in TINSUNEB were diagnosed with congestive heart failure.

Cardiac failure, congestive cardiac failure or left ventricular failure were reported in 0,8 % of patients with solid tumours and 1 % of patients treated with placebo. In a reported Phase 3 pNET study, 1,2 % patient who received sunitinib as contained in TINSUNEB had treatment-related fatal cardiac failure.

The relationship between receptor tyrosinase kinase (RTK) inhibition and cardiac function remains unclear but seems to be a class effect. Reported data from non-clinical *(in vitro and in vivo*) studies, at doses higher than the recommended human dose, indicate that sunitinib as contained in TINSUNEB has the potential to inhibit the cardiac action potential repolarisation process (e.g., prolongation of QT interval). Increases in the QTc interval to over 500 msec reported in 0,5 % and changes from baseline in excess of 60 msec reported in 1,1 % of the solid tumour patients in the study; both these parameters are reported as potentially significant changes.

QT interval prolongation

At approximately twice the therapeutic concentrations, sunitinib as contained in TINSUNEB has been reported to prolong the QTcF (Fredericia's correction) interval. QT interval prolongation may lead to an increased risk for ventricular dysrhythmias including torsade de pointes. Torsade de pointes has been reported in < 0,1 % of patients exposed to sunitinib as contained in TINSUNEB. TINSUNEB 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. Concomitant treatment with strong CYP3A4 inhibitors, which may increase plasma concentrations of sunitinib as contained in TINSUNEB, should be used with caution and the dose of TINSUNEB reduced (see section 4.2 and 4.5).

Hypertension

Patients treated with TINSUNEB should have regular blood pressure assessments.

Hypertension was a very common adverse event reported in clinical trials in patients with solid tumours, including primarily GIST and cytokine-refractory RCC. Dosing of sunitinib as contained in

TINSUNEB, was reduced or temporarily delayed in approximately 2,7 % of this patient population. None of these patients were discontinued from treatment with sunitinib as contained in TINSUNEB. Severe hypertension (> 200 mmHg systolic or 110 mmHg diastolic) reported in 4,7 % of this patient population. Hypertension has been reported in approximately 33,9 % of patients receiving sunitinib as contained in TINSUNEB for treatment-naïve MRCC. Severe hypertension reported in 12 % of treatment-naïve patients on sunitinib as contained in TINSUNEB. Hypertension has been reported in

26,5 % of patients receiving sunitinib as contained in TINSUNEB, in a Phase 3 pNET study, compared to 4,9 % of patients receiving placebo.

Severe hypertension reported in 10 % of pNET patients on sunitinib as contained in TINSUNEB and 3 % of patients on placebo. Patients should be screened for hypertension and controlled as appropriate. Temporary suspension of TINSUNEB therapy 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 TINSUNEB, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

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

Acquired hypothyroidism has been reported in 6,2 % of GIST patients. Hypothyroidism has been reported as an adverse event in 16 % of patients on sunitinib as contained in TINSUNEB, in the treatment-naïve MRCC study and in 4 % of subjects across 2 cytokine-refractory MRCC studies. Overall 7 % of the cytokine-refractory MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In a Phase 3 pNET study, hypothyroidism has been reported in 7,2 % of the study patients receiving sunitinib as contained in TINSUNEB and in 1,2 % patients on placebo.

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

Seizures

In reported clinical studies of sunitinib as contained in TINSUNEB, seizures have been reported in subjects with radiological evidence of brain metastases. In addition, there have been rare (< 1 %) reports, some fatal, of subjects presenting with seizures and radiological evidence of reversible posterior leukoencephalopathy syndrome (RPLS). Patients with seizures and signs/symptoms consistent with 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 TINSUNEB 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 therapy with sunitinib as contained in TINSUNEB. Temporary interruption of TINSUNEB 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 TINSUNEB therapy following a major surgical intervention should be based upon clinical judgement of recovery from surgery.

Osteonecrosis of the Jaw (ONJ)

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

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

Venous thromboembolic events

In a reported GIST study, 3 % of patients on sunitinib as contained in TINSUNEB, experienced venous thromboembolic events; 72 % were Grade 3 deep vein thrombosis (DVT). 3 % of patients receiving sunitinib as contained in TINSUNEB for treatment-naïve MRCC had venous thrombolic events reported such as pulmonary embolism.

