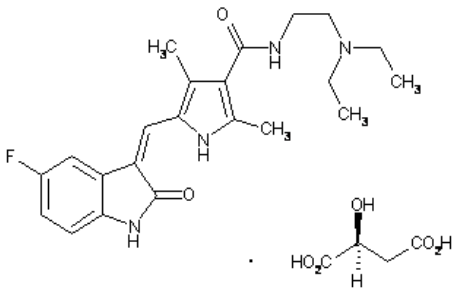
PT. PFIZER INDONESIA
Local Product Document

Generic Name: Sunitinib Malate
Trade Name: SUTENT®
CDS Effective Date: December 16, 2019
Supersedes: February 12, 2015

DESCRIPTION

SUTENT®, an oral multi-kinase inhibitor targeting several receptor tyrosine kinases (RTK), is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with *N*-[2-(diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-1,2-dihydro-2-oxo-*3H*-indol-3-ylidine)methyl]-2,4-dimethyl-*1H*-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2.C_4H_6O_5$ and the molecular weight is 532.6 Daltons. The chemical structure of sunitinib malate is:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

SUTENT® (sunitinib malate) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide, and red iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Sunitinib malate is a small molecule that inhibits multiple RTKs, some of which are implicated in tumor 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 an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs 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.

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Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFRβ, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression and/or inhibited in metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFRβ- and VEGFR2-dependent tumor angiogenesis *in vivo*.

Pharmacokinetic properties
The pharmacokinetics of sunitinib and sunitinib malate have been evaluated in 135 healthy volunteers and in 266 patients with solid tumors.

Absorption
Maximum plasma concentrations (C_{max}) of sunitinib are generally observed between 6 and 12 hours (T_{max}) following oral administration. Food has no effect on the bioavailability of sunitinib. Sunitinib may be taken with or without food.

Distribution
Binding of sunitinib and its primary metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration dependence in the range of 100 – 4000 ng/mL. The apparent volume of distribution (Vd/F) for sunitinib was 2230 L. In the dosing range of 25-100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose.

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

In-vitro studies indicate that sunitinib neither induces nor inhibits major CYP enzymes, including CYP3A4 (see Section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS**).

Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure.

Elimination
Excretion is primarily via feces. In a human mass balance study of [^{14}C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4%, and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%.

Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the

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primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

The pharmacokinetics were similar in healthy volunteers and in the solid tumor patient populations tested, including patients with gastrointestinal stromal tumor (GIST) and metastatic renal cell carcinoma (MRCC) (see Section **CLINICAL STUDIES**).

Special Populations
Population pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age, body weight, creatinine clearance, race, gender or ECOG score on the pharmacokinetics of sunitinib or the active metabolite.

Weight, performance status: Population pharmacokinetic analyses of demographic data indicate that no starting dose adjustments are necessary for weight or Eastern Cooperative Oncology Group (ECOG) performance status.

Gender: Available data indicate that females could have about 30% lower apparent clearance (CL/F) of sunitinib than males: this difference, however, does not necessitate starting dose adjustments.

The pharmacokinetics of sunitinib have not been evaluated in pediatric patients.

Hepatic Insufficiency
Sunitinib and its primary metabolite are mainly metabolized by the liver. Systemic exposures after a single dose of sunitinib were similar in subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment compared to subjects with normal hepatic function. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment.

Renal Impairment
Population pharmacokinetic analyses have shown that sunitinib pharmacokinetics were unaltered in patients with calculated creatinine clearances in the range of 42-347 mL/min. Systemic exposures after a single dose of SUTENT® 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 hemodialysis in subjects with ESRD, the total systemic exposures were lower by 47% for sunitinib and 31% for its primary metabolite compared to subjects with normal renal function.

Cardiac Electrophysiology
QT interval prolongation was investigated in a Phase 1 trial with 24 evaluable patients, aged 20-87 years, with advanced malignancies. At therapeutic plasma concentrations, the maximum QTcF mean change from baseline was 9.6 msec (90% confidence interval [CI] 15.1 msec). At approximately twice the therapeutic concentrations, the maximum QTcF mean change from baseline was 15.4 msec (90% CI 22.4 msec). Moxifloxacin (400 mg) used as a positive control showed a 5.6 msec maximum mean QTcF change from baseline. No subjects experienced an effect on the QTc interval greater than Grade 2 (CTCAE version 3.0). No patient presented with a

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cardiac arrhythmia (see Section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

CLINICAL STUDIES

The clinical safety and efficacy of SUTENT® have been studied in patients with gastrointestinal stromal tumor (GIST) after progression on or intolerance to imatinib mesylate, and in patients with metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy and in patients with unresectable pNET.

Efficacy is based on time to tumor progression (TTP) and an increase in survival in GIST.

Efficacy is based on progression-free survival (PFS) and objective response rates (ORR) for treatment-naive and cytokine-refractory MRCC, respectively and on PFS for pNET.

Gastrointestinal Stromal Tumor (GIST)

Study A

Study A was a two-arm, international, randomized, double-blind, placebo-controlled trial of SUTENT® in patients with GIST who had disease progression during prior imatinib mesylate (imatinib) treatment or who were intolerant of imatinib. The primary objective was to compare time-to-tumor progression (TTP) in patients receiving SUTENT® plus best supportive care *versus* patients receiving placebo plus best supportive care. Secondary objectives included progression-free survival (PFS), objective response rate (ORR), and overall survival (OS). Patients were randomized (2:1) to receive either 50 mg SUTENT® or placebo orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) until disease progression or withdrawal from the study for another reason. Treatment was unblinded at the time of disease progression. Patients randomized to placebo were then offered crossover to open-label SUTENT®, and patients randomized to SUTENT® were permitted to continue treatment per investigator judgment.

The intent-to-treat (ITT) population included 312 patients. Two-hundred seven patients were randomized to the SUTENT® arm, and 105 patients were randomized to the placebo arm. Baseline age, gender, race and ECOG performance status were comparable between the placebo and SUTENT® groups. Prior exposure to imatinib was similar between the two study arms. Demographics and patient characteristics are shown in Table 1.

Table 1 – Baseline Demographics in Study A

	SUTENT® (N=207)	**Placebo (N=105)**
Gender [N (%)]		
Male	132 (64)	64 (61)
Female	75 (36)	41 (39)
Self-identified Race [N (%)]		
White	183 (88)	92 (88)
Asian	10 (5)	5 (5)
Black	8 (4)	4 (4)
Not reported	6 (3)	4 (4)
Age Group [N (%)]		
<65 years	143 (69)	76 (72)
≥65 years	64 (31)	29 (28)

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Performance Status [N (%)]		
0	92 (44)	48 (46)
1	113 (55)	55 (52)
2	2 (1)	2 (2)
Prior Treatment [N (%)]		
Surgery (other than biopsy)	194 (94)	98 (93)
Radiotherapy	16 (8)	16 (15)
Imatinib Outcome [N (%)]		
Intolerance	9 (4)	4 (4)
Progression within 6 months	36 (17)	17 (16)
Progression beyond 6 months	162 (78)	84 (80)

A planned interim efficacy and safety analysis was performed after 149 TTP events had occurred. There was a statistically significant advantage for SUTENT® over placebo in the primary endpoint of TTP, as well as in the secondary endpoint of progression-free survival. Data were not mature enough to determine the overall survival benefit. Efficacy results are summarized in Table 2.

Table 2 – GIST Efficacy Results (interim analysis)

Efficacy Parameter	**Study A**			
	SUTENT® (N = 207)	**Placebo (N = 105)**	**P-value (log-rank test)**	**HR (95% CI)**
Time to Tumor Progression[a] [median, weeks (95% CI)]	27.3 (16.0, 32.1)	6.4 (4.4, 10.0)	<0.0001*	0.33 (0.23, 0.47)
Progression Free Survival[b] [median, weeks (95% CI)]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	<0.0001*	0.33 (0.24, 0.47)
Objective Response Rate (PR) [%, (95% CI)]	6.8 (3.7, 11.1)	0	0.006[c]	

Abbreviations: CI=Confidence interval, HR=Hazard ratio, PR=Partial response.

* A comparison is considered statistically significant if the p-value is <0.0042 (O'Brien Fleming stopping boundary).

[a] Time from randomization to progression; deaths prior to documented progression were censored at time of last radiographic evaluation.

[b] Time from randomization to progression or death due to any cause.

[c] Pearson chi-square.

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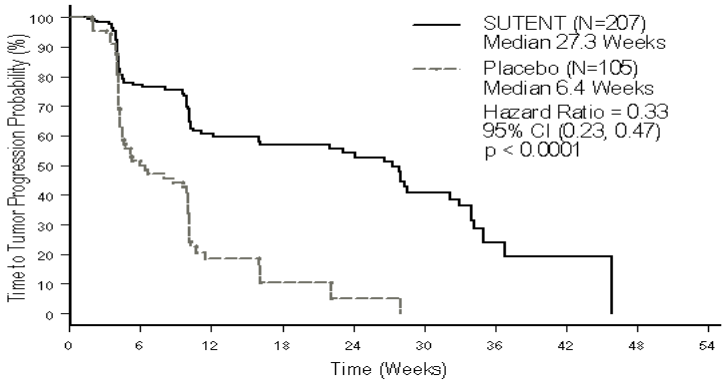
Figure 1. Kaplan-Meier Curve of TTP in Study A (Intent-to-Treat Population)



At the time of the pre-specified interim analysis, the median TTP on sunitinib was 28.9 weeks (95% CI: 21.3, 34.1) as assessed by the Investigator and 27.3 weeks (95% CI: 16.0, 32.1) as assessed by the Independent Review and was statistically significantly longer than the TTP of 5.1 weeks (95% CI: 4.4, 10.1) as assessed by the Investigator and 6.4 weeks (95% CI: 4.4, 10.0) as assessed by the Independent Review. The difference in overall survival was statistically in favor of sunitinib (hazard ratio [HR]: 0.491 [95% CI: 0.290, 0.831]); the risk of death was 2 times higher in subjects in the placebo arm compared to the sunitinib arm. Additional efficacy information is presented below in Table 3.

