HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

20 September 2006

SUTENT 12.5 mg, capsule
Bottle of 30 (CIP: 376 265-0)

SUTENT 25 mg, capsule
Bottle of 30 (CIP: 376 266-7)

SUTENT 50 mg, capsule
Bottle of 30 (CIP: 376 267-3)

Applicant: PFIZER

Sunitinib

List I
Medicinal product for hospital prescription only.
To be prescribed only by oncologists or haematologists or doctors specializing in oncology.
Medicinal product requiring specific monitoring during treatment.

Marketing Authorisation (MA) Date: July 19, 2006

Reason for application: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Sunitinib

1.2. Background
Sunitinib is a protein-kinase inhibitor with a double action mechanism: a direct antitumor effect by blocking cell proliferation and an antitumor effect associated with an anti-angiogenic action.

1.3. Indication
SUTENT is indicated:
- For the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance.
- For the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy.

Efficacy data are based on time to tumour progression and an increase in survival in GIST and on objective response rates for metastatic renal cell carcinoma.

1.4. Dosage
The recommended dose of SUTENT is one 50 mg dose orally, taken daily for 4 consecutive weeks, followed by a 2-week rest period (schedule 4/2), corresponding to a complete cycle of 6 weeks.

Dose modifications in 12.5-mg steps may be applied based on individual safety and tolerability. The daily dose should not exceed 87.5 mg nor be decreased below 37.5 mg.

Co-administration of potent CYP3A4 inducers such as rifampin, should be avoided. 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) based on careful monitoring of tolerability.

Co-administration of SUTENT with potent CYP3A4 inhibitors, such as ketoconazole, should be avoided. If this is not possible the doses of SUTENT may need to be reduced to a minimum of 37.5 mg daily, based on careful monitoring of the tolerability.

The choice of an alternate concomitant medication with no, or minimal potential to induce or inhibit CYP3A4 should be considered.

Use in children: The safety and efficacy of SUTENT have not been established in children. SUTENT should not be used in children until further data become available.
Use in elderly: Approximately 25% of the subjects in clinical studies of SUTENT were 65 or over. No significant differences in safety or effectiveness were observed between younger and older patients.
Hepatic insufficiency: No clinical study has been performed in patients with hepatic impairment.
Renal insufficiency: No clinical study has been performed in patients with renal impairment.

SUTENT may be taken with or without food.
If a dose is missed the patient should not take an additional dose but should take the usual prescribed dose on the following day.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2006 Classification

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Protein kinase inhibitors
L01XE04	Sunitinib

2.2. Medicines in the same therapeutic category

Comparator drugs

- For the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST), after failure of imatinib mesylate treatment due to resistance or intolerance.

None

- For the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy.

Sorafenib (NEXAVAR).

2.3. Medicines with a similar therapeutic aim

None

3 ANALYSIS OF AVAILABLE DATA

3.1. In the indication: "Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), after failure of imatinib mesylate treatment due to resistance or intolerance".

The company submitted the results of 2 studies:

- A Phase I/II study (study RTKC-0511-013)
- A Phase III study (study A6181004)

Phase I/II study

The objective of the study was to determine the dosing regimen of sunitinib and to evaluate its efficacy and its safety.

Design

Non-comparative study evaluating the efficacy and safety of sunitinib in 97 patients with gastrointestinal stromal tumours (GIST) after failure of imatinib treatment (GLIVEC) due to resistance or intolerance.

55 patients received 50 mg per day of sunitinib (corresponding to a 4/2 dosing schedule: a daily dose for 4 consecutive weeks followed by a 2-week rest period).

The mean duration of treatment was 40.5 weeks.

Results

Baseline patient characteristics

The mean age of patients was 53.9 years.

Most of the patients had an ECOG[1] score of 0 or 1. All patients had been operated for their GIST.

Failure of imatinib treatment was due to disease progression in 96.4% of patients (53/55) and intolerance in 3.6% of patients (2/55)

The primary endpoints of the study were:

- Median time without tumour progression (progression being defined as an increase of at least 20% in the largest diameter of the lesion observed by imaging)
- Median time without tumour progression or death during the 28 days after the last dose of treatment
- Objective response rate defined by the proportion of patients with a complete or partial response. A partial response was defined by a reduction of at least 30% in the largest diameter of the lesion noted by imaging during treatment

Efficacy was analysed on 55 patients.