Pulmonary embolism

Pulmonary embolism has been reported in approximately 2,2 % of patients with solid tumours who received sunitinib as contained in TINSUNEB. None of these events reported in a patient discontinuing treatment with sunitinib as contained in TINSUNEB; 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 reported in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib as contained in TINSUNEB. 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. TINSUNEB 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 contained in TINSUNEB as monotherapy and in combination with bevacizumab. Discontinue TINSUNEB 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 TINSUNEB treatment in patients with moderate to severe proteinuria has not been systematically evaluated. Discontinue TINSUNEB in patients with nephrotic syndrome.

Hypoglycaemia

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

Renal function

Cases of renal impairment, renal failure and/or acute renal failure, in some cases with fatal outcome, have been reported (see section 4.8).

Risk factors associated with renal impairment/failure in patients receiving sunitinib included, in addition to underlying RCC (Renal cell carcinoma), older age, diabetes mellitus, underlying renal impairment, cardiac failure, hypertension, sepsis, dehydration/hypovolaemia, and rhabdomyolysis.

Fistula

If fistula formation occurs, sunitinib treatment should be interrupted. Limited information has been reported on the continued use of sunitinib in patients with fistulae (see section 4.8).

Hypersensitivity/angioedema

If angioedema due to hypersensitivity occurs, TINSUNEB treatment should be interrupted and standard medical care provided (see section 4.8).

Infections

Serious infections, with or without neutropenia, including some with a fatal outcome, have been reported.

Sunitinib therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Viral reactivation

Hepatitis B reactivation, including fatal outcomes have reported in patients treated with sunitinib as contained in TINSUNEB. Hepatitis B virus (HBV) status should be established before initiating treatment with TINSUNEB. Patients should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting and jaundice) and appropriate therapy should be instituted as indicated. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Class effects of Tyrosine Kinase Inhibitors (TKIs) such as contained in TINSUNEB

Although TKIs may have different kinase inhibition profiles and/or off target binding profiles, there is some evidence that the TKIs share to a variable degree, class related cerebrovascular adverse events (e.g. cerebrovascular accident, transient ischaemic attack, ischaemic stroke, and cerebral infarction).

These cerebrovascular adverse 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 TINSUNEB should be carefully monitored, and relevant risk factors managed to reduce the risk for these class related cerebrovascular adverse events.

Treatment with TINSUNEB should be discontinued, and alternative treatment options be considered in patients who developed these class related cerebrovascular adverse events.

Excipient

TINSUNEB contains mannitol and may have a laxative effect.

This medicinal product contains less than 1 mmol (23 mg) sodium per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

When TINSUNEB is co-administered with other medicines, there is a potential for medicine interaction.

Reported *in vitro* studies indicate that sunitinib as contained TINSUNEB neither induces nor inhibits major CYP enzymes, including CYP3A4. The dose of TINSUNEB may need to be reduced based

on tolerability when co-administered with CYP3A4 inhibitors. The dose of TINSUNEB may need to be increased when it is co-administered with potent CYP3A4 inducers.

Medicines that may increase TINSUNEB plasma concentrations

Concurrent administration of sunitinib as contained in TINSUNEB with the CYP3A4 inhibitor, ketoconazole, reported in 49 % and 51 % increase in sunitinib C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib as contained in TINSUNEB in healthy volunteers.

Administration of TINSUNEB with other inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase TINSUNEB 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 TINSUNEB may need to be reduced (see section 4.2, Dose modifications).

Medicines that may decrease TINSUNEB plasma concentrations

Concomitant use of sunitinib as contained in TINSUNEB, with the CYP3A4 inducer, rifampicin, have been reported to result in a more than 23 % and 46 % reduction in sunitinib C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of TINSUNEB in healthy volunteers.

Administration of TINSUNEB 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 TINSUNEB concentrations. To maintain TINSUNEB target concentrations, dose adjustment of TINSUNEB, or selection of co-medications with less enzyme induction potential, should be considered.

Effect of Breast Cancer Resistance Protein (BCRP) inhibitors

Limited reported clinical data are available on the interaction between sunitinib as contained in TINSUNEB and BCRP inhibitors and the possibility of an interaction between sunitinib and other BCRP inhibitors cannot be excluded.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Teratogenicity has been reported in animal studies.