After the positive interim analysis of efficacy and safety, at the recommendation of the independent Data and Safety Monitoring Board (DSMB), the study was unblinded and patients on the placebo arm were offered open-label sunitinib treatment.

A total of 255 patients received sunitinib in the open-label treatment phase of the study, including 99 patients who were initially treated with placebo. In this final analysis, the placebo arm included those subjects randomized to placebo who subsequently received open-label sunitinib treatment.

The final analyses of primary and secondary endpoints of the study reaffirmed the results obtained at the time of the interim analysis, as shown in the Table 3 below:

Table 3 – Summary of Efficacy Endpoints (ITT population)

	Double-Blind Treatment[a]				
	Median (95% CI)		**Hazard Ratio (HR)**		**Placebo Cross-Over Group**
Endpoint	**Sunitinib**	**Placebo**	**(95% CI)**	**p-value**	**Treatment[b]**
Primary: TTP (weeks)					
Interim	27.3 (16.0, 32.1)	6.4 (4.4, 10.0)	0.329 (0.233, 0.466)	<0.001	-
Final	26.6 (16.0, 32.1)	6.4 (4.4, 10.0)	0.339 (0.244, 0.472)	<0.001	10.4 (4.3, 22.0)
Secondary					
Interim					

	Double-Blind Treatment[a]				
	Median (95% CI)		Hazard Ratio (HR)		Placebo Cross-Over Group
Endpoint	**Sunitinib**	**Placebo**	**(95% CI)**	**p-value**	**Treatment[b]**
PFS (weeks)[c]	24.1 (11.1, 28.3)	6.0 (4.4, 9.9)	0.333 (0.238, 0.467)	<0.001	-
ORR (%)[d]	6.8 (3.7, 11.1)	0 (-)	NA	0.006	-
OS (weeks)[e]	-	-	0.491 (0.290, 0.831)	0.007	-
Final					
PFS (weeks)	22.9 (10.9, 28.0)	6.0 (4.4, 9.7)	0.347 (0.253, 0.475)	<0.001	-
ORR (%)[d]	6.6 (3.8, 10.5)	0 (-)	NA	0.004	10.1 (5.0, 17.8)
OS (weeks)	72.7 (61.3, 83.0)	64.9 (45.7, 96.0)	0.876 (0.679, 1.129)	0.306	-

Abbreviations: CI=confidence interval; ITT=intent-to-treat; NA=not applicable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TTP=time to tumor progression.

[a] Results of double-blind treatment are from the ITT population and using central radiologist measurement, as appropriate.

[b] Efficacy results for the 99 subjects who crossed over from placebo to sunitinib after unblinding. Baseline was reset at cross-over and efficacy analyses were based on investigators assessment.

[c] The interim PFS numbers have been updated based on a recalculation of the original data.

[d] Results for ORR are given as percent of subjects with confirmed response with the 95% CI.

[e] Median not achieved because the data were not yet mature.

Median overall survival in the ITT population was 72.7 weeks and 64.9 weeks (HR. 0.876, 95% CI, 0.679 – 1.129, p = 0.306) in the SUTENT® and placebo arms respectively. In this analysis, the placebo arm included those patients randomized to placebo who subsequently received open label - SUTENT® treatment.

Study B

Study B was an open-label, multi-center, single-arm, dose-escalation study conducted in patients with GIST following progression on or intolerance to imatinib. Following identification of the recommended Phase 2 regimen (50 mg once daily on Schedule 4/2), 55 patients in this study received the 50 mg dose of SUTENT® on treatment Schedule 4/2. Partial responses were observed in 5 of 55 patients [9.1% PR rate, 95% CI (3.0, 20.0)].

Metastatic Renal Cell Carcinoma (MRCC)

The use of single agent SUTENT® in the treatment of cytokine-refractory MRCC was investigated in two single-arm, multi-center studies. All patients enrolled into these studies experienced failure of prior cytokine-based therapy. In Study 1, failure of prior cytokine therapy was based on radiographic evidence of disease progression defined by RECIST or World Health Organization (WHO) criteria during or within 9 months of completion of 1 cytokine therapy treatment (interferon-α, interleukin-2, or interferon-α plus interleukin-2; patients who were treated with interferon-α alone must have received treatment for at least 28 days). In Study 2, failure of prior cytokine therapy was defined as disease progression or unacceptable

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treatment-related toxicity. The primary endpoint for both studies was ORR. Duration of response (DR) was also evaluated.

One hundred six patients were enrolled into Study 1, and 63 patients were enrolled into Study 2. Patients received 50 mg SUTENT® on Schedule 4/2. Therapy was continued until the patients met withdrawal criteria or had progressive disease. The baseline age, gender, race and ECOG performance statuses of the patients were comparable between Studies 1 and 2. Approximately 86-94% of patients in the two studies were white. Men comprised 65% of the pooled SUTENT® population. The median age was 57 years and ranged from 24 to 87 years in the studies. All patients had an ECOG performance status <2 at the screening visit.

The baseline malignancy and prior treatment history of the patients were comparable between Studies 1 and 2. Across the two studies, 95% of the pooled population of patients had at least some component of clear-cell histology. All patients in Study 1 were required to have a histological clear-cell component. Most patients enrolled in the studies (97% of the pooled population) had undergone nephrectomy; prior nephrectomy was required for patients enrolled in Study 1. All patients had received one previous cytokine regimen. Metastatic disease present at the time of study entry included lung metastases in 81% of patients. Liver metastases were more common in Study 1 (27% vs. 16% in Study 2) and bone metastases were more common in Study 2 (51% vs. 25% in Study 1); 52% of patients in the pooled population had at least 3 metastatic sites. Patients with known brain metastases or leptomeningeal disease were excluded from both studies.

Results of Studies 1 and 2
The ORR and DR data from Studies 1 and 2 are provided in Table 4.

Table 4 – MRCC Efficacy Results

Efficacy Parameter	**Study 1 (N = 106)**	**Study 2 (N = 63)**
Objective Response Rate (PR) [%, (95% CI)]	25.5[1] (17.5, 34.9)	36.5[2] (24.7, 49.6)
Duration of Response [median, weeks (95% CI)]	27.1(24.4, *)	54 (34.3, 70.1)

Abbreviations: CI=Confidence interval, PR=Partial response.
[1] Assessed by blinded core radiology laboratory.
[2] Assessed by investigators.
* Data not mature enough to determine upper confidence limit.

There were 27 PRs in Study 1 as assessed by a core radiology laboratory for an ORR of 25.5% (95% CI: 17.5, 34.9). There were 23 PRs in Study 2 as assessed by the investigators for an ORR of 36.5% (95% CI: 24.7, 49.6). The majority (>90%) of objective disease responses were observed during the first four cycles; the latest reported response was observed in cycle 10. DR data from Study 1 is premature as only 4 of 27 patients (15%) responding to treatment had experienced disease progression. At the time of the data cutoff, Study 1 was ongoing with 44 of 106 patients (41.5%) continuing treatment, and 11 of the 63 patients (17.5%) enrolled on Study 2 continued to receive SUTENT® on continuation protocols.

Pancreatic Neuroendocrine Tumours (pNET)
A supportive phase 2, open-label, multi-center study evaluated the efficacy and safety of

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single-agent SUTENT® 50 mg daily on Schedule 4/2 [4 weeks on treatment, 2-week rest period] in patients with unresectable pNET. In a pancreatic islet cell tumour cohort of 66 patients, the primary endpoint of response rate was 17%. A pivotal phase 3, multi-centre, international, randomized, double-blind placebo-controlled study of single-agent sunitinib was conducted in patients with unresectable pNET. Patients were required to have documented progression, based on RECIST, within the prior 12 months and were randomized (1:1) to receive either 37.5 mg sunitinib once daily without a scheduled rest period (n=86) or placebo (n=85). The primary objective was to compare Progression-Free Survival (PFS) in patients receiving sunitinib *versus* patients receiving placebo. Other endpoints included Overall Survival (OS), Objective Response Rate (ORR), Patient-reported Outcomes (PRO), and safety. Demographics were comparable between the sunitinib and placebo groups. Additionally, 49% of sunitinib patients had non-functioning tumours *versus* 52% of placebo patients and 92% patients in both arms had liver metastases. Use of somatostatin analogs was allowed in the study. A total of 66% of sunitinib patients received prior systemic therapy compared with 72% of placebo patients. In addition, 24% of sunitinib patients had received somatostatin analogs compared with 22% of placebo patients. A clinically significant advantage in investigator-assessed PFS for sunitinib over placebo was observed. The median PFS was 11.4 months for the sunitinib arm compared to 5.5 months for the placebo arm [hazard ratio: 0.418 (95% CI: 0.263, 0.662), p-value =0.0001]; similar results were observed when derived tumour response assessments based upon application of RECIST to investigator tumour measurements were used to determine disease progression, as shown in Table 6. A hazard ratio favouring SUTENT® was observed in all subgroups of baseline characteristics evaluated, including an analysis by number of prior systemic therapies. A total of 29 patients in the sunitinib arm and 24 in the placebo arm had received no prior systemic treatment; among these patients, the hazard ratio for PFS was 0.365 (95% CI: 0.156, 0.857), p=0.0156. Similarly, among 57 patients in the sunitinib arm (including 28 with 1 prior systemic therapy and 29 with 2 or more prior systemic therapies) and 61 patients in the placebo arm (including 25 with 1 prior systemic therapy and 36 with 2 or more prior systemic therapies) who had received prior systemic therapy, the hazard ratio for PFS was 0.456 (95% CI: 0.264, 0.787), p=0.0036.

