HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

21 September 2011

SUTENT 12.5 mg, hard capsules
B/28 (CIP code: 382 102-2)

SUTENT 25 mg, hard capsules
B/28 (CIP code: 382 103-9)

SUTENT 50 mg, hard capsules
B/28 (CIP code: 382 104-5)

Applicant: PFIZER

sunitinib

ATC Code: L01XE04

List I
Medicine for hospital prescription only. Prescription restricted to oncology or haematology specialists or doctors with cancer training. Medicine requiring specific monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 19 July 2006 - Amendment to Marketing Authorisation: 11 January 2007 - 1 January 2011

Reason for request: Inclusion on list of medicines refundable by National Health Insurance and approved for hospital use in the extension of the indication "for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults".

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Sunitinib

1.2. Indication

"Gastrointestinal stromal tumour (GIST) in adults:
SUTENT is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST), after failure of imatinib treatment due to resistance or intolerance.

Metastatic renal cell carcinoma (MRCC) in adults:
SUTENT is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC).

Pancreatic neuroendocrine tumours (pNET):
SUTENT is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults. Experience with SUTENT as first-line treatment is limited"

1.3. Dosage

"Therapy should be initiated by a physician experienced in the administration of anti-cancer agents.
For pNET,[1] the recommended dose of SUTENT is 37.5 mg taken orally once daily without a scheduled rest period."

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[1] Pancreatic neuroendocrine tumours

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L 01X	Other antineoplastic agents
L01XE	Protein kinase inhibitors
L01XE04	Sunitinib

2.2. Medicines in the same therapeutic category

Comparator medicines
None

2.3. Medicines with a similar therapeutic aim

SUTENT is the only medicinal product to have received Marketing Authorisation for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

Cytotoxics used primarily as concomitant treatments:
- adriamycine (ADRIBLASTINA) and its generics
- streptozocine (ZANOSAR)
- Fluoro-uracile (FLUORO URACILE ICN) and its generics

3. ANALYSIS OF AVAILABLE DATA

The file submitted comprises two studies:

- one non-comparative phase II study (RTKC-0511-015) included a heterogeneous population (carcinoid tumours and pancreatic neuroendocrine tumours) and used a different dosage (daily dose of 50 mg according to the regimen 4/2 [4 weeks of treatment, 2 weeks scheduled rest period]) to that in the Marketing Authorisation. Due to this, the results from this study will not be described.

- a pivotal study A6181111, the results from which are analysed below.

3.1. Efficacy

Study A6181111
A randomised, double-blind study compared sunitinib (SUTENT) to placebo in patients with an advanced unresectable pancreatic neuroendocrine tumour.

The primary efficacy endpoint was progression-free survival (PFS), defined as the time between randomisation and the first date of the first documented progression of the disease or death from any cause.

The secondary endpoints were:
- overall survival (defined as the interval between randomisation and death from any cause).
- objective response rate (complete or partial confirmed according to RECIST criteria[2]),
- duration of response,
- response duration,
- quality of life evaluated using the EORTC QLQ-C30 questionnaire;
- safety.

Randomisation was used to assign the patients to one of the following two groups:
- sunitinib 37.5 mg/day orally (continuous administration)
- placebo

Treatment was continued up until progression of the disease occurred or toxicity, judged as unacceptable by the clinical investigator.
The use of a somatostatin analogue-based symptomatic treatment was authorised for each group.

The main inclusion criteria were as follows:
- diagnosis of a well differentiated pancreatic neuroendocrine tumour confirmed by histology or cytology (according to WHO classification, 2000.)
- localised disease, locally advanced or metastatic with progression documented via imagery (CT, MRI or octreotide scintigraphy scan) during the 12 months prior to the start of the study
- tumour not treatable with surgery, radiotherapy or an associated curative treatment.

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[2] Corresponds to criteria used to assess the response of solid tumours and is summarised as follows:
- Full response: disappearance of all tumour lesions
- Partial response: reduction of 30% of the greatest lesion diameter
- Disease progression: increase of 20% of the highest lesion diameter
- Stable disease: changes in tumour size not meeting the conditions indicated previously.

- presence of at lease one measurable target lesion for subsequent assessment meeting RECIST criteria
- ECOG performance index equal to 0 or 1
- life expectancy of the patient greater than or equal to 3 months
- patients aged over 18
- previous treatments with chemotherapy, loco-regional treatment (e.g. chemoembolisation) or interferon was authorised, only if the toxicity was ≤ grade 1 at the point of entry into the study and that the last treatment took place at least 4 weeks before the start of the study.