Female patients and female sexual partners of male patients receiving genotoxic anticancer medicines, should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 6 months (which covers the growth and maturation phase of folliculogenesis). Due to the genotoxic potential of sunitinib , women of childbearing age must use effective contraception during treatment with sunitinib and for 6 months after treatment discontinuation.

Male patients should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives after the last dose) plus 90 days (i.e., 60-75 days for sperm production plus 10-14 days for the transport to epididymis). Men must be advised to use effective methods of contraception and not to father a child during treatment with sunitinib and in the 3 months following its discontinuation.

Pregnancy

TINSUNEB is contraindicated in pregnancy as safety has not been reported.

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

TINSUNEB has minor influence on the ability to drive and use machines. Patients should be advised that they may experience dizziness during treatment with TINSUNEB.

4.8 Undesirable Effects

Summary of the safety profile

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

The most very common adverse events of any grade included: fatigue; gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting; skin discolouration; rash; hand-foot syndrome (palmar-plantar erythrodysaesthesia); dry skin; hair colour changes; mucosal inflammation; asthenia; dysgeusia; anorexia and hypertension. Fatigue, hypertension and neutropenia were the most common adverse events of Grade 3 maximum severity; and increased lipase was the most frequently reported adverse event of Grade 4 maximum severity in patients with solid tumours.

Tabulated summary of adverse reactions

The treatment-emergent, all causality frequency of adverse events reported in patients who received sunitinib as contained in TINSUNEB in single-medicine studies in advanced RCC, GIST and pNET and from reported post-marketing experience are listed below, by system organ class, frequency category and grade of severity.

Adverse events reported in sunitinib single-medicine studies in advanced RCC, GIST and pNET experience:

System organ class	**Frequent**	**Less frequent**
Infections and infestations	Infections[$], Viral infections[a], Respiratory infections[b],*, Abscess[c],*, Fungal infections[d], Urinary tract infection, Skin infections[e], Sepsis[f],*	Necrotising fasciitis*, Bacterial infections[g]
Blood and lymphatic system disorders	Neutropenia, Leukopenia, Thrombocytopenia, Anaemia, Lymphopenia	Thrombotic microangiopathy[i, j],# Pancytopenia
Immune system disorders		Hypersensitivity, Angioedema
Endocrine disorders	Hypothyroidism	Hyperthyroidism, Thyroiditis

Metabolism and nutrition disorders	Decreased appetite, Dehydration[#], Hypoglycaemia	Tumour lysis syndrome[#],
Psychiatric disorders	Insomnia, Depression	-
Nervous System disorders	Dysgeusia[h], Headache, Dizziness, Paraesthesia, Taste disturbance[h], Neuropathy peripheral, Paraesthesia, Hypoaesthesia, Hyperaesthesia	Cerebral haemorrhage[#], Cerebrovascular accident[#], Ischaemic stroke, Transient ischaemic attack, Cerebral infarction, Reversible posterior encephalopathy syndrome, Ageusia
Eye disorders	Periorbital oedema, Eyelid oedema, Increased lacrimation	-

Cardiac disorders	Myocardial ischaemia [k,#], Decreased ejection fraction[l]	Myocardial infarction [m,#] Cardiac failure[#], Congestive cardiac failure, Prolonged electrocardiogram QT, Cardiomyopathy[,#], Left ventricular failure[#], Torsade de pointes.
Vascular disorders	Hypertension, Deep vein thrombosis, Hot flush, Flushing	Tumour haemorrhage[#], Aneurysms and artery dissections [n]
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Epistaxis, Oropharyngeal pain[o] , Haemoptysis[p,#], Pleural effusion, Pulmonary embolism[,#], Cough, Nasal congestion, Nasal dryness	Pulmonary haemorrhage*, Respiratory failure*
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain[q], Stomatitis[r] Constipation, Dyspepsia, Gastrointestinal haemorrhage[#], Oesophagitis, Gastro-oesophageal reflux disease, Oral pain,	Pancreatitis, Gastrointestinal perforation[#], Anal fistula, Colitis[i]

