HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 February 2008

TORISEL 25 mg/ml concentrate and diluent for solution for infusion
1 vial of concentrate and 1 vial of diluent (CIP: 571 783-7)

Applicant: WYETH PHARMACEUTICALS FRANCE

temsirolimus

ATC Code: L01XE09

List I
Medicinal product for hospital use only. Prescription restricted to oncology or haematology specialists or cancer specialised doctors. Medicinal product requiring specific monitoring during treatment.

Date of Marketing Authorisation (centralised procedure): 19 November 2007

Orphan drug

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

temsirolimus

It is an inhibitor of the protein mTOR, which controls the induction of transcription of numerous mRNAs involved in carcinogenesis.

1.2. Indication

“TORISEL is indicated for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors.”

1.3. Dosage

“TORISEL must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

The recommended dose of temsirolimus for advanced renal cell carcinoma administered intravenously is 25 mg infused over a 30- to 60-minute period once weekly.

Patients should be given intravenous diphenhydramine 25 to 50 mg (or similar antihistamine)

Treatment with TORISEL should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. No special dose modification is required for any of the populations that have been studied (gender, elderly).

Management of suspected adverse reactions may require temporary interruption and/or dose reduction of temsirolimus therapy. If a suspected reaction is not manageable with dose delays, then temsirolimus may be reduced by 5 mg/week decrements.

Paediatric patients

Experience in paediatric patients is limited. The safety and effectiveness in paediatric patients have not been established. Therefore, the use of TORISEL in the paediatric population is not recommended until further information on effectiveness and safety is available.

Elderly patients

No specific dose adjustment is necessary.

Renal impairment

No dose adjustment of temsirolimus is recommended in patients with renal impairment. Temsirolimus should be used with caution in patients with severe renal impairment.

Hepatic impairment

Temsirolimus should be used with caution in patients with hepatic impairment. Use of temsirolimus in patients with severe hepatic impairment is not recommended.”

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01X	Other antineoplastic agents
L01XE	Protein kinase inhibitors
L01XE09	temsirolimus

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

- ROFERON-A (interferon alpha-2a) indicated in the treatment of advanced renal cancer
- PROLEUKIN (interleukin-2) indicated in the treatment of metastatic renal cell carcinoma
- SUTENT (sutinib) indicated in the treatment of advanced and/or metastatic renal cell carcinoma (MRCC)
- NEXAVAR (sorafenib) indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or who are considered unsuitable for such therapy.

3 ANALYSIS OF AVAILABLE DATA

The company has submitted the results of a phase III study, the objective of which was to evaluate the efficacy and tolerance of temsirolimus alone or in combination with interferon alpha compared with interferon alpha in 626 patients with advanced renal cell carcinoma.
Since the marketing authorisation was granted only for administration of temsirolimus monotherapy, only the results for the temsirolimus alone arm versus interferon alpha will be described in this opinion.

3.1. Efficacy results

Methodology:

Randomised, open-label study comparing temsirolimus with interferon alpha in 416 patients (209 in the temsirolimus arm and 207 in the interferon alpha arm).

Inclusion criteria:

- histologically or cytologically confirmed advanced renal cell carcinoma not previously treated systemically
- 3 or more of 6 prognostic risk factors (Motzer's 5 criteria plus at least 2 metastatic sites):
  - LDH level > 1.5 times the upper limit of normal
  - haemoglobin less than the lower limit of normal
  - corrected serum calcium > 2.5 mmol/l
  - less than one year from time of initial renal cell carcinoma diagnosis to randomisation
  - Karnofsky performance status[1] of 60 or 70
  - at least 2 metastatic sites.

[1] The Karnofsky Performance Status (KPS), ranging from 0 to 100, evaluates a patient's physical abilities. A score < 70 means the patient's general condition is affected.

Dosing regimen:
Patients were randomly assigned to receive either temsirolimus 25 mg weekly or subcutaneous interferon injections 3 times a week at an initial dose of 3 MIU the first week, 9 MIU the second week and 18 MIU from the third week.
Treatment continued until disease progression, symptomatic deterioration or appearance of adverse effects.
Patients were premedicated with antihistamine before each temsirolimus injection and with paracetamol before each interferon alpha injection.