A sensitivity analysis of PFS was conducted where progression was based upon investigator-reported tumour measurements and where all subjects censored for reasons other than study termination were treated as PFS events. This analysis provided a conservative estimate of the treatment effect of sunitinib and supported the primary analysis, demonstrating a hazard ratio of 0.507 (95% CI: 0.350, 0.733) and p=0.000193. The pivotal study in pancreatic NET was terminated prematurely at the recommendation of an independent Drug Monitoring Committee, and the primary endpoint was based upon investigator assessment, both of which may have affected the estimates of the treatment effect.

In order to rule out bias in the investigator-based assessment of PFS, a blinded independent central review (BICR) of scans was performed and supported the investigator assessment, as shown in Table 5.

Table 5 - pNET Efficacy Results from the Phase 3 Study

Efficacy Parameter	**SUTENT® (n=86)**	**Placebo (n=85)**	**HR (95% CI)**	**p-value**

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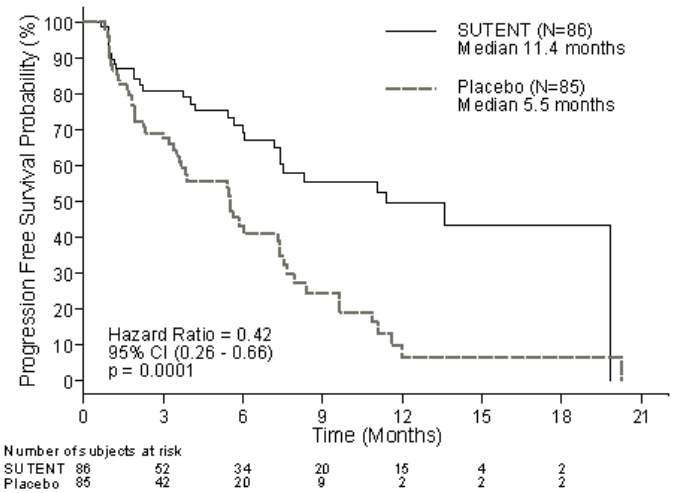
Progression-Free Survival [median, months (95% CI)] by Investigator Assessment	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	0.418 (0.263, 0.662)	0.0001[a]
Progression-Free Survival [median, months (95% CI)] by derived tumour response assessment based upon application of RECIST to investigator tumour assessments	12.6 (7.4, 16.9)	5.4 (3.5, 6.0)	0.401 (0.252, 0.640)	0.000066[a]
Progression-Free Survival [median, months (95% CI)] by blinded independent central review of tumour assessments	12.6 (11.1, 20.6)	5.8 (3.8, 7.2)	0.315 (0.181, 0.546)	0.000015[a]
Overall Survival [median, months (95% CI)]	20.6 (20.6, NR)	NR (15.5, NR)	0.409 (0.187, 0.894)	0.0204[a]
Objective Response Rate [%, (95% CI)]	9.3 (3.2, 15.4)	0	NA	0.0066[b]

Abbreviations: CI=Confidence interval, HR=Hazard ratio, NA=Not applicable, NR=Not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; pNET= pancreatic neuroendocrine tumors; RECIST= Response Evaluation Criteria in Solid Tumors.
[a]2-sided unstratified log-rank test.
[b]Fisher's Exact test.

Figure 2 - Kaplan-Meier Curve of PFS in the pNET Phase 3 Study



Abbreviations: CI=confidence interval; N=number of subjects; PFS=progression free survival; pNET=pancreatic neuroendocrine tumors.

OS data were not mature at the time of the analysis. There were 9 deaths in the sunitinib arm and 21 deaths in the placebo arm. A statistically significant difference in ORR favouring sunitinib over placebo was observed.

Upon disease progression, patients were unblinded and placebo patients could have been offered access to open-label SUTENT® in a separate extension study. As a result of the early study

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closure, remaining patients were unblinded and offered access to open-label SUTENT® in an extension study. A total of 59 patients from the placebo arm received SUTENT® in an extension study.

Results from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQC-30) showed that the overall global health-related quality of life and the five functioning domains (physical, role, cognitive, emotional and social) were maintained for patients on sunitinib treatment as compared to placebo with limited adverse symptomatic effects.

PRECLINICAL SAFETY DATA

In rat and monkey repeated-dose toxicity studies up to 9-months duration, the primary target organ effects were identified in the gastrointestinal tract (emesis and diarrhea in monkeys), adrenal gland (cortical congestion and/or hemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats), hemolymphopoietic system (bone morrow hypocellularity, and lymphoid depletion of thymus, spleen, and lymph node), exocrine pancreas (acinar cell degranulation with single cell necrosis), salivary gland (acinar hypertrophy), bone joint (growth plate thickening), uterus (atrophy) and ovaries (decreased follicular development). All findings occurred at clinically relevant sunitinib plasma exposure levels. Additional effects, observed in other studies included QTc interval prolongation, LVEF reduction, pituitary hypertrophy, and testicular tubular atrophy, increased mesangial cells in kidney, hemorrhage in GI tract and oral mucosa, and hypertrophy of anterior pituitary cells. Changes in the uterus (endometrial atrophy) and bone growth plate (physeal thickening or dysplasia of cartilage) are thought to be related to the pharmacological action of sunitinib. Most of these findings were reversible after 2 to 6 weeks without treatment.

Genotoxicity The genotoxic potential of sunitinib was assessed *in vitro* and *in vivo*. Sunitinib was not mutagenic in bacteria using metabolic activation provided by rat liver. Sunitinib did not induce structural chromosome aberrations in human peripheral blood lymphocyte cells *in vitro.* Polyploidy (numerical chromosome aberrations) was observed in human peripheral blood lymphocytes *in vitro*, both in the presence and absence of metabolic activation. Sunitinib was not clastogenic in rat bone marrow *in vivo.* The major active metabolite was not evaluated for genotoxic potential.

Carcinogenicity The carcinogenic potential of sunitinib has been evaluated in rasH2 transgenic mice. Gastroduodenal carcinomas, an increased incidence of background haemangiosarcomas, and/or gastric mucosal hyperplasia have been observed at doses of ≥25 mg/kg/day following 1- or 6-months duration (≥7.3 times the AUC in patients administered the RDD). No proliferative changes were observed in rasH2 transgenic mice at 8 mg/kg/day (≥0.7 times the AUC in patients administered the RDD). The relevance of the carcinogenicity findings observed in the rasH2 transgenic mouse to humans following 1- and 6-months sunitinib treatment is unclear.

Reproductive and Developmental Toxicity No effects on male or female fertility were observed in reproductive toxicity studies. However, in repeated-dose toxicity studies performed in rats and monkeys, effects on female fertility were observed in the form of follicular atresia, degeneration of corpora lutea, endometrial changes in the uterus and decreased uterine and ovarian weights at clinically relevant systemic exposure levels. Effects on male fertility in rat were observed in the form of tubular atrophy in the testes, reduction of spermatozoa in epididymides and colloid depletion in prostate and seminal vesicles at plasma exposure levels 25-fold higher than observed

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in clinic.

In rats, embryo-foetal mortality was evident as significant reductions in the number of live foetuses, increased numbers of resorptions, increased post-implantation loss, and total litter loss in 8 of 28 pregnant females at plasma exposure levels 5.5-fold higher than observed in clinic. In rabbits, reductions in gravid uterine weights and number of live foetuses were due to increases in the number of resorptions, increases in post-implantation loss and complete litter loss in 4 of 6 pregnant females at plasma exposure levels 3-fold higher than observed in clinic. Sunitinib treatment in rats during organogenesis resulted in developmental effects at ≥5 mg/kg/day consisting of increased incidence of foetal skeletal malformations, predominantly characterized as retarded ossification of thoracic/lumbar vertebrae and occurred at plasma exposure levels 6-fold higher than is observed in clinic. In rabbits, developmental effects consisted of increased incidence of cleft lip at plasma exposure levels approximately equal to that observed in clinic, and cleft lip and cleft palate at plasma exposure levels 2.7-fold higher than observed in clinic.

CLINICAL PARTICULARS

INDICATIONS AND USAGE

SUTENT® is indicated for the treatment of gastrointestinal stromal tumor (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. Efficacy is based on time to tumor progression and an increase in survival.

SUTENT® is indicated for the treatment of metastatic renal cell carcinoma (MRCC) after failure of cytokine-based therapy. Approval for metastatic renal cell carcinoma is based on partial response rates and duration of responses. There are no randomized trials of SUTENT® demonstrating clinical benefit, such as increased survival or improvement in disease-related symptoms in renal cell carcinoma.

SUTENT® is indicated for the treatment of patients with pancreatic neuroendocrine tumors (pNET).

DOSAGE AND ADMINISTRATION

The recommended dose of SUTENT® for treatment of GIST and metastatic RCC is one 50-mg oral dose taken once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2) to comprise a complete cycle of 6 weeks.

The recommended dose of SUTENT® for pNET is 37.5 mg (3 Capsules of 12.5 mg concomitantly) taken orally once daily without a schedule rest period.

SUTENT® 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.