[1] The ECOG (Eastern Cooperative Oncology Group) scale value is used to evaluate the patients' general status and as a prognostic factor. This scale is scored from 0 to 4.
0: Fully active, without restriction
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chairs.

Efficacy for the 3 primary endpoints
The median time to tumour progression was 34.0 weeks (95% CI 22.0 – 46.0).
The median time without tumour progression or death was 34.0 weeks (95% CI: 22.0 – 46.0).
The objective response rate was 9.1% including no complete response.

Adverse events
The most frequent adverse events were hypertension (20% of patients) fatigue (16.4%), diarrhoea (10.9%), neutropenia (7.3%) and hand-foot syndrome (9.1%).

Phase III study
Randomised (2:1) double-blind study comparing the efficacy and safety of sunitinib at a dosage of 50 mg per day according to a schedule 4/2 (daily dose for 4 consecutive weeks followed by a 2-week rest period) with those of placebo in 312 GIST patients after failure of imatinib.

The primary endpoint was median time to tumour progression[2].
Secondary endpoints were median time to progression or death, objective response rate, median response duration and overall survival.
These criteria were evaluated by the investigator and an independent review board.

Results
Table 1: Baseline patient characteristics

Characteristics	Sunitinib group (n=207)	Placebo group (n=105)
Mean age	57.1	55.2
ECOG Score[3]		
0	92 (44.4%)	48 (45.7%)
1	113 (54.6%)	55 (52.4%)
Surgery, n (%)	204 (98.6%)	104 (99%)
Failure of imatinib, n (%)		
Intolerance	9 (4.3%)	4 (3.8%)
Disease progression	198 (95.7%)	101 (96.2%)
≤ 6 months	36 (17.4%)	17 (16.2%)
≥ 6 months	162 (78.3%)	84 (80.0%)

The mean duration of treatment was 17.4 weeks in the sunitinib group and 10.3 weeks in the placebo group.
Patients were followed up for 13 months.

[2] With the same definition as that of the phase II study
[3] The ECOG (Eastern Cooperative Oncology Group) scale value is used to evaluate the patients' general status and as a prognostic factor. This scale is scored from 0 to 4.
0: Fully active, without restriction
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chairs.

Efficacy

Primary endpoint:

The median time to progression (evaluated by the independent review board) was 27.3 weeks (i.e. 6.8 months) in the sunitinib group *versus* 6.4 weeks (or 1.6 months) in the placebo group (RR=0.329 95% CI:0.233-0.466. p <0.001).

The median time to progression (evaluated by the investigator) was 28.9 weeks (i.e. 7.2 months) in the sunitinib group *versus* 5.1 weeks (or 1.3 months) in the placebo group (RR=0.281. p <0.001).

Secondary endpoints:

The median time to progression or death was 24.6 weeks (or 6.2 months) in the sunitinib group *versus* 6.4 weeks (or 1.6 months) in the placebo group (RR=0.333. p <0.001).

The objective response rate was 6.8% including no complete response.

Disease progression was observed in 39.6% of patients (82/207) in the sunitinib group *versus* 63.8% patients (67/105) in the placebo group.

29 deaths were recorded among the 207 patients in the sunitinib group *versus* 27 in the 105 patients of the placebo group (RR = 0.491. p=0.007). The reduction in the risk of death was 50%.

Median survival and median response duration were not evaluated because they were not reached in the 2 treatment groups.

The results expressed by the investigator were not different from those of the independent committee

Safety

Safety was evaluated for 304 patients (202 in the sunitinib group; 102 in the placebo group).

The most frequent adverse events were: fatigue, diarrhoea, nausea, anorexia, abdominal pain, skin depigmentation, vomiting, constipation.

The most frequent grade 3 adverse events were: neutropenia, fatigue, anaemia and palmar-plantar erythrodysaesthesia syndrome.

Treatment discontinuation due to adverse events was observed in 9% of patients in the sunitinib group (n=19) and 8% of patients in the placebo group.

Conclusion

A phase III study, carried out in 312 patients with GIST after failure of imatinib, showed a statistically significant improvement of approximately 5 months in the median time to tumour progression in the SUTENT group in comparison with placebo (27.3 weeks in the sunitinib group *versus* 6.4 weeks in the placebo group, p<0.001). The objective response rate was 6.8%; only partial responses were observed.

The reduction in the risk of death was 50%.