	Glossodynia, Abdominal distension, Gingival bleeding, Dry mouth, Flatulence	
Hepato-biliary disorders		Cholecystitis[rs] ,,Hepatic failure[#] [hepatitis B reactivation (including fatal events)]
Skin and subcutaneous tissue disorders	Hand-foot syndrome (Palmar-plantar erythrodysaesthesia syndrome), Skin discolouration[t] , Rash[u] , Hair color changes, Dry skin, Alopecia, Erythema, Pruritus, Skin exfoliation, Blister, Skin lesion, Skin reaction, Nail disorder, Eczema, Skin hyperpigmentation, Hyperkeratosis, Dermatitis	Exfoliative dermatitis, Erythema multiforme[#], Stevens-Johnson syndrome[#], Pyoderma, Toxic epidermal necrolysis*

Musculoskeletal and connective tissue disorders	Pain in extremity, Arthralgia, Myalgia, Back pain, Musculoskeletal pain, Muscle spasms, Muscular weakness	Osteonecrosis of jaw, Fistula formation[#], Rhabdomyolysis[#], Myopathy.
Renal and urinary disorders	Renal failure[#], Chromaturia, Proteinuria, Renal failure acute*	Renal impairment, Urinary tract hemorrhage, Nephrotic syndrome
General disorders and administration site conditions	Fatigue[v], Mucosal inflammation, Oedema[w], Pyrexia, Chills, Influenza like illness, Chest pain	Impaired healing
Investigations	Increased lipase, Increased amylasex, Decreased white blood cell count, Decreased platelet count, Decreased hemoglobin, Decreased weight, Aspartate amino transferase increased, Alanine amino transferase increased, Blood creatinine increased, Blood pressure increased, Blood uric acid increased.	Increased blood creatine phosphokinase, increased blood thyroid stimulating hormone

* Including fatal events.

[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] Dysgeusia, ageusia, and taste disturbance.

[i] Colitis and colitis ischemic.

[j,] Thrombotic microangiopathy: The following terms have been combined: thrombotic microangiopathy, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome.

[k,] Myocardial ischaemia: The following terms have been combined: acute coronary syndrome, angina pectoris, unstable angina, coronary artery occlusion, myocardial ischaemia

[l,] Decreased ejection fraction: The following terms have been combined: decreased ejection fraction and abnormal ejection fraction

[m,] Myocardial infarction: The following terms have been combined: acute myocardial infarction, myocardial infarction, silent myocardial infarction

[n,] Aneurysms and artery dissections: The following terms have been combined: aneurysm ruptured, aortic aneurysm, aortic aneurysm rupture and aortic dissection.

[o,] Oropharyngeal pain: The following terms have been combined: pharyngolaryngeal pain and oropharyngeal pain

[p,] Haemoptysis: The following terms have been combined: hemoptysis and pulmonary haemorrrhage

[q,] Abdominal pain: The following terms have been combined: abdominal pain, lower abdominal pain, upper abdominal pain

[r,] Stomatitis: The following terms have been combined: stomatitis and aphthous stomatitis

[s,] Cholecystitis: The following terms have been combined: cholecystitis and acalculous cholecystitis

[t] Skin discolouration: The following terms have been combined: skin discolouration, yellow skin, pigmentation disorder

[u,] Rash: The following terms have been combined: dermatitis psoriasiform, exfoliative rash, rash, erythematous rash, follicular rash, generalized rash, macular rash, maculopapular rash, popular rash, pruritic rash

[v] Fatigue: The following terms have been combined: fatigue and asthenia

[w] Oedema: The following terms have been combined: face oedema, oedema, peripheral oedema

[x] Increased amylase: The following terms have been combined: 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 reported during post-approval use of sunitinib as contained in TINSUNEB.

System organ class	**Frequency unknown**
Infections and infestations	Respiratory infections (e.gpneumonia, bronchitis), urinary tract infections, skin infections (e.g., cellulitis) sepsis/septic shock and abscess (e.g., oral, genital, anorectal, skin, limb, visceral), bacterial or