Dose Modification

Safety and Tolerability

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

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For pNET, dose modification in 12.5 mg increments or decrements may be applied based on individual safety and tolerability. The maximum dose administered in the Phase 3 pNET study was 50 mg daily.

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

CYP3A4 Inhibitors/Inducers
Co-administration of SUTENT® with potent CYP3A4 inducers, such as rifampin, should be avoided (see Section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS**). If this is not possible, the dose of SUTENT® may need to be increased in 12.5 mg increments to a maximum of 87.5 mg (GIST and RCC), or 62.5 mg (pNET) daily, based on careful monitoring of tolerability.

Co-administration of SUTENT® with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided (see Section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS**). If this is not possible, the dose of SUTENT® may need to be reduced in 12.5 mg decrements to a minimum of 37.5 mg (3 Capsules of 12.5 mg concomitantly) (GIST and MRCC), or 25 mg (pNET) daily.

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

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

Use in the Elderly: Dose adjustments are not required in elderly patients. Approximately 34% of the subjects in clinical studies of sunitinib were 65 years of age or over. No significant differences in safety or efficacy were observed between younger and older patients.

Hepatic Insufficiency: No dose adjustment is necessary when administering sunitinib to patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Sunitinib was not studied in subjects with severe (Child-Pugh Class C) hepatic impairment (see Section **Pharmacokinetic properties**).

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

CONTRAINDICATIONS
Use of SUTENT® is contraindicated in patients with hypersensitivity to sunitinib malate or to any other component of SUTENT®.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Adverse events described in the following sections for MRCC patients are derived from Study 1 and Study 2. Adverse events discussed for GIST patients are derived from Study A, the randomized, placebo-controlled trial.

Left Ventricular Dysfunction

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In the two MRCC studies, twenty-five patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In GIST Study A, 22 patients (11%) on SUTENT® and 3 patients (3%) on placebo had treatment-emergent LVEF values below the LLN. Nine of twenty-two GIST patients on SUTENT® with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction- 1 patient; addition of antihypertensive or diuretic medications- 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT® had Grade 3 reductions in left ventricular systolic function to LVEF <40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In GIST Study A, 1 patient (<1%) on SUTENT® and 1 patient (1%) on placebo died of diagnosed heart failure; 2 patients (1%) on SUTENT® and 2 patients (2%) on placebo died of treatment-emergent cardiac arrest.

Patients who presented with cardiac events within 12 months prior to SUTENT® administration, such as myocardial infarction (including severe/unstable angina), coronary/peripheral artery bypass graft, symptomatic congestive heart failure (CHF), cerebrovascular accident or transient ischemic attack, or pulmonary embolism were excluded from SUTENT® clinical studies. It is unknown whether patients with these concomitant conditions may be at a higher risk of developing drug-related left ventricular dysfunction. Physicians are advised to weigh this risk against the potential benefits of the drug. These patients should be carefully monitored for clinical signs and symptoms of CHF while receiving SUTENT®. Baseline and periodic evaluations of LVEF should also be considered while the patient is receiving SUTENT®. In patients without cardiac risk factors, a baseline evaluation of ejection fraction should be considered.

In the presence of clinical manifestations of CHF, discontinuation of SUTENT® is recommended. The dose of SUTENT® should be interrupted and/or reduced in patients without clinical evidence of CHF but with an ejection fraction <50% and >20% below baseline.

Hemorrhagic Events

Treatment-emergent bleeding events occurred in 44/169 patients (26%) receiving SUTENT® for MRCC and 37/202 patients (18%) receiving SUTENT® in GIST Study A, compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Treatment-related bleeding events, excluding epistaxis, occurred in 21.7% of patients receiving sunitinib in the Phase 3 pNET study compared to 9.85% of patients receiving placebo. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In GIST Study A, 14/202 patients (7%) receiving SUTENT® and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in Study A taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

Hemorrhagic events reported through post-marketing experience, some of which were fatal, have included GI, respiratory, tumor, urinary tract and brain hemorrhages. Tumor-related hemorrhage has been observed in patients treated with SUTENT®. These events may occur suddenly, and in the case of pulmonary tumors may present as severe and life-threatening hemoptysis or pulmonary hemorrhage. Fatal pulmonary hemorrhage occurred in 2 patients receiving SUTENT® on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Both patients had squamous cell histology. SUTENT® is not approved for use in patients with NSCLC. Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving SUTENT® on Study A. Tumor hemorrhages were observed as early as cycle 1

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and as late as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the Study A placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage has not been observed in patients with MRCC. Clinical assessment of these events should include serial complete blood counts (CBCs) and physical examinations.

QT Interval Prolongation

At approximately twice the therapeutic concentrations, sunitinib has been shown to prolong the QTcF (Fridericia's correction) interval (see Section **Special Populations**). There were no patients with greater than Grade 2 Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) QT/QTc interval prolongation. QT interval prolongation may lead to an increased risk for 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 patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. Concomitant treatment with strong CYP3A4 inhibitors, which may increase sunitinib plasma concentrations, should be used with caution and the dose of sunitinib reduced (see Sections **DOSAGE AND ADMINISTRATION** and **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS**).

Hypertension

Hypertension (all grades) was reported in 48/169 MRCC patients (28%), 31/202 GIST patients on SUTENT® (15%), and 11/102 GIST patients on placebo (11%). Grade 3 hypertension was reported in 10 MRCC patients (6%), 9 GIST patients on SUTENT® (4%), and none of the GIST patients on placebo. Hypertension was reported in 26.5% of subjects receiving sunitinib in a Phase 3 pNET study, compared to 4.9% of subjects receiving placebo. Severe hypertension occurred in 10% of pNET subjects on sunitinib and 3% of subjects on placebo. No Grade 4 hypertension was reported. SUTENT® dosing was reduced or temporarily delayed for hypertension in 6/169 MRCC patients (4%), none of the patients in GIST Study A. No patients were discontinued from treatment with SUTENT® due to systemic hypertension. Severe hypertension (>200 mmHg systolic or 110 mmHg diastolic) occurred in 10/169 MRCC patients (6%), 8/202 GIST patients on SUTENT® (4%), and 1/102 GIST patients on placebo (1%). 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.

Adrenal Function

Adrenal toxicity was noted in non-clinical repeat dose studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Histological changes of the adrenal gland were characterized as hemorrhage, necrosis, congestion, hypertrophy and inflammation. In clinical studies, CT/MRI obtained in 336 patients after exposure to one or more cycles of SUTENT® demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of SUTENT®. Among patients with normal baseline ACTH stimulation testing, one patient developed consistently abnormal test results during treatment that are unexplained and may be related to treatment with SUTENT®. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of

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12-16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

Physicians prescribing SUTENT® are advised to monitor for adrenal insufficiency in patients who experience stress such as surgery, trauma or severe infection.

Aneurysms and Artery Dissections

The use of 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.

Thyroid Dysfunction

Baseline laboratory measurement of thyroid function is recommended and patients with hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction on sunitinib treatment.

Acquired hypothyroidism was noted in 6.2% of GIST subjects on sunitinib *versus* 1% on placebo. Hypothyroidism was reported as an adverse event in 7 patients (4%) receiving sunitinib across the two cytokine-refractory MRCC studies; in 61 patients (16%) on sunitinib and three patients (<1%) in the IFN-α arm in the treatment-naïve MRCC study. Additionally, TSH elevations were reported in 4 cytokine-refractory MRCC patients (2%). Overall, 7% of the MRCC population had either clinical or laboratory evidence of treatment-emergent hypothyroidism. In the phase 3 pNET study, hypothyroidism was reported in 6 (7.2%) subjects receiving sunitinib and in one (1.2%) subject on placebo.

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

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.

Skin and Tissues

Skin discoloration, possibly due to the drug color (yellow) was a very common adverse reaction reported in clinical trials. Patients should be advised that depigmentation of the hair or skin may occur during treatment with SUTENT®. Other possible dermatologic effects may include dryness, thickness or cracking of skin, blister or rash on the palms of the hands and soles of the feet. These 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, SUTENT® treatment 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 SUTENT® therapy at a lower dose after resolution of the reaction; some of these patients also received concomitant treatment with corticosteroids or antihistamines.

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Gastrointestinal Disorders

Gastrointestinal disorders, such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting were the most commonly reported treatment-related gastrointestinal events. Supportive care for gastrointestinal adverse events requiring treatment may include anti-emetic or anti-diarrheal medication.

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

Hematological Events

Decreased absolute neutrophil counts and decreased platelet counts were reported in clinical trials. Such events were not cumulative, were typically reversible and generally did not result in treatment discontinuation. No GIST patients receiving placebo experienced either Grade 3 or 4 neutropenia or thrombocytopenia. The rates of dose reductions and delays for hematologic abnormalities were 4% and 2% for neutropenia, 2% and 0% for anemia, and 1% and 1% for thrombocytopenia for MRCC and GIST patients, respectively. One MRCC patient with an adverse event report of Grade 4 thrombocytopenia discontinued treatment. In addition, some cases of fatal hemorrhage associated with thrombocytopenia were reported through post-marketing experience.

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

Patients receiving SUTENT® should be monitored regularly for myelosuppression.

Cardiovascular

Cardiovascular events, including heart failure, cardiomyopathy, myocardial ischemia and myocardial infarction, some of which were fatal, have been reported through post-marketing experience. Use sunitinib with caution in patients who are at risk for, or who have a history of, these events.

Two patients with MRCC experienced Grade 3 myocardial ischemia, one had Grade 2 “cardiovascular toxicity” reported as an adverse event and one patient experienced a fatal myocardial infarction while on treatment.