The median survival and median response duration were not evaluated as they were not reached in the 2 treatment groups.

3.2. In the indication "treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy"

The company submitted:

- The results of 2 phase II studies (study RTKC-015-014[4], study A6181006[5])
- The results of a third study comparing sunitinib with interferon-alpha as first-line treatment in patients with metastatic renal cell carcinoma. As this study does not correspond to the current indication of the MA, it will not be analyzed.

SUTENT obtained a conditional MA in this indication on the basis of the clinical results of these 2 phase II studies.

The objective of the two phase II studies was to evaluate the efficacy and safety of sunitinib administered at the dosage of 50 mg according to a 4/2 schedule in patients with metastatic renal cell carcinoma refractory to cytokine therapy (interleukin 2 or interferon alpha).

The primary endpoint was the objective response rate.

The objective response rate was defined by the proportion of patients with a complete or partial response to treatment (corresponding to a reduction of at least 30% of the largest diameter of the lesion noted by imaging).

Secondary endpoints were the median response duration, time without progression or death and median overall survival.

Study RTKC-015-014

Non-comparative phase II study in 63 patients with metastatic renal cell carcinoma.

Results

Baseline patient characteristics

The mean age of patients was 59.3 years.
Most of the patients had an ECOG score of 0 or 1.
92.1% of patients had undergone nephrectomy and all had been treated by cytokine.
During cytokine therapy, disease progression was observed in 69.8% of patients (44/63).
The mean duration of sunitinib treatment was 38.8 weeks.
The maximum duration of follow-up was 22 months.

Efficacy

The objective response rate (primary endpoint) was 36.5% (95% CI:24.7-49.6) including no complete response.

The median response duration was 54 months (95% CI: 34.3-70.1).
The median time to progression or death was 37.7 weeks (95% CI: 24.0 – 46.4; i.e. 9.4 months).
Median overall survival was 71.1 weeks. After a median follow-up of one year, survival was 59.7% (95%CI: 46.6-70.5).

A stabilization of the disease was observed in 39.7% of patients.
Disease progression was observed in 11.1% of patients and 52% died.

[4] Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, Li JZ, Bello CL, Theuer CP, George DJ, Rini BI. Activity of SU11248. a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol. 2006 Jan 1;24(1):16-24.

[5] Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, Michaelson MD. Sunitinib in patients with metastatic renal cell carcinoma. JAMA. 2006 Jun 7;295: 2516-2524

Safety
The most frequent adverse events were: fatigue (in 38% of patients), diarrhoea (24%), nausea (19%), stomatitis (19%), dyspepsia (16%), constipation and vomiting (13%). The most frequently observed laboratory abnormalities were lymphopenia, neutropenia, anaemia and increased blood lipase.

Thirty-three patients (52.4%) presented grade 3 adverse events mainly represented by fatigue, increased blood lipase, an increase in amylase and leucopenia.

Adverse events caused treatment discontinuation in 11 patients (17.5%).

Study A6181006

Design

Non-comparative phase II study in 106 patients with metastatic renal cell carcinoma.

Results

Baseline patient characteristics
The mean age of patients was 55.8 years.
Most of the patients had an ECOG score of 0 or 1.
All the patients had undergone nephrectomy and had been treated by cytokines.
During cytokine therapy, disease progression was observed in 59.4% of patients (63/106).
The mean duration of sunitinib treatment was 22.2 weeks.

Efficacy
The analysis was carried out on 105 patients.
The objective response rate was 34% (95% CI: 25-44) in all patients with no complete response.
According to the independent review panel, only 97 patients were evaluable. The response rate in these patients was 38%.
Median time to progression or death was 33.2 weeks (95% CI: 31.2 – 58. i.e. 8.3 months) (32.4 weeks according to the investigator).
The median response duration and overall median survival were not reached.

Disease progression or stabilization of the disease during less than 3 months was observed in 37% of patients and 16% died.

Safety
The results were analysed for all patients.
The most frequent adverse events were: fatigue (50% of patients), diarrhoea (46%), nausea (44%), dysgueusia (47%).
Fifty-one patients (48%) presented grade 3 adverse events. The most frequent grade 3 adverse events were: fatigue, an increase in lipase and hypertension.
Adverse events caused treatment discontinuation in 11 patients (10.4%).

