



פברואר 2017

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פייזר פרמצבטיקה ישראל בע"מ

רופא/ה, רוקח/ת נכבד/ה,

ברצוננו להודיעך על עדכון בעלונים לרופא ולצרכן של **Sutent 12.5 mg, Sutent 25 mg, Sutent 50 mg** קו תחתי משמעו תוספת טקסט, קו חוצה משמעו מחיקת טקסט, הדגשה משמעה החמרה.

Sunitinib (as malate) 12.5 mg, Sunitinib (as malate) 25 mg, Sunitinib (as malate) 50 mg

#### **Indicated for:**

Sutent is indicated for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate.

Sutent is indicated for the treatment of advanced renal cell carcinoma.

Treatment of unresectable or metastatic, well differentiated pancreatic neuroendocrine tumours (pNET) with disease progression.

#### **להלן העדכונים העיקריים בעלון לרופא:**

### **4. CLINICAL PARTICULARS**

#### **4.2 Posology and method of administration**

##### Hepatic impairment

No starting dose adjustment is recommended when administering sunitinib to patients with mild or moderate (Child-Pugh class A and B) hepatic impairment.

~~Sunitinib and its primary metabolite are primarily metabolized by the liver.~~

~~Systemic exposures after a single dose of sunitinib were similar in subjects with mild or moderate (Child-Pugh Class A and B) hepatic impairment compared to subjects with normal hepatic function.~~

Sunitinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see section 5.2).

~~Studies in cancer patients have excluded patients with ALT or AST >2.5 x ULN or, if due to liver metastases, >5.0 x ULN.~~

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#### **4.4 Special warnings and precautions for use**

##### Haemorrhage and tumour bleeding

Haemorrhagic events, some of which were fatal, reported through post-marketing experience have included gastro-intestinal, respiratory, ~~tumor~~, urinary tract and brain haemorrhages.

Bleeding events occurred in 18% of patients receiving sunitinib in a phase 3 GIST Study compared to 17% of patients receiving placebo. In patients receiving sunitinib for treatment-naïve MRCC, 39% had bleeding events compared to 11% of patients receiving IFN- $\alpha$ . Seventeen (4.5%) patients on sunitinib *versus* 5 (1.7%) of patients on IFN- $\alpha$  experienced Grade 3 or greater bleeding events. Of patients receiving sunitinib for cytokine-refractory MRCC, 26% experienced bleeding. 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. Routine assessment of this event should include complete blood counts and physical examination.

Epistaxis was the most common haemorrhagic adverse reaction, having been reported for approximately half of the patients with solid tumours who experienced haemorrhagic events. Some of the epistaxis events were severe, but very rarely fatal.

Events of tumour haemorrhage, sometimes associated with tumour necrosis, have been reported; some of these haemorrhagic events were fatal.

In clinical trials, tumour haemorrhage occurred in approximately 2% of patients with GIST. These events may occur suddenly, and in the case of pulmonary tumours, may present as severe and life-threatening

haemoptysis or pulmonary haemorrhage. Cases of pulmonary haemorrhage, some with a fatal outcome, have been observed in clinical trials and have been reported in post-marketing experience in patients treated with sunitinib for MRCC, GIST and lung cancer. SUTENT is not approved for use in patients with lung cancer. Less common bleeding events in GIST or MRCC patients included rectal, gingival, upper gastrointestinal, genital, and wound bleeding. In GIST Study A, 14/202 patients (7%) receiving sunitinib 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. Most events in MRCC patients were Grade 1 or 2; there was one Grade 5 event of gastric bleed in a treatment naïve patient.

Bleeding events (excluding epistaxis) occurred in 19% of patients receiving sunitinib for the treatment of pNET compared to 4% of patients receiving placebo. If comedication with anticoagulant occurs, coagulation factors have to be monitored closely.

Treatment emergent Grade 3 and 4 tumor hemorrhage occurred in 5/202 patients (3%) with GIST receiving sunitinib on Study A. Tumor hemorrhages were observed as early as Cycle 1 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.

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

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#### Adrenal Function

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

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 sunitinib demonstrated no evidence of adrenal hemorrhage or necrosis. ACTH stimulation testing was performed in approximately 400 patients across multiple clinical trials of sunitinib. 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 sunitinib. Eleven additional patients with normal baseline testing had abnormalities in the final test performed, with peak cortisol levels of 12–16.4 mcg/dL (normal >18 mcg/dL) following stimulation. None of these patients were reported to have clinical evidence of adrenal insufficiency.

#### 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.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### Medicinal products that may increase sunitinib plasma concentrations

In healthy volunteers, concomitant administration of a single dose of sunitinib with the potent CYP3A4 inhibitor ketoconazole resulted in an increase of the combined [sunitinib + primary metabolite]  $C_{max}$  and  $AUC_{0-\infty}$  values of 49% and 51%, respectively.

Administration of sunitinib with potent CYP3A4 inhibitors (e.g. ritonavir, itraconazole, erythromycin, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole, grapefruit juice) may increase sunitinib concentrations.

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#### Medicinal products that may decrease sunitinib plasma concentrations

In healthy volunteers, concomitant administration of a single dose of sunitinib with the CYP3A4 inducer rifampicin resulted in a reduction of the combined [sunitinib + primary metabolite]  $C_{\max}$  and  $AUC_{0-\infty}$  values of 23% and 46%, respectively.

Administration of sunitinib with potent CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, ~~rifabutin, rifapentin~~, phenobarbital or herbal preparations containing St. John's Wort/*Hypericum perforatum*) may decrease sunitinib concentrations. Combination with CYP3A4-inducers should therefore be avoided, or selection of an alternate concomitant medicinal product, with no or minimal potential to induce CYP3A4 should be considered. If this is not possible, the dose of SUTENT may need to be increased in 12.5 mg increments (up to 87.5 mg per day for GIST and MRCC or 62.5 mg per day for pNET), based on careful monitoring of tolerability (see section 4.2).