Results:

A total of 171 patients were randomised in this study.
The median age was 56 years in the sunitinib group and 57 in the placebo group.
A total of 53 patients (30%) were on first-line treatment: 29 in the sunitinib group and 24 in the placebo group had never received systemic treatment previously. Approximately half of the patients in each group (49% of patients receiving sunitinib, 52% of patients receiving the placebo) had a non-functional tumour and 92% of patients in the two groups had liver metastases.

The median progression-free survival (Primary endpoint) was 11.4 months in the sunitinib group versus 5.5 months in the placebo group (HR=0.418 [CI 95% (0.263; 0.662), with an advantage of 5.9 months in favour of sunitinib.

In February 2009, during the third review of tolerance data and although the study protocol planned for an intermediate analysis of 130 PFS events and a final analysis of 260 PFS events, the review board judged the efficacy based on the results available after the occurrence of 81 events and recommended that the study be stopped. The board considered that this result was sound and used the intermediate analysis of sensitivity data below:
- 20 PRS events: HR = 0.408,
- 50 PFS events: HR = 0.376,
- 73 PFS events: HR = 0.397,
- 81 PFS events: HR = 0.418.

These analyses were not part of the protocol and are for exploratory purposes only.

Overall survival data was not complete at the time of the analysis; there were nine deaths in the sunitinib group and 21 deaths in the placebo group.

The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group (two patients had a complete response and six patients had a partial response).
The median tumour response time was 8.1 months.

Analysis of the results for quality of life using the QLQ-C30 questionnaire did not show any deterioration in the sunitinib group compared with the placebo, except for one case of diarrhoea during all cycles and one case of insomnia during cycles 2 to 7.

Sub-group analysis showed an HR of 0.456 (CI 95%: 0.264 – 0.787) in patients that received one or two previous systemic therapies. The sub-group of patients not previously treated concerned only a small number (n=53), thus no conclusions can be drawn.

The Committee noted that this study was stopped prematurely by the review board, taking into account only the results for the progression-free survival endpoint, but without following the methodological guidelines which allowed the level of evidence of results obtained to be considered satisfactory (some have been specified previously), in particular with the performance of three intermediate analyses (during which the efficacy was assessed) but not included in the protocol.
In this context, reservations can be made:

- on the quality of the study protocol, with significant initial under-estimation of the level of effect of the treatment and the number (and/or the methods) of intermediate analyses required,
- and on the decisions made by the review board, not following the methodology plan.

Furthermore, despite different analyses of sensitivity (clearly of an exploratory nature given the context), the result is formally not significant if the problem of alpha risk is taken into consideration. In addition, the level of effect was probably over-estimated; the magnitude of this over-estimation remaining unknown.
Finally, given the methodological inadequacies mentioned above, the level of evidence of results for this study remains low.

3.2. Adverse effects

Discontinuation of treatment due to adverse events involved 18 patients (21.7%) from the sunitinib group and 14 patients (17.1%) from the placebo group. These events were primarily fatigue, diarrhoea, abdominal pain and hepatic impairment (two cases in each group).
The most commonly observed Grade 3-4 adverse events in the sunitinib group were neutropaenia (12.0% of patients on sunitinib versus 0% of patients in the placebo group), arterial hypertension (9.6% of patients on sunitinib versus 0% of patients in the placebo group), leukopaenia (6.0% of patients on sunitinib versus 0% of patients in the placebo group), palmar-plantar erythrodysaesthesia "hand-foot syndrome" (6.0% of patients on sunitinib versus 0% of patients in the placebo group).

3.3. Conclusion

A randomised, double-blind study compared sunitinib with placebo in patients with an advanced unresectable pancreatic neuroendocrine tumour.
More than two thirds (70%) of patients had received one or two previous systemic therapies.
The results available are from the intermediate analysis carried out on 81 events, although the protocol specified an intermediate analysis of 130 progression-free survival events and a final analysis of 260 events. The premature stopping of the study was decided by the review board for the study.
These 81 events were observed in 171 patients with a median age of 56 years, 53 (30%) of whom were on first-line treatment, with approximately half having a non functional tumour and 92% with liver metastases.

The median progression-free survival (primary endpoint) was 11.4 months in the sunitinib group versus 5.5 months in the placebo group (HR=0.418 [CI 95% (0.263; 0.662).
Overall survival data were not mature at the time of the analysis (only a few events were recorded). There were nine deaths in the sunitinib arm and 21 deaths in the placebo arm.
The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group (two patients had a complete response and six patients had a partial response).
Analysis of the results for quality of life using the QLQ-C30 questionnaire did not show any deterioration in the sunitinib group compared with the placebo, except for one case of diarrhoea during all cycles and one case of insomnia during cycles 2 to 7.