Cardiac failure, cardiac failure congestive, or left ventricular failure were reported in 0.8% of subjects with solid tumors and 1% of subjects treated with placebo. In the Phase 3 pNET study, 1 (1.2%) subject who received sunitinib had treatment-related fatal cardiac failure.

Data from non-clinical (*in vitro* and *in vivo*) studies indicate that sunitinib has the potential to inhibit the cardiac action potential repolarization process (e.g., prolongation of QT interval). In GIST Study A, 23 patients (11%) on SUTENT® *versus* 12 (12%) on placebo had observed QT prolongation greater than 20 milliseconds from baseline. No consistent, clinically significant QTc prolongation has been observed in completed clinical studies.

Pancreatitis

Pancreatitis has been reported in clinical trials of sunitinib. Grade 3 and 4 increases in serum lipase were observed in 23 (14%) and 4 (2%), respectively, of 169 patients receiving SUTENT® for MRCC. Grade 3 and 4 increases in serum amylase were observed in 8 (5%) and 1 (1%)

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MRCC patients, respectively. Increases in lipase levels were transient and were generally not accompanied by signs or symptoms of pancreatitis in subjects with various solid tumors. Pancreatitis has been observed rarely (<1%) in patients receiving SUTENT® for GIST or MRCC. If symptoms of pancreatitis are present, patients should have SUTENT® discontinued and be provided with appropriate supportive care.

Hepatotoxicity

Hepatotoxicity has been observed in patients treated with sunitinib. Cases of hepatic failure, some with a fatal outcome, were observed in <1% of solid tumor patients treated with sunitinib. Monitor liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) before initiation of treatment, during each cycle of treatment, and as clinically indicated. Sunitinib should be interrupted for Grade 3 or 4 hepatic-related adverse events and discontinued if there is no resolution.

Seizures

In clinical studies of sunitinib, seizures have been observed 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 sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Surgical Procedures

Cases of impaired wound healing have been reported during sunitinib therapy. Temporary interruption of sunitinib therapy is recommended for precautionary reasons in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of therapy following major surgical intervention. Therefore, the decision to resume sunitinib therapy following a major surgical intervention should be based upon clinical judgment of recovery from surgery.

Osteonecrosis of the Jaw (ONJ)

Cases of ONJ have been reported in patients treated with SUTENT®. The majority of cases occurred in patients who had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk. Caution should therefore, be exercised when SUTENT® and i.v. bisphosphonates are used either simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. Prior to treatment with SUTENT®, a dental examination and appropriate preventive dentistry should be considered. In patients who have previously received or are receiving i.v. bisphosphonates, invasive dental procedures should be avoided if possible (see Section **UNDESIRABLE EFFECTS**).

Tumor Lysis Syndrome (TLS)

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

Necrotizing Fasciitis

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Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported. Sunitinib therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.

Thrombotic Microangiopathy
Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), sometimes leading to renal failure or a fatal outcome, has been reported in clinical trials and in post-marketing experience of sunitinib as monotherapy and in combination with bevacizumab. Discontinue sunitinib in patients developing TMA. Reversal of the effects of TMA has been observed after treatment discontinuation.

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

Hypoglycemia
Decreases in blood glucose, in some cases clinically symptomatic, have been reported during sunitinib treatment. Blood glucose levels in diabetic patients should be checked regularly in order to assess if anti-diabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Other commonly reported adverse events included fatigue, high blood pressure, bleeding, swelling, mouth pain/irritation and taste disturbance.

Patients should be advised to inform their health care providers of all concomitant medications, including over-the-counter medications and dietary supplements (see Section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS**).

Laboratory Tests
CBCs with platelet count and serum chemistries including phosphate should be performed at the beginning of each treatment cycle for patients receiving treatment with SUTENT®.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS
Drugs that may **increase** sunitinib plasma concentrations
Concomitant administration of sunitinib with the strong CYP3A4 inhibitor ketoconazole resulted in a 49% and 51% increase of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of sunitinib malate in healthy volunteers.

Administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) may increase sunitinib concentrations. Concomitant administration with inhibitors should therefore, be avoided, or the selection of an alternate concomitant medication with no, or minimal potential to inhibit CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be reduced (see Section **DOSAGE AND ADMINISTRATION**).

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Drugs that may **decrease** sunitinib plasma concentrations

Concomitant administration of SUTENT® with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction of the complex [sunitinib + primary active metabolite] C_{max} and $AUC_{0-\infty}$ values, respectively, after a single dose of SUTENT® in healthy volunteers. Administration of sunitinib with strong inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or *Hypericum perforatum* also known as St. John's Wort) may decrease sunitinib concentrations. Concomitant administration with inducers should therefore, be avoided, or selection of an alternate concomitant medication with no, or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dosage of sunitinib may need to be increased (see Section **DOSAGE AND ADMINISTRATION**).

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

There are no studies in pregnant women using SUTENT®. Studies in animals have shown reproductive toxicity including fetal malformations (see Section **PRECLINICAL SAFETY DATA**). SUTENT® should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the fetus. If SUTENT® is used during pregnancy or if the patient becomes pregnant while on treatment with SUTENT®, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with SUTENT®.

Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and post-natal development study in pregnant rats. Maternal body weight gains were reduced during gestation and lactation at ≥1 mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimate exposure ≥2.3 times the AUC in patients administered the recommended daily dose [RDD]). Reduced offspring body weights were observed during the pre-weaning and post-weaning periods at 3 mg/kg/day. No development toxicity was observed at 1 mg/kg/day (approximate exposure ≥0.9 times the AUC in patients administered the RDD).

Fertility

Based on non-clinical findings, male and female fertility may be compromised by treatment with SUTENT® (see Section **PRECLINICAL SAFETY DATA**).

Lactation

Sunitinib and/or its metabolites are excreted in rat milk. It is not known whether sunitinib or its primary active metabolite are excreted in human milk. Because active substances are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breast-feed while taking SUTENT®.

Pediatric Use

The safety and efficacy of SUTENT® in pediatric patients have not been studied in clinical trials.
Physeal dysplasia was observed in Cynomolgus monkeys with open growth plates treated for ≥3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0 and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The

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incidence and severity of physeal dysplasia were dose-related and were reversible upon cessation of treatment however findings in the teeth were not. A no effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats, the no effect level in bones was ≤2 mg/kg/day.

Geriatric Use
Of the 450 patients with solid tumors reported from clinical studies of SUTENT®, 115 (25.6%) were 65 and over. No overall differences in safety or effectiveness were observed between younger and older patients.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE
No studies on the effects on the ability to drive or operate machinery have been performed. Patients should be advised that they may experience dizziness during treatment with sunitinib.

UNDESIRABLE EFFECTS
Table 6 presents the adverse drug reactions (ADRs) from single-agent studies in advanced RCC, GIST and pNET and from the post-marketing experience. A dataset that pooled the 10 single-agent studies in the marketed indications was used to calculate the treatment-emergent, all-causality frequency category. For the ADRs that were reported from post-marketing experience but not reported in the pooled clinical trial dataset, the frequencies were calculated using the Rule of 3/X methodology. ADRs are listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

Table 6. Adverse Reactions Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Infections and Infestations	Infections*			
Blood and Lymphatic System Disorders	Neutropenia Leukopenia Thrombocytopenia Anaemia	Lymphopenia		Thrombotic microangiopathy[a,]**
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	Headache Dysgeusia	Dizziness Paraesthesia	Cerebral haemorrhage** Cerebrovascular accident** Transient ischaemic attack	Cerebral infarction Posterior reversible encephalopathy syndrome Ageusia
Eye Disorders		Periorbital oedema Eyelid oedema		

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
		Lacrimation increased		
Cardiac Disorders		Myocardial ischemia[b,**] Ejection fraction decreased[c]	Myocardial infarction[d,**] Cardiac failure** Cardiomyopathy** Cardiac failure congestive Electrocardiogram QT Prolonged	Left ventricular failure** Torsade de pointes
Vascular Disorders	Hypertension	Deep vein thrombosis	Aneurysms and artery dissections[e,**] Tumour haemorrhage**	
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea Epistaxis	Pulmonary embolism** Haemoptysis[g,**] Pleural effusion Oropharyngeal pain[f]		
Gastrointestinal Disorders	Abdominal pain[h] Diarrhoea Vomiting Nausea Dyspepsia Stomatitis[i] Constipation	Gastrointestinal haemorrhage** Oesophagitis Abdominal distension Gastro-oesophageal reflux disease Oral pain Glossodynia Gingival bleeding Dry mouth Flatulence	Gastrointestinal perforation** Pancreatitis	
Hepatobiliary Disorders			Hepatic failure** Cholecystitis[j]	
Skin and Subcutaneous Tissue Disorders	Rash[l] Palmar-plantar erythrodysaesthesia syndrome Skin discolouration[k] Hair colour changes Dry skin	Skin reaction Skin lesion Erythema Pruritus Skin exfoliation Blister Alopecia Nail disorder	Dermatitis exfoliative	Stevens-Johnson syndrome** Erythema multiforme** Pyoderma gangrenosum
Musculoskeletal,	Pain in extremity	Myalgia	Fistula formation**	Rhabdomyolysis**

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10,000 to <1/1000
Connective Tissue and Bone Disorders	Arthralgia		Osteonecrosis of Jaw	Myopathy
Renal and Urinary Disorders		Renal failure** Proteinuria Chromaturia	Renal impairment Haemorrhage urinary tract	Nephrotic syndrome
General Disorders and Administration Site Conditions	Fatigue[m] Mucosal inflammation Oedema[n] Pyrexia	Chills Influenza like illness		
Investigations		Haemoglobin decreased Platelet count decreased White blood cell count decreased Lipase increased Blood uric acid increased Amylase increased[o] Weight decreased	Blood creatine phosphokinase increased Blood thyroid stimulating hormone increased	

* Infections and infestations are described in the subsection Description of Selected Adverse Reactions.