Primary endpoint: median overall survival[2]

Secondary endpoints:
- median progression-free survival time, evaluated by the investigators (by imaging and evaluation of deterioration in patients' symptoms) and an independent committee (by imaging)
- objective response rate (percentage of patients with a complete or partial response)
- clinical benefit rate, defined as the proportion of patients with an objective response or disease stabilisation lasting 24 weeks
- median time to treatment failure
- quality of life, evaluated on two criteria: TWiST[3] (Time Without Symptoms of disease and Toxicity of treatment) and Q-TWiST[4] (Quality-adjusted TWiST).

[2] The study protocol planned:
- an initial interim analysis once 164 deaths had occurred
- a second interim analysis once 430 deaths had occurred.
Although the limit of significance laid down in the protocol had been reached by the time of this second interim analysis, the study continued. The results of the final analysis are therefore available.
[3] The TWiST method consists of comparing treatments in terms of the mean survival time during which patients show no sign of toxicity due to treatment or any symptom of the disease.
[4] The Q-TWiST method takes into account the survival times during which the patients are asymptomatic and/or show signs of toxicity by multiplying each of these periods by a weighting coefficient ranging from 0 (no quality of life) to 1 (perfect quality of life).

Results (ITT population)

The median duration of treatment was 17 weeks in the temsirolimus arm and 8 weeks in the interferon alpha arm.

Main patient characteristics at inclusion:

	Interferon alpha (n=207) n (%)	temsirolimus (n=209) n (%)
Age (years) <65 ≥ 65 Mean (s.d.)	 142 (69) 65 (31.4) 59.2 (10.4)	 145 (69) 64 (30.6) 58.7 (10.0)
Karnofsky Performance Status > 70 60 - 70	 34 (16.5) 171 (83)	 41 (19.6) 168 (80.4)
Risk factors LDH >1.5 N Hb < normal limit corrected serum calcium > 2.5 mmol/l Time from diagnosis to inclusion < 1 year Karnofsky Performance Status ≤ 70 ≥ 2 metastatic sites.	 48 (23) 168 (81) 72 (35) 164 (79.2) 171 (83) 165 (79.7)	 36 (17) 172 (82) 54 (26) 174 (83.3) 168 (80) 166 (79.4)
Number of risk factors ≥ 3 out of 6 < 3 out of 6	 196 (95) 11 (5)	 195 (93) 14 (7)
Risk classification according to MSKCC criteria Poor prognosis (≥ 3 of the first 5 factors) Intermediate prognosis (1 or 2 of the first 5 factors)	 157 (76) 50 (24)	 145 (69) 64 (31)
Previous nephrectomy	139 (67.1)	139 (66.5)

Initial patient characteristics were comparable in the two treatment arms.

Results for the primary endpoint: (ITT analysis)

Median overall survival was 10.9 months [8.6; 12.7] in the temsirolimus arm versus 7.3 months [6.1; 8.8] in the interferon alpha arm (HR = 0.78; 95%CI: [0.63; 0.97]; p=0.0252).

Results for the secondary endpoints:

- median progression-free survival:

According to the analysis by an independent committee, this median progression-free survival was 3.2 months in the interferon alpha arm versus 5.6 months in the temsirolimus arm (HR = 0.74, 95% CI [0.60; 0.91], p=0.0042).

Median progression-free survival as evaluated by the investigators was 1.9 months in the interferon alpha arm versus 3.8 months in the temsirolimus arm (HR = 0.75, 95% CI [0.60; 0.90], p = 0.0028).

- objective response rate:

No statistically significant difference was observed between the two treatment arms.

- clinical benefit rate:
In the temsirolimus arm, 32.1% of patients achieved stabilisation of the disease at 24 weeks or an objective response to treatment versus 15.5% of patients in the interferon alpha arm (p<0.001).

- median time to treatment failure: it was 3.8 months in the temsirolimus arm and 1.9 months in the interferon alpha arm (p<0.0001).