The main reactions observed in the sunitinib group were haematological (neutropaenia) and intestinal (diarrhoea).
The updating of tolerance data in other indications highlighted the risk of osteonecrosis of the jaw (Afssaps - 30 December 2010) which should be particularly taken into consideration in patients who have previously received or are being concomitantly treated with diphosphonates, and justifies a dental examination and care before being treated with SUTENT.

Finally, the data comparing sunitinib versus placebo in the treatment of advanced pancreatic neuroendocrine tumours is based on a single study, the results of which are from an intermediate analysis, not specified in the protocol, and which suggest that there is an improvement in progression-free survival with sunitinib. Due to inadequacies in the methodology (see section 3.1), the level of evidence for this study remains low.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Pancreatic neuroendocrine tumours carry a life-threatening prognosis; this medicinal product is intended as a reducing and/or stabilizer design of tumor
The efficacy/adverse effects ratio is low;
It is a first- or second-line therapy;
There are few treatment alternatives;

Public health benefit:

The incidence of pancreatic cancer in France is estimated at about 10,100 new cases a year (National Health Monitoring Institute (InVs) projections 2010). In 2005, it represented 2.3% of all incidences of cancer and was the fifth cause of death from cancer with 7,782 deaths, of which 51.4% were male and represented 5.3% of all death linked to a cancer. The burden of pancreatic cancer is therefore high.

Nevertheless, the burden of patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET), who could benefit treatment by sutent is weak due to limited number of patients. .

The improvement in the management of patients with cancer and their quality of life is a public health need, which is an established priority (Law of 9 August 2004 on public health policy, Cancer Plan 2009-2013, Plan to improve the quality of life of patients with chronic diseases).

From the results available for the only phase III study stopped prematurely, and the inadequate quality of evidence linked to the intermediate nature of the analysis of data, the theoretical impact of sunitinib in terms of reducing morbidity and mortality cannot be determined.

Furthermore, no improvement in quality of life was demonstrated in the pivotal study and an increase of adverse gastrointestinal problems and insomnia were recorded in this same study.

The transferability of the results of the pivotal study to clinical practice is not assured, given the premature stopping of the study

SUTENT is not expected to have an impact on the health system.

It is not possible to determine whether SUTENT will have the capacity to meet an identified public health need.

Consequently, the public health benefit of SUTENT in this indication is not quantifiable.

The actual benefit provided by SUTENT is moderate.

4.2. Improvement in actual benefit

Given the clinical data available from a pivotal study which had methodological inadequacies (see section 3.1), the transparency Committee considers that SUTENT does not provide an improvement in actual benefit (level V) in the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults.

4.3. Therapeutic use

Neuroendocrine pancreatic tumours (pNET) are generally considered as being an indolent disease and simple monitoring is justifiable, especially if the tumours are localised, well-differentiated and with small size. Currently, treatment is based on surgery even if there are liver metastases. Other treatments could be considered on liver injuries like chemoembolization, radiotherapy or cryotherapy. Patients with unresectable locally advanced or metastatic forms of the disease with progression are a sub-group with a poor prognosis and a life expectancy of 1-3 years. Usual treatment comprises combinations of anthracycline based chemotherapy with doxorubicine - streptozocine regimens. The objective response rate observed after this combination was 69% over a period of 18 months[3] nevertheless these results were not confirmed with other studies.,
SUTENT is a first-line or second-line therapy. However, the low level of evidence demonstrating its use in the treatment of well-differentiated pancreatic neuroendocrine tumours with disease progression means that it can not be placed alongside other treatments currently available.

4.4. Target population

The target population for SUTENT according to the Marketing Authorisation wording is represented by patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET).

In 2010, 10,140pancreatic cancer cases were reported in France (5,300 males and 4,840 females).
Neuroendocrine tumours represented 2% of all pancreatic cancers, or 200 patients, and amongst those 85% were well-differentiated tumours.
The number of patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) would therefore be 170 patients per year.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services in this extension of indication.

At the request of the Ministry of Health, the transparency Committee would like the laboratory to provide data allowing the impact of SUTENT to be assessed from a register of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression in adults, compared with other treatments. These data should allow the progress of patients treated to be described, in terms of morbidity and mortality at two years.

1.1.1. Packaging: Appropriate for the prescription conditions.

1.1.2. Reimbursement rate: 100%

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[3] Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1992; 326 (8): 563-5.