** Event may be fatal.

Abbreviations: ADR=adverse drug reaction, GIST=gastrointestinal stromal tumor; n=number of subjects; pNET=pancreatic neuroendocrine tumors; RCC=renal cell carcinoma.

[a] Thrombotic microangiopathy: The following terms have been combined: Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, and Hemolytic uremic syndrome.

[b] Myocardial ischemia: The following terms have been combined: Acute coronary syndrome, Angina pectoris, Angina unstable, Coronary artery occlusion, and Myocardial ischaemia.

[c] Ejection fraction decreased: The following terms have been combined: Ejection fraction decreased and Ejection fraction abnormal.

[d] Myocardial infarction: The following terms have been combined: Acute myocardial infarction, Myocardial infarction, and Silent myocardial infarction.

[e] Aneurysms and artery dissections: The following terms have been combined: Aneurysm ruptured, Aortic aneurysm, Aortic aneurysm rupture, and Aortic dissection.

[f] Oropharyngeal pain: The following terms have been combined: Pharyngolaryngeal pain and Oropharyngeal pain.

[g] Hemoptysis: The following terms have been combined: Hemoptysis and Pulmonary haemorrhage.

[h] Abdominal pain: The following terms have been combined: Abdominal pain, Abdominal pain lower, and Abdominal pain upper.

[i] Stomatitis: The following terms have been combined: Stomatitis and Aphthous stomatitis.

[j] Cholecystitis: The following terms have been combined: Cholecystitis and Acalculous cholecystitis.

[k] Skin discolouration: The following terms have been combined: Skin discolouration, Yellow skin, and Pigmentation disorder.

[l] Rash: The following terms have been combined: Dermatitis psoriasiform, Exfoliative rash, Rash, Rash erythematous, Rash follicular, Rash generalised, Rash macular, Rash maculopapular, Rash papular, and Rash pruritic.

[m] Fatigue: The following terms have been combined: Fatigue and Asthenia.

[n] Oedema: The following terms have been combined: Face oedema, Oedema, and Oedema peripheral.

[o] Amylase increased: The following terms have been combined: Amylase and Amylase increased.

ADR frequencies presented in this section represent the frequencies of the events that occurred in sunitinib-treated subjects regardless of causality assessment.

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The most important serious adverse reactions associated with sunitinib treatment of patients with solid tumors [1] were pulmonary embolism, thrombocytopenia, tumor hemorrhage, febrile neutropenia, and hypertension (see Section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

The most common ADRs of any grade included: fatigue; gastrointestinal disorders, such as diarrhea, nausea, stomatitis, dyspepsia, and vomiting; skin discoloration; rash; palmar-plantar erythrodysesthesia; dry skin; hair color changes; mucosal inflammation; asthenia; dysgeusia; anorexia and hypertension. Fatigue, hypertension, and neutropenia were the most common ADRs of Grade 3 maximum severity, and increased lipase was the most frequently occurring ADR of Grade 4 maximum severity in subjects with solid tumors.

Epistaxis, was the most frequent hemorrhagic ADR, having been reported for approximately half of the subjects with solid tumors[2] who experienced hemorrhagic events (see Section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

In clinical studies of sunitinib, seizures have been observed in subjects with radiological evidence of brain metastases. In addition, there have been reports (<1%), some fatal, of subjects presenting with seizures and radiological evidence of RPLS (see Section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Description of Selected Adverse Reactions

Infections and Infestations

Cases of serious infection (with or without neutropenia), in some cases with fatal outcome, have been reported. The infections observed most commonly with sunitinib treatment are infections typically seen in cancer patients, e.g., respiratory infections (e.g., pneumonia, bronchitis) - *common*, urinary tract infections - *common*, skin infections (e.g., cellulitis) - *common*, sepsis/septic shock - *uncommon*, and abscess (e.g., oral, genital, anorectal, skin, limb, visceral) - *common*. Infections may be bacterial (e.g., intra-abdominal, osteomyelitis) - *common*, viral (e.g., nasopharyngitis, oral herpes) - *common*, or fungal (e.g., candidiasis: oral, esophageal) – *common*. Rare cases of necrotizing fasciitis, including of the perineum, sometimes fatal, have been reported (see Section **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Blood and Lymphatic System Disorders

Rare cases of thrombotic microangiopathy, in some cases with fatal outcome, have been reported. Temporary suspension of sunitinib is recommended; following resolution, treatment may be resumed at the discretion of the treating physician.

Vascular Disorders

Arterial thromboembolic events (ATE)

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

[1] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.
[2] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

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Venous thromboembolic events (VTE)
In the double-blind treatment phase of GIST study, 7 patients (3%) on sunitinib and none on placebo experienced VTE; 5 of the 7 were Grade 3 deep vein thrombosis (DVT), and 2 were Grade 1 or 2. Four of these 7 GIST patients discontinued treatment following first observation of DVT. Thirteen patients (3%) receiving sunitinib for treatment-naïve MRCC and 4 (2%) patients in the 2 cytokine-refractory MRCC studies had VTE reported. Nine of these patients had pulmonary embolism: 1 was Grade 2 and 8 were Grade 4. Eight patients had DVT: 1 with Grade 1, 2 with Grade 2, 4 with Grade 3, and 1 with Grade 4. One patient with pulmonary embolism in the cytokine-refractory MRCC study experienced dose interruption. In treatment-naïve MRCC patients receiving IFN-α, 6 (2%) VTE occurred; 1 (<1%) patient experienced a Grade 3 DVT and 5 (1%) patients had pulmonary embolism, all Grade 4. In the adjuvant treatment of RCC study, pulmonary embolism was reported in 2.0% of patients receiving sunitinib and 0.7% of patients receiving placebo. DVT was reported in 0.3% of patients receiving sunitinib and placebo.

Pulmonary embolism was reported in approximately 2.2% of patients with solid tumors[3] who received sunitinib. None of these events resulted in a patient discontinuing treatment with sunitinib; however, a dose reduction or temporary delay in treatment occurred in a few cases. There were no further occurrences of pulmonary embolism in these patients after treatment was resumed.

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

Long-term Safety in RCC
The long-term safety of sunitinib in patients with metastatic RCC was analyzed across 9 completed clinical studies conducted in the first-line, bevacizumab-refractory and cytokine-refractory treatment settings. The analysis included 5739 patients, of whom 807 (14%) were treated for ≥2 years up to 6 years. Prolonged treatment with sunitinib was not 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

[3] From initial clinical trials including primarily patients with GIST and cytokine-refractory MRCC.

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PT Pfizer Indonesia
Email: IDN.AEReporting@pfizer.com
Website: www.pfizersafetyreporting.com

OVERDOSE
No overdose of SUTENT® was reported in completed clinical studies. In non-clinical studies mortality was observed following as few as 5 daily doses of 500 mg/kg (3000 mg/m^2) in rats. At this dose, signs of toxicity included impaired muscle coordination, head shakes, hypoactivity, ocular discharge, piloerection and gastrointestinal distress. Mortality and similar signs of toxicity were observed at lower doses when administered for longer durations. Treatment of overdose with SUTENT® should consist of general supportive measures. There is no specific antidote for overdosage with SUTENT®. If indicated, elimination of unabsorbed drug should be achieved by emesis or gastric lavage. Cases of overdose have been reported; some cases were associated with adverse reactions consistent with the known safety profile of sunitinib, or without adverse reactions.

PHARMACEUTICAL PARTICULARS
List of Excipients
12.5 mg hard capsules
Capsule content
Mannitol
Croscarmellose sodium
Povidone (K-25)
Magnesium stearate

Capsule shell
Gelatin
Red iron oxide
Titanium dioxide

Printing ink
Shellac
Propylene glycol
Sodium hydroxide
Povidone
Titanium dioxide

Storage Condition
Store below 30°C. Keep in dry place.

Supply
SUTENT® 12.5 mg capsules;
Box, HDPE bottle @ 30 capsules; Reg. No.: DKI0754200701A1

HARUS DENGAN RESEP DOKTER

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Manufactured and Released by:
Pfizer Italia S.r.l.,
Ascoli, Italy

Imported by:
PT Pfizer Indonesia
Jakarta, Indonesia

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Leaflet kemasan: Informasi bagi pengguna

Kapsul keras SUTENT® 12,5 mg

Sunitinib

Bacalah seluruh isi leaflet ini dengan cermat sebelum Anda mulai meminum obat ini karena terdapat informasi penting untuk Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, hubungi dokter atau apoteker Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, meskipun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda merasakan efek samping apa pun, konsultasikan dengan dokter Anda. Termasuk segala bentuk kemungkinan efek samping yang tidak tercantum di dalam leaflet ini. Lihat bagian 4.

Isi leaflet ini

1. Penjelasan tentang SUTENT® dan kegunaannya

SUTENT® diindikasikan untuk pengobatan tumor stromal gastrointestinal (GIST) setelah kegagalan dalam pengobatan menggunakan imatinib mesilat dikarenakan resistansi atau intoleransi. Efikasi didasarkan pada waktu perkembangan tumor dan peningkatan kelangsungan hidup.