- quality of life:
Time without symptoms of disease and toxicity of treatment (TWiST) was 7.3 months in the temsirolimus arm and 5.7 months in the interferon arm (p=0.021). The Q-TWiST result was 10.6 months in the temsirolimus arm and 8.7 months in the interferon arm (p<0.0098). No quality of life evaluation data are available for the commonly used scales (FACT-G[5] and FKSI[6]).

3.2. Adverse events

The main adverse effects observed in the temsirolimus arm (n=208) compared with the interferon alpha arm (n=200) were as follows: anaemia (45.2% versus 42%), rash (37% versus 5.5%), hyperlipidaemia (27.4% versus 14.5%), hyperglycaemia (25.5% versus 11%), hypercholesterolaemia (24.5% versus 4.5%), peripheral oedema (26.4% versus 8%), pain (27.9% versus 15%), diarrhoea (27.4% versus 19.5%) and stomatitis (19.7% versus 3.5%).
The following adverse effects were more common in the interferon group: pyrexia (49.5% of patients versus 24.5% of patients in the temsirolimus arm), anorexia (43.5% versus 31.7%), and vomiting (28.5% versus 19.2%).
Grade 3-4 adverse effects were more common in the interferon alpha arm (77.5% of patients) than in the temsirolimus arm (66.8%). The most common adverse effects observed were: anaemia (21.5% of patients in the interferon arm versus 19.7% of patients in the temsirolimus arm), asthenia (26% versus 11.1%), and hyperglycaemia (1.5% versus 10.6%).
Treatment discontinuations due to adverse effects involved 18.3% of patients in the temsirolimus arm and 30.5% of patients in the interferon alpha arm.

3.3. Conclusion

The efficacy and tolerance of temsirolimus in the treatment of renal cell carcinoma were evaluated in a phase III, open-label, randomised, comparative study versus interferon alpha including 416 patients. This study was conducted on untreated patients with an unfavourable prognosis (who had at least 3 or the 6 prognostic risk factors).
Median overall survival, the primary endpoint, was 10.9 months in the temsirolimus arm versus 7.3 months in the interferon alpha arm (HR = 0.78; 95%CI: [0.63; 0.97], p=0.0252); i.e. an absolute gain of 3.6 months.
According to the analysis by an independent committee, the median progression-free survival was 3.2 months in the interferon alpha arm versus 5.6 months in the temsirolimus arm (HR = 0.74, 95% CI [0.60; 0.91], p=0.0042).
No statistically significant difference was observed between the two treatment arms on the objective response rate endpoint.
A statistically significant improvement in patients' quality of life assessed by TWiST and Q-TWiST was observed.

[5] The FACT-G (Functional Assessment of Cancer Therapy - General) is a scale for assessing the impact of cancer on quality of life. It is composed of 27 items (total max. score = 108) and 4 dimensions (Physical well-being (PWB) (max. score = 28), Social well-being (SWB) (max. score = 28), Emotional well-being (EWB) (max. score = 24) and Functional well-being (FWB) (max. score = 28).
[6] The FKSI (Functional Assessment of Cancer Therapy - Kidney Symptom Index) is a scale for assessing symptoms associated with renal cancer and its treatments, composed of 15 items (max. score = 60). The FKSI-DRS dimension of the FKSI, comprising 9 items (max. score = 36) more specifically assesses the impact of treatment on the disease symptoms.

The most common adverse effects observed with temsirolimus were gastrointestinal, dermatological and metabolic.
Grades 3-4 adverse effects were more common in the interferon alpha arm.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Renal cell carcinoma is the most frequent type of renal cancer. It is life-threatening. Urological (haematuria, low back pain) and systemic signs (weight loss, pyrexia) are the most frequent clinical signs. In patients with an unfavourable prognosis, the mean overall survival is 6 months[7].
This drug is intended to provide curative treatment.
Its efficacy/adverse effects ratio is high.
This product is first-line medication for the treatment of advanced renal cell carcinoma patients with an unfavourable prognosis.
There are alternative medicinal products available.