Conclusion

During two non-comparative phase II studies evaluating the efficacy of sunitinib in a total of 169 patients with metastatic renal cell carcinoma, a global response rate (primary endpoint) of from 34 to 38% was observed depending on the study, with no complete response. Results for median survival and overall survival are only available for one study.

There are no comparative data making it possible to quantify the therapeutic effect of sunitinib

As underlined in the Summary of Product Characteristics (SPC), additional data on this product are expected and in particular the effects in terms of progression-free survival.

The main adverse events were gastrointestinal (nausea, vomiting) or systemic reactions (fatigue).

4 CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual Benefit

In the indication: "Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), after failure of imatinib mesylate treatment".

Gastrointestinal stromal tumours are rare mesenchymal tumours that usually develop in the stomach and small intestine. Symptoms include gastrointestinal bleeding, abdominal pain or abdominal discomfort. These tumours are life-threatening.
This medicinal product is intended as curative treatment.
The efficacy/adverse effects ratio is high.
This medicinal product is used for second-line therapy.
There is no alternative therapy

Impact on public health

Gastrointestinal stromal tumours represent a small public health burden.

Improving the management of GIST is a therapeutic necessity falling within the scope of an identified public health priority, which is to improve the management of cancer and rare diseases (GTNDO[6], Rare Diseases Plan).

Developing a response to this need is all the more important as there is currently no effective treatment in the event of failure or intolerance to imatinib mesilate.

A review of the clinical studies shows that:

-SUTENT may be expected to have a moderate theoretical impact on morbidity and mortality. Taking into account the very small population of patients concerned, this drug may only be expected to have a low impact in practice at population level on morbidity and mortality.

-SUTENT may provide a partial response to a public health need.

Consequently, SUTENT is expected to have an impact on public health in this indication. This impact is low.

The actual benefit of SUTENT is substantial.

[6] National Technical Objective Definition group - DGS 2003

In the indication "treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy"

Renal cell carcinoma is the most frequent renal cancer. It is life-threatening. Urological (haematuria, low back pain) and systemic signs (weight loss, pyrexia) are the most frequent clinical signs.

This medicinal product is intended as curative treatment.

The efficacy/adverse effects ratio is high.

This medicinal product is used for second-line therapy.

There is an alternative medication, sorafenib (NEXAVAR).

Public health benefit

Advanced renal cell carcinoma represents a moderate public health burden.

Improving the management of renal cell carcinoma is a theraputic necessity falling withing the scope of an identified public health priority, which is to improve the management of cancer (GTNDO[7], Rare Diseases Plan).

Because of the lack of randomised comparative studies and the low level of proof provided by only the phase II clinical studies in the dossier, the expected impact of SUTENT on morbidity and mortality is difficult to quantify. However, taking into account the results obtained on the global response rate, at best a low impact at population level may be expected in practice on morbidity and mortality. SUTENT may therefore provide a partial response to a public health need.

Consequently, SUTENT is expected to have an impact on public health in this indication. This impact is low.

The actual benefit of SUTENT is substantial.

4.2. Improvement in actual benefit

In GIST

SUTENT provides an important improvement in actual benefit (IAB II) in the management of unresectable and/or metastatic malignant GIST, after failure of imatinib mesylate treatment due to resistance or intolerance.

In advanced and/or metastatic renal cell carcinoma

The Transparency Committee regrets the lack of comparative studies permitting quantification of the therapeutic effect (of sunitinib. Taking into account the previous lack of alternative therapy, SUTENT provides a moderate improvement in actual benefit (IAB III) for the treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy.

The Transparency Committee acknowledges the quantity of the effect observed in the study comparing SUTENT to interferon alpha as a first line treatment for MRCC and will reexamine SUTENT once the data from this study has been validated by the health authorities.

4.3. Role in treatment strategy

In the indication: "Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), after failure of imatinib mesylate treatment due to resistance or intolerance[8]".

Complete surgical resection of the tumour is the only potentially curative treatment of GIST (localised or locally advanced tumours).

[7] National Technical Objective Definition group - DGS 2003

[8] Gastrointestinal stromal tumours (GIST) – Guideline of the French Gastrointestinal Oncology Federation (version of 29-04-2005)

If metastases are present (mainly intra-abdominal, peritoneal and hepatic), resection of the primary tumour is indicated in the event of clinical signs (i.e. occlusion, haemorrhage) and should be performed where possible (depending on other underlying disease and the extent of the surgery) before treatment to avoid the occurrence of local complications.
The efficacy of systemic chemotherapy in GIST at an advanced or metastatic stage is very low, with response rates of between 0 and 10%.
Imatinib (GLIVEC) is the reference treatment for locally advanced or metastatic GIST. It is recommended to continue treatment until disease progression, intolerance or refusal by the patient.
In the event of intolerance or resistance to imatinib, only sunitinib currently has an indication.