	fungal Infections, necrotising fasciitis, perineum sometimes fatal
Blood and lymphatic system disorders	Thrombotic microangiopathy, haemolytic uraemic syndrome
Immune system disorders	Hypersensitivity reactions, including angioedema
Metabolism and nutrition disorders	Tumour Lysis Syndrome (some cases fatal), decreases in blood glucose
Nervous system disorders	Taste disturbance, including ageusia
Cardiac disorders	Cardiac failure, congestive cardiac failure, prolonged QT interval and torsade de pointes, cardiomyopathy, myocardial ischaemia, left ventricular failure and myocardial infarction(in some cases with fatal outcome)
Vascular disorders	Arterial thromboembolic events (some fatal) including cerebrovascular accident, transient ischaemic attack, ischaemic stroke and cerebral infarction. 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 (including fatal events), hepatitis B reactivation (including fatal events) and cholecystitis, particularly acalculous cholecystitis
Skin and subcutaneous tissue disorders	Pyoderma gangrenosum, erythema multiforme and Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders	Myopathy and/or rhabdomyolysis, with or without acute renal failure, (in some cases with fatal outcome). 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. Fistula formation, sometimes associated with tumour necrosis and/or regression(in some cases with fatal outcome), teonecrosis of the jaw (ONJ), 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
Renal and urinary disorders	Renal impairment and/or failure, in some cases with fatal outcome. Cases of proteinuria and cases of nephrotic syndrome
Investigations	Increased TSH and increased blood uric acid have been reported.

Haemorrhagic events	Pulmonary, gastrointestinal, tumour, urinary tract, and brain haemorrhage

Long-term safety in MRCC

The long-term safety of sunitinib in patients with metastatic RCC was analysed across 9 reported clinical studies conducted in the first-line, bevacizumab-refractory and cytokine refractory treatment settings. 14 % of the study patients were treated for ≥ 2 years up to 6 years. Prolonged treatment with sunitinib was not reported to be associated with new types or increased severity of treatment-related adverse events and except for hypothyroidism, toxicity was not cumulative.

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

4.9 Overdose

There is no specific antidote for over dosage with TINSUNEB.

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:

Category and class: A 26 Cytostatic Agents

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

PHARMACOLOGICAL ACTION

Mode of Action

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), 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 (PDGFRb, 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 PDGFRb- and VEGFR2-dependent tumour angiogenesis.

5.2 Pharmacokinetic properties

Absorption

Sunitinib is absorbed after oral administration with maximum concentrations (C_{max}) generally reported 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.

Metabolism

The reported *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 reported 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 reported to be 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 reported in patients with severe (Child-Pugh Class C) hepatic impairment.

Renal insufficiency

Population pharmacokinetic analyses have been reported and were not altered in a number of study subjects with a reported creatinine clearance (CLcr) of > 80 mL/min, many subjects with CLcr of 50 – 80 mL/min and some subjects with CLcr of 30 – 49 mL/min. Systemic exposures after a single dose of sunitinib were similar in subjects with severe renal impairment (CLcr < 30 mL/min) compared to subjects with normal renal function (CLcr > 80 mL/min). Although sunitinib and its primary metabolite were not eliminated through haemodialysis in subjects with end-stage renal disease (ESRD), the total systemic exposures were lower by 47 % for sunitinib and 31 % for its primary metabolite compared to subjects with normal renal function.

Following oral administration in healthy volunteers, the elimination half-lives of sunitinib and its primary active desethyl metabolite have been reported to be 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} has been reported to 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

have been reported to be achieved within 10 to 14 days. By day 14, combined plasma concentrations of sunitinib and is active metabolite have been reported to be 62,9 - 101 ng/mL which are target concentrations predicted from reported 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 have been reported with repeated daily administration or with repeated cycles in the dosing regimens tested. The pharmacokinetics were similar in all solid tumour populations tested and in healthy volunteers.

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

Mannitol, Croscarmellose Sodium, Povidone (K30), Magnesium Stearate, Purified Water.

Empty Gelatin Capsule Shell

Iron oxide black, Iron oxide red, Iron oxide yellow, Titanium dioxide, Gelatin and Water

Printing ink

Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, purified water, potassium hydroxide and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months.

Store at or below 25 °C.

Keep in the original container in order to protect from light.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

TINSUNEB is available in 28 or 30 hard capsules supplied in HDPE bottles with PP closure (CR Cap) and induction seal liner and/ or in packs of 28 or 30 hard capsules supplied in PVC/PCTFE/Al blisters in a carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext 1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBERS

TINSUNEB 12,5: 56/26/0935

TINSUNEB 25 : 56/26/0936
TINSUNEB 50 **:** 56/26/0937

9. DATE OF FIRST AUTHORISATION

28 May 2024

10. DATE OF REVISION OF THE TEXT

17 September 2025