Public health benefit:
Advanced renal cell carcinoma represents a moderate public health burden. In the population corresponding to the indication (patients who have at least 3 of the 6 prognostic risk factors) there is only a modest burden, because of the smaller number of patients involved in comparison to the total number of advanced renal cell carcinoma patients in France.
Improved management of this disease is a public health need falling within the scope of the fight against cancer.
In light of the available data, temsirolimus (TORISEL) may be expected to have a small impact in terms of reducing morbidity and mortality compared with interferon alpha in the first-line treatment of metastatic renal cell cancer and in the population of patients with an unfavourable prognosis. The available data are too limited for an evaluation of the product's impact on quality of life
Temsirolimus (TORISEL) is likely to provide a partial response to the identified public health need.
Consequently, TORISEL is expected to benefit public health in this indication. This benefit is low.

The actual benefit is substantial.

4.2. Improvement in actual benefit

In view of the results obtained in a population with an unfavourable prognosis and the size of the effect observed, the Transparency Committee considers that TORISEL provides a substantial improvement in actual benefit (IAB level II) compared with interferon alpha (ROFERON-A) in advanced renal cell carcinoma patients with at least 3 of the 6 prognostic risk factors.

[7] Robert J. Motzer and Ronald M. Bukowski. Targeted therapy for metastatic renal cell carcinoma. J Clin Oncol 2006;24 : 5601 – 5608.

4.3. Therapeutic use

The objective of treatment for patients at the metastatic stage is to improve overall survival and quality of life.

Medical treatment in the metastatic phase is usually based on immunotherapy (interferon and interleukin-2). In addition, nephrectomy in patients treated with interferon provides a benefit in terms of survival time in patients with metastases. Nephrectomy when it is performed in patients in good general health and treated with interferon may significantly improve patient survival[8].
Chemotherapy with cytotoxic drugs is not very effective. No randomized study has shown the benefit of chemotherapy on survival compared to a control group.

Interferon gives a slight but real benefit and is one of the standard treatments for metastatic renal cell carcinoma. Interferon causes troublesome but not very serious adverse effects, such as chills and pyrexia (flu-like syndrome).
In contrast, no study has demonstrated a survival advantage due to the use of interleukin-2. Interleukin-2 is being used less and less because of its toxicity.

A protein kinase inhibitor, sunitinib (SUTENT), has recently proved superior to interferon alpha in first-line treatment for metastatic renal cell carcinoma in terms of progression-free survival.

Role of temsirolimus in treatment strategy

In light of the available results, TORISEL appears to be a new form of first-line treatment for advanced renal cell carcinoma only in patients with an unfavourable prognosis. There are currently no data available for assessing TORISEL in relation to its comparators, particularly SUTENT.
There are currently no data available for assessing its use as first-line treatment for patients with a favourable or intermediate prognosis.

4.4. Target population

The target population of TORISEL comprises advanced or metastatic renal cell carcinoma patients with. an unfavourable prognosis.
This population may be estimated from the following data:
- in France, there are more than 8,000 new cases of kidney cancer per year[9].
- renal cell carcinoma represents 85%[10] of kidney cancers, i.e. 6,800 cases per year.
- 50% of patients are diagnosed at an advanced or metastatic stage from the outset. One third of patients, initially diagnosed at a localised stage, will progress towards an advanced or metastatic stage.

Overall, the advanced and metastatic stages represent 5,440 patients.
- roughly 20%[11] of advanced and metastatic renal cell carcinoma patients have at least 3 prognostic risk factors.

The target population for TORISEL is thus estimated to be approximately 1,000 patients per year.

[8] Study by Flanigan (2001) of 241 patients, 3-month improvement in overall survival
Study by Mickish (2001) of 85 patients, 8-month improvement in overall survival
[9] INVS. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000 (Change in cancer incidence and mortality in France from 1978 to 2000)
[10] EMEA – Public summary of positive opinion for orphan designation of sunitinib for the treatment of renal cell carcinoma
[11] Robert J. Motzer and Ronald M. Bukowski. Targeted therapy for metastatic renal cell carcinoma. J Clin Oncol 2006;24: 5601–5608

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosage given in the marketing authorisation.