In the indication "treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy"

Management of advanced renal cell carcinoma[9]
The aim of treatment of patients with metastatic disease is to improve overall survival and quality of life. However, until now, no treatment has been shown to improve quality of life because only few trials have been carried out with this objective.

The gold standard drug therapy of metastatic disease is immunotherapy (interferon and interleukin 2). Nephrectomy increases the duration of survival in patients receiving interferon and with metastatic disease. In fact, in patients treated with interferon and with a good performance status, nephrectomy is likely to improve patient survival significantly[10].
Cytotoxic chemotherapy is not very effective. No randomized trial has shown a survival benefit of chemotherapy compared with a control group.

Interferon is one of the standard treatments for metastatic renal cell carcinoma, with a modest but real therapeutic benefit. Its use is associated with non serious undesirable effects, such as shivering and fever (flu-like syndrome). On the other hand, no trial has shown a benefit of interleukin 2 treatment in terms of survival.

Role of SUTENT in treatment strategy
Taking into account the lack of any alternative treatment after failure of immunotherapy, sunitinib, like sorafenib, provides a new medication for 2nd-line treatment of renal cell carcinoma.

4.4. Target population

In the indication: "Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), after failure of imatinib mesylate treatment due to resistance or intolerance".
SUTENT treatment in intended for patients with unresectable and/or metastatic malignant gastrointestinal stromal tumours after failure of imatinib treatment.
This population may be estimated from the following data:

- In France, the incidence of GIST is estimated to be approximately 550 cases/year[11]
- 20% of GIST are non-resectable and require treatment by imatinib (expert opinion)
- 50% of patients are diagnosed at a metastatic stage from the outset
- Primary resistance to imatinib is observed in 15% of patients, secondary resistance in 40% of patients[12]
- 5% of patients are intolerant to imatinib.

[9] Arnaud Méjean et al. Tumeurs du rein. Progrès en urologie (2004), 14. 997-1035
[10] Flanigan R., Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer.
[11] Les tumeurs stromales gastrointestinales: prévalence et incidence en France. Société Nationale Française de Gastroentérologie. 2004
[12] Chandu de Silva M.V., Reid R. Gastrointestinal stromal tumours. Orphanet. February 2005

On the basis of this data, the target population of SUTENT in this indication is estimated to be approximately 230 patients.

In the indication "treatment of advanced and/or metastatic renal cell carcinoma (MRCC) after failure of interferon-alpha or interleukin-2 based therapy"

The target population of SUTENT is represented by patients with advanced or metastatic renal cell carcinoma (MRCC) requiring second-line treatment after failing interferon-alpha or interleukin-2 based therapy.

This population may be estimated from the following data:

- In France, there are more than 8,000 new cases of kidney cancer per year.
- Renal cell carcinoma represents 85%[13] of kidney cancers, i.e. 6,800 cases per year.
- 50% of patients are diagnosed at an advanced or metastatic stage from the outset[14]. One third of patients will progress to advanced or metastatic disease[15].
  Overall, the advanced and metastatic stages represent 5,440 patients.
- Approximately 90% of these patients receive immunotherapy and 70% fail this treatment.

The target population of SUTENT in this indication is estimated to be approximately 3,400 cases per year.

Overall, the target population of SUTENT is estimated to be approximately 3,630 patients.

4.5. Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the new indication.

Packaging: Appropriate for the prescription conditions

Reimbursement rate 100%.

[13] EMEA – public summary of positive opinion for orphan designation of sorafenib tosylate for the treatment of renal cell carcinoma

[14] Godley PA, Taylor M. Renal cell carcinoma. Curr Opin Oncol 2001; 13: 199-203.
Bleumer I, Oosterwijk E, De Mulder P, Mulders PF. Immunotherapy for renal cell carcinoma. Eur Urol 2003; 44: 65-75.

[15] Godley PA, Taylor M. Renal cell carcinoma. Curr Opin Oncol 2001; 13: 199-203.