SUTENT® diindikasikan untuk pengobatan karsinoma sel ginjal metastasis (MRCC) setelah kegagalan dengan terapi berbasis sitokin. Persetujuan untuk karsinoma sel ginjal metastasis didasarkan pada laju respons parsial atau durasi respons. Tidak terdapat uji coba acak SUTENT® yang menunjukkan manfaat klinis seperti peningkatan kelangsungan hidup atau perbaikan gejala yang berhubungan dengan penyakit dalam karsinoma sel ginjal.

SUTENT® diindikasikan untuk pengobatan terhadap pasien yang menderita tumor neuroendokrin pankreas (pNET).

Jika Anda memiliki pertanyaan terkait cara kerja SUTENT® atau alasan mengapa obat ini diresepkan untuk Anda, silakan tanyakan kepada dokter Anda.

2. Hal yang perlu Anda ketahui sebelum meminum SUTENT®

Jangan meminum SUTENT®

- Jika Anda alergi terhadap sunitinib atau bahan lain yang terkandung dalam SUTENT® (lihat daftar pada bagian 6).

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Peringatan dan langkah-langkah pencegahan

Konsultasikan dengan dokter Anda sebelum meminum SUTENT®:

- **Jika Anda memiliki tekanan darah tinggi.** SUTENT® dapat meningkatkan tekanan darah. Dokter mungkin akan memeriksa tekanan darah Anda selama pengobatan dengan SUTENT®, dan Anda mungkin akan diberi obat untuk menurunkan tekanan darah, bila diperlukan.

- **Jika Anda memiliki atau pernah mengidap penyakit darah, gangguan perdarahan, atau memar.** Pengobatan dengan SUTENT® dapat meningkatkan risiko perdarahan atau menyebabkan perubahan jumlah sel-sel tertentu dalam darah yang dapat menyebabkan anemia atau mempengaruhi kemampuan pembekuan darah. Jika Anda meminum warfarin atau asenokumarol, obat-obatan yang mengencerkan darah untuk mencegah pembekuan darah, maka risiko terjadinya perdarahan menjadi semakin besar. Laporkan kepada dokter Anda jika mengalami perdarahan selama pengobatan dengan SUTENT®.

- **Jika Anda memiliki atau pernah memiliki aneurisma (pembesaran dan pelemahan dinding pembuluh darah) atau adanya sobekan pada dinding pembuluh darah.**

- **Jika Anda memiliki gangguan jantung.** SUTENT® dapat menyebabkan gangguan jantung. Laporkan kepada dokter jika Anda merasa sangat lelah, sesak napas, atau mengalami pembengkakan pada kaki dan pergelangan kaki.

- **Jika Anda mengalami perubahan ritme jantung yang abnormal.** SUTENT® dapat menyebabkan abnormalitas ritme jantung Anda. Dokter Anda dapat melakukan pemeriksaan elektrokardiogram untuk mengevaluasi gangguan ini selama Anda menjalani pengobatan dengan SUTENT®. Laporkan kepada dokter jika Anda merasa pusing, lemah, atau mengalami denyut jantung yang abnormal selama meminum SUTENT®.

- **Jika Anda baru saja mengalami gangguan pembekuan darah dalam vena dan/atau arteri (jenis-jenis pembuluh darah) Anda, termasuk stroke, serangan jantung, emboli, atau trombosis.** Segera hubungi dokter jika Anda mengalami gejala seperti nyeri dada atau tekanan pada dada, nyeri pada lengan, punggung, leher, atau rahang Anda, sesak napas, kebas atau lemah pada salah satu sisi tubuh Anda, kesulitan bicara, sakit kepala, atau pening selama menjalani pengobatan dengan SUTENT®.

- **Jika Anda memiliki atau pernah memiliki kerusakan pada pembuluh darah terkecil yang dikenal sebagai Mikroangiopati Trombotik (TMA).** Sampaikan kepada dokter jika Anda mengalami demam, sangat lelah, lelah, memar, perdarahan, bengkak, gangguan orientasi, kehilangan penglihatan, dan kejang.

- **Jika Anda mengalami gangguan kelenjar tiroid.** SUTENT® dapat menyebabkan gangguan kelenjar tiroid. Laporkan kepada dokter jika Anda menjadi lebih mudah lelah, merasa tubuh Anda lebih dingin dibandingkan orang lain atau suara Anda menjadi berat selama meminum SUTENT®. Fungsi tiroid Anda harus diperiksa sebelum Anda meminum SUTENT® dan secara teratur selama Anda meminumnya. Jika kelenjar tiroid Anda tidak memproduksi hormon tiroid dalam jumlah yang cukup, Anda mungkin perlu menjalani terapi penggantian hormon tiroid.

- **Jika Anda mengalami atau pernah mengalami gangguan pankreas atau kandung empedu.** Laporkan kepada dokter jika Anda mengalami tanda dan gejala berikut ini: nyeri pada area perut (abdomen atas), mual, muntah, dan demam. Ini semua mungkin disebabkan oleh peradangan pada pankreas atau kandung empedu.

- **Jika Anda mengalami atau pernah mengalami gangguan hati.** Laporkan kepada dokter jika Anda mengalami tanda dan gejala gangguan hati berikut ini selama menjalani pengobatan dengan SUTENT®: gatal, mata atau kulit menguning, air seni berwarna gelap, dan rasa nyeri atau tidak nyaman pada area perut bagian atas sebelah kanan. Dokter akan melakukan tes darah untuk memeriksa fungsi hati Anda sebelum dan selama pengobatan dengan SUTENT®, dan sesuai indikasi klinis.

- **Jika Anda mengalami atau pernah mengalami gangguan ginjal.** Dokter akan memantau fungsi ginjal Anda.

- **Jika Anda akan menjalani pembedahan atau baru saja menjalani operasi.** SUTENT® dapat mempengaruhi penyembuhan luka Anda. Biasanya penggunaan SUTENT® akan dihentikan jika Anda harus menjalani operasi. Dokter Anda akan memutuskan kapan saat yang tepat untuk memulai terapi dengan SUTENT® kembali.

- **Anda mungkin akan disarankan untuk menjalani pemeriksaan gigi sebelum memulai pengobatan dengan SUTENT®.**
  - Jika Anda mengalami atau pernah mengalami rasa nyeri di dalam mulut, gigi dan/atau rahang, pembengkakan atau sariawan di dalam mulut, rahang yang terasa kebas atau berat, atau gigi goyah, segera laporkan kepada dokter dan dokter gigi Anda.
  - Jika Anda perlu menjalani terapi gigi atau bedah gigi invasif, laporkan kepada dokter gigi Anda bahwa Anda tengah menjalani pengobatan dengan SUTENT® khususnya jika Anda juga menerima atau pernah menerima bisfosfonat intravena. Bisfosfonat adalah obat-obatan yang digunakan untuk mencegah komplikasi tulang yang mungkin pernah diberikan untuk gangguan kesehatan lainnya.

- **Jika Anda mengalami atau pernah mengalami gangguan kulit atau jaringan subkutan.** Selama Anda menjalani pengobatan ini, Anda berpotensi mengalami "pyoderma gangrenosum" (infeksi kulit yang nyeri) atau "necrotizing fasciitis" (infeksi kulit/jaringan lunak yang menyebar cepat dan dapat mengancam keselamatan jiwa). Kondisi ini umumnya dapat pulih kembali setelah obat dihentikan. Ruam kulit parah (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) telah dilaporkan terjadi selama penggunaan sunitinib, yang awalnya muncul sebagai bintik-bintik kemerahan menyerupai target atau bercak-bercak melingkar sering kali dengan gelembung di bagian tengah pada tubuh. Ruam dapat berkembang menjadi lepuh yang menyebar luas atau pengelupasan kulit dan dapat mengancam jiwa. Jika Anda mengalami ruam atau gejala kulit semacam ini, segera laporkan kepada dokter Anda.

- **Jika Anda mengalami atau pernah mengalami kejang.** Segera laporkan kepada dokter Anda jika Anda memiliki tekanan darah tinggi, sakit kepala, atau hilangnya penglihatan.

- **Jika Anda mengidap diabetes.** Kadar gula darah pada pasien diabetes harus diperiksa secara teratur untuk mengevaluasi apakah dosis obat anti-diabetes perlu disesuaikan guna meminimalkan risiko rendahnya kadar gula darah.

Pasien anak-anak dan remaja

SUTENT® tidak disarankan untuk orang berusia di bawah 18 tahun. SUTENT® belum diteliti pada anak-anak dan remaja.

Obat-obatan lain dan SUTENT®

Laporkan kepada dokter atau apoteker jika Anda sedang meminum, baru-baru ini meminum, atau mungkin meminum obat-obatan lain, termasuk obat-obatan yang diperoleh tanpa resep bahkan obat-obatan yang tidak diresepkan.

Beberapa jenis obat dapat mempengaruhi kadar SUTENT® dalam tubuh Anda. Anda harus melapor kepada dokter jika Anda sedang meminum obat-obatan yang mengandung zat aktif berikut ini:

- ketoconazole, itraconazole – yang digunakan untuk mengobati infeksi jamur.
- erythromycin, clarithromycin, rifampicin – yang digunakan untuk mengobati infeksi
- ritonavir – yang digunakan untuk mengobati HIV
- dexamethasone – kortikosteroid yang digunakan untuk berbagai kondisi
- phenytoin, carbamazepine, phenobarbital – yang digunakan untuk mengobati epilepsi atau gangguan neurologis lainnya
- obat-obatan herbal yang mengandung St. John's Wort (Hypericum perforatum) – yang digunakan untuk mengobati depresi dan kegelisahan

SUTENT® dengan makanan dan minuman

Anda harus menghindari konsumsi jus *grapefruit* selama menjalani pengobatan dengan SUTENT®.