#### 4.6 Fertility, pregnancy and lactation

##### Contraception in males and females

Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving treatment with SUTENT.

##### Pregnancy

##### Pregnancy Category D

There are no studies in pregnant women using sunitinib. Studies in animals have shown reproductive toxicity including foetal malformations (see section 5.3). SUTENT should not be used during pregnancy or in women not using effective contraception, unless the potential benefit justifies the potential risk to the foetus.

~~As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of sunitinib should be expected to result in adverse effects on pregnancy. There are no adequate and well-controlled studies of sunitinib in pregnant women.~~

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 postnatal 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  $\geq 0.9$  times the AUC in patients administered the RDD).~~

~~Sunitinib did not cause genetic damage when tested in in vitro assays (bacterial mutation [AMES Assay], human lymphocyte chromosome aberration) and an in vivo rat bone marrow micronucleus test.~~

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#### 4.7 Effects on ability to drive and use machines

~~No studies on the effects~~ **SUTENT has minor influence** ~~on the ability to drive and use machines have been performed.~~ Patients should be advised that they may experience dizziness during treatment with sunitinib.

#### 4.8 Undesirable effects

##### Summary of the safety profile

The most serious adverse reactions associated with sunitinib, some fatal, are renal failure, heart failure, pulmonary embolism, gastrointestinal perforation, and haemorrhages (e.g. respiratory tract, gastrointestinal, tumour, urinary tract, and brain haemorrhages). The most common adverse reactions of any grade (experienced by -patients in RCC, GIST, and pNET registrational trials) included decreased appetite, taste disturbance, hypertension, fatigue, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia and vomiting), ~~rash, dry skin, hair color changes, mucosal inflammation, asthenia~~, skin discolouration, and palmar-plantar erythrodysesthesia syndrome. These symptoms may diminish as treatment continues. Hypothyroidism may develop during treatment. Haematological disorders (e.g. neutropoenia, thrombocypoenia, and anaemia) are amongst the most common adverse drug reactions.

Fatal events other than those listed in section 4.4 above or in section 4.8 below that were considered possibly related to sunitinib included multi-system organ failure, disseminated intravascular coagulation, peritoneal haemorrhage, adrenal insufficiency, pneumothorax, shock, and sudden death.

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## 5. PHARMACOLOGICAL PROPERTIES

### 5.3 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 diarrhoea in monkeys); adrenal gland (cortical congestion and/or haemorrhage in rats and monkeys, with necrosis followed by fibrosis in rats); haemolymphopoietic system (bone marrow 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, haemorrhage in gastrointestinal 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.

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#### 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 ~~18-fold higher than observed in clinic~~ 25 times the systemic exposure in humans.

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~~ 5.5 times the systemic exposure in humans. 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~~ 3 times the systemic exposure in humans. Sunitinib treatment in rats during organogenesis resulted in developmental effects at  $\geq 5$  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 ~~5.5-fold higher than is observed in clinic~~ 5.5 times the systemic exposure in humans. 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~~ 2.7 times the systemic exposure in humans.

~~Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats.~~  
Sunitinib (0.3, 1.0, 3.0 mg/kg/day) was evaluated in a pre- and postnatal development study in pregnant rats.  
Maternal body weight gains were reduced during gestation and lactation at  $\geq 1$  mg/kg/day but no maternal reproductive toxicity was observed up to 3 mg/kg/day (estimate exposure  $\geq 2.3$  times the AUC in patients administered the 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  $\geq 0.9$  times the AUC in patients administered the RDD).

#### להלן העדכונים העיקריים בעלון לצרכן:

#### 2. לפני השימוש בתרופה

אם אתה לוקח או לקחת לאחרונה תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח או לקחת לאחרונה:

- תרופות שבשילוב עם סוטנט® מעלות את ריכוזו בדם:  
נפאזול, קטוקונאזול, איטראקונאזול, זריקונאזול (אנטי פטרייתיים), אריתרומיצין, קלריתרומיצין, טליתרומיצין (אנטיביוטיקות), אטאזאנאביר, אינדינאביר, נלפינאביר, ריטונאביר, סקוויןאביר (לטיפול בנגיף האיידס), מיץ אשכוליות.
- תרופות שבשילוב עם סוטנט® מורידות את ריכוזו בדם:  
דקסמטזון (קורטיקוסטרואיד המשמש לטיפול במצבים שונים כמו אלרגיה/ הפרעות נשימה או מחלות עור), פניטואין, קרבמזפין, פנוברביטל (לאפילפסיה ומחלות נוירולוגיות אחרות), ריפאמפיין, דיפאבוטין, דיפאפנטין (אנטיביוטיקות), הצמח היפריקום (St. John's Wort) (לטיפול בדיכאון).
- וארפארין (לטיפול בקרישיות יתר) - יש להיות במעקב רפואי אחרי רמות מדדי קרישת דם.
- תרופות לטיפול בהפרעות קצב לב, תרופות להורדת כולסטרול ממשפחת הסטינים ותרופות ממשפחת הביספוספונטים (כגון: פוסאלאן) במתן תוך ורידי טרם או במהלך הטיפול עם סוטנט®.

העלונים המעודכנים נשלחו למשרד הבריאות לצורך פרסומם במאגר התרופות שבאתר משרד הבריאות:  
<https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h>

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פרמצבטיקה ישראל בע"מ, שנקר 9, ת.ד. 12133 הרצליה פיתוח, 46725.

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