Kehamilan dan menyusui

Jika Anda sedang hamil atau kemungkinan hamil, laporkan kepada dokter Anda.

SUTENT® tidak boleh digunakan selama kehamilan kecuali jika diperlukan. Dokter akan mendiskusikan dengan Anda potensi risiko meminum SUTENT® selama kehamilan.

Jika Anda berpotensi hamil, Anda harus menggunakan metode kontrasepsi yang andal selama menjalani pengobatan dengan SUTENT®.

Laporkan kepada dokter jika Anda sedang menyusui. Jangan menyusui selama menjalani pengobatan dengan SUTENT®.

Mengemudi dan menjalankan mesin

Jika Anda mengalami pening atau rasa lelah yang tidak umum, berhati-hatilah saat mengemudi atau menggunakan mesin.

3. Cara meminum SUTENT®

Minumlah selalu obat ini dengan tepat sesuai petunjuk dokter Anda. Tanyakan kepada dokter jika Anda merasa tidak yakin.

Dokter akan meresepkan dosis yang tepat untuk Anda, bergantung pada jenis kanker yang akan diobati. Jika Anda menjalani pengobatan karena GIST atau MRCC, dosis yang umum adalah 50 mg satu kali sehari selama 28 hari (4 minggu), diikuti dengan 14 hari (2 minggu) istirahat (tanpa obat), dalam siklus selama 6 minggu. Jika Anda menjalani pengobatan karena pNET, dosis yang umum adalah 37,5 mg (3 Kapsul dosis 12,5 mg sekaligus) satu kali sehari tanpa periode istirahat.

Dokter Anda akan menentukan dosis tepat yang perlu Anda minum serta jika dan ketika Anda perlu menghentikan pengobatan dengan SUTENT®.

Anda dapat meminum SUTENT® sebelum atau sesudah makan.

Jika Anda meminum SUTENT® melebihi dosis yang seharusnya

Jika Anda tidak sengaja meminum kapsul melebihi jumlah yang ditentukan, segera laporkan ke dokter Anda. Anda mungkin memerlukan penanganan medis.

Jika Anda lupa meminum SUTENT®

Jangan meminum dosis ganda untuk menggantikan dosis yang terlupa.

4. Kemungkinan efek samping

Seperti semua obat-obatan yang ada, obat ini dapat menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Anda harus segera menghubungi dokter Anda jika mengalami salah satu efek samping serius tersebut (lihat juga **Apa yang harus Anda ketahui sebelum meminum SUTENT®**):

Gangguan jantung. Laporkan kepada dokter jika Anda merasa kelelahan yang berat, sesak napas, atau pembengkakan pada kaki dan pergelangan kaki. Ini semua merupakan gejala gangguan jantung yang mungkin meliputi gagal jantung dan gangguan otot jantung (kardiomiopati).

Gangguan paru atau pernapasan. Laporkan kepada dokter Anda jika Anda mengalami batuk, nyeri dada, sesak napas mendadak, atau batuk berdarah. Ini semua mungkin merupakan gejala suatu gangguan yang disebut emboli paru yang terjadi ketika darah yang membeku masuk ke paru-paru Anda.

Gangguan ginjal. Laporkan kepada dokter jika Anda mengalami perubahan frekuensi berkemih atau tidak berkemih sama sekali yang mungkin merupakan gejala gagal ginjal.

Perdarahan. Segera laporkan kepada dokter jika Anda mengalami gejala atau gangguan perdarahan serius selama menjalani pengobatan dengan SUTENT® berikut ini: perut (abdomen) nyeri dan bengkak, muntah darah, feses hitam dan pekat, air seni berdarah, sakit kepala atau perubahan kondisi mental Anda, batuk berdarah, atau dahak berdarah dari paru atau saluran pernapasan.

Penghancuran tumor menimbulkan lubang pada usus. Laporkan kepada dokter Anda jika Anda mengalami nyeri abdomen parah, demam, mual, muntah, terdapat darah dalam feses, atau perubahan kebiasaan buang air besar.

Kemungkinan efek samping lainnya selama penggunaan SUTENT® di antaranya:

Efek samping yang sangat umum (dapat dialami oleh lebih dari 1 di antara 10 pasien)
- Infeksi
- Neutropenia
- Leukopenia
- Trombositopenia
- Anemia
- Hipotiroidisme
- Penurunan nafsu makan
- Insomnia
- Gangguan atau berkurangnya indra pengecap
- Sakit kepala
- Hipertensi
- Dispnea
- Epistaksis
- Diare
- Mual

- Muntah
- Nyeri abdomen
- Stomatitis
- Konstipasi
- Dispepsia
- Sindrom tangan-kaki (*Hand-foot syndrome*)
- Diskolorasi kulit
- Ruam
- Perubahan warna rambut
- Kulit kering
- Nyeri ekstremitas
- Nyeri sendi
- Kelelahan
- Peradangan mukosa
- Edema
- Demam

Efek samping yang umum (dapat dialami oleh 1 hingga 10 orang di antara 100 pasien)
- Limfopenia
- Dehidrasi
- Hipoglikemia
- Depresi
- Pusing
- Parestesia
- Edema periorbital
- Edema kelopak mata
- Peningkatan produksi air mata / lakrimasi
- Iskemia miokard
- Penurunan fraksi ejeksi
- Bekuan darah di pembuluh darah
- Nyeri orofaring
- Batuk darah
- Retensi cairan termasuk di sekeliling paru-paru
- Emboli paru
- Perdarahan gastrointestinal
- Esofagitis
- Penyakit refluks gastroesofagus
- Nyeri mulut
- Glosodinia
- Distensi abdomen
- Perdarahan gusi
- Mulut kering
- Kembung
- Rambut rontok
- Eritema
- Gatal pada kulit
- Pengelupasan kulit
- Blister
- Lesi kulit
- Reaksi kulit
- Gangguan kuku

- Nyeri otot
- Gagal ginjal
- Perubahan warna pada urin
- Protein di urin
- Menggigil
- Penyakit menyerupai influenza
- Peningkatan kadar lipase
- Peningkatan kadar amilase
- Peningkatan asam urat darah
- Penurunan jumlah sel darah putih
- Penurunan jumlah trombosit
- Penurunan kadar hemoglobin
- Penurunan berat badan

Efek samping yang tidak umum (dapat dialami oleh 1 hingga 10 orang di antara 1.000 pasien)
- Hipersensitivitas
- Hipertiroidisme
- Perdarahan serebral
- Stroke
- Serangan iskemik transien
- Infark miokard
- Gagal jantung
- Gagal jantung kongestif
- QT Elektrokardiogram Berkepanjangan
- Kardiomiopati
- Perdarahan tumor
- Pankreatitis
- Perforasi gastrointestinal
- Peradangan kandung empedu
- Gagal hati
- Dermatitis eksfoliatif
- Osteonekrosis Rahang
- Pembentukan fistula
- Gangguan ginjal
- Perdarahan saluran kemih
- Peningkatan fosfokinase kreatinin darah
- Peningkatan hormon penstimulasi tiroid darah
- Pembesaran dan pelemahan dinding pembuluh darah atau adanya sobekan pada dinding pembuluh darah (aneurisma dan diseksi arteri)

Efek samping yang langka (dapat dialami oleh 1 hingga 10 orang di antara 10.000 pasien)
- Mikroangiopati trombosis
- Angioedema
- Peradangan kelenjar tiroid
- Sindrom lisis tumor
- Infark serebral
- Sindrom ensefalopati reversibel posterior
- Ageusia
- Gagal ventrikel kiri
- Torsade de pointes
- Eritema multiforme

- Sindrom Stevens-Johnson
- Pioderma gangrenosum
- *Rhabdomyolysis*
- Miopati
- Sindrom nefrotik

Pelaporan efek samping

Jika Anda mengalami efek samping, konsultasikan dengan dokter Anda. Ini termasuk juga segala bentuk efek samping yang tidak tercantum di dalam leaflet ini. Dengan melaporkan efek samping, Anda dapat membantu memberikan lebih banyak informasi perihal keamanan obat ini.

5. Cara menyimpan SUTENT®

- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Jangan menggunakan obat ini melebihi tanggal kedaluwarsa yang tertera pada kemasan luar dan label setelah tanda "EXP". Tanggal kedaluwarsa mengacu pada tanggal terakhir di bulan tersebut.
- Simpan di bawah suhu 30°C pada tempat yang kering.
- Shelf life: 3 tahun (36 bulan).
- Jangan meminum obat ini jika kemasannya rusak atau menunjukkan tanda-tanda kerusakan.

Jangan membuang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada apoteker cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan SUTENT®

Kapsul keras SUTENT® 12,5 mg

Zat aktifnya adalah sunitinib. Setiap kapsul mengandung sunitinib malate yang setara dengan 12,5 mg sunitinib.

Bahan lainnya adalah:
- *Isi kapsul:* Mannitol, Croscarmellose Sodium, Povidone (K-25), dan Magnesium Stearate.
- *Cangkang kapsul:* Gelatin, Red Iron Oxide, dan Titanium Dioxide.
- *Tinta cetak:* Shellac, Propylene Glycol, Sodium Hydroxide, Povidone, dan Titanium Dioxide.

Wujud SUTENT® dan isi kemasannya

SUTENT® 12,5 mg tersedia dalam kapsul gelatin keras dengan tutup dan badan berwarna oranye, legap, berisi granul berwarna kuning hingga oranye. No. Reg.: DKI0754200701A1.

Tersedia dalam kemasan botol plastik berisi 30 kapsul.

HARUS DENGAN RESEP DOKTER

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