The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

27 January 2010

TORISEL 25 mg/ml, concentrate for solution and diluent for solution for infusion
Box containing 1 vial of concentrate for solution 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 doctors with cancer training. Medicine requiring special monitoring during treatment.

Date of designation as orphan drug in the treatment of mantle cell lymphoma: 06 November 2006

Date of Marketing Authorisation (centralised European): 19 November 2007
Date of extension of the indication: 21 August 2009

Reason for the request: Inclusion on the list of medicines approved for hospital use in the extension of the indication “treatment of adult patients with relapsed and/or refractory mantle cell lymphoma”.

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Temsirolimus

1.2. Indications

“Renal cell carcinoma (RCC)
TORISEL is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors (see SPC).

Mantle cell lymphoma (MCL)
TORISEL is indicated for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma [MCL] (see SPC)." 

1.3. Dosage

“Renal cell carcinoma
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 (see SPC for instructions on dilution, administration and disposal)."

“Mantle cell lymphoma
The recommended dosing regimen of temsirolimus for mantle cell lymphoma is 175 mg, infused over a 30-60 minute period once weekly for 3 weeks followed by weekly doses of 75 mg, infused over a 30-60 minute period.

The starting dose of 175 mg was associated with a significant incidence of adverse events and required dose reductions/delays in the majority of patients. The contribution of the initial 175 mg doses to the efficacy outcome is currently not known.”

“Paediatric patients
Experience in paediatric patients is rare. The safety and efficacy 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 (see SPC).

Hepatic impairment
Temsirolimus should be used with caution in patients with hepatic impairment. The use of temsirolimus in patients with moderate (total bilirubin elevated to a value 1.5 to 3 times the upper limit of the normal range [normal] and ASAT higher than normal) or severe (total bilirubin elevated to a value 3 times normal and ASAT higher than normal) hepatic impairment is not recommended (see SPC)."
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)
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

Comparator medicines
No other protein kinase inhibitor is indicated in mantle cell lymphoma.

2.3. Medicines with a similar therapeutic aim

Medicines indicated in non-Hodgkin's lymphoma, either as monotherapy, in combination or in dosing regimens, include in particular:
- ADRIBLASTINE (doxorubicin) and its generics
- CHLORAMINOPHENE (chlorambucil)
- CORTANCYL (prednisone) and its generics
- ENDOXAN (cyclophosphamide)
- FARMORUBICINE (epirubicin) and its generics
- HOLOXAN (ifosfamide)
- NOVANTRONE (mitoxantrone) and its generics
- ONCOVIN (vincristine) and its generics
- VEPESIDE (etoposide) and its generics
3. ANALYSIS OF AVAILABLE DATA

The submitted dossier comprises a phase III study (3066K1-305-WW)\(^1\).

3.1. Efficacy

Open, randomised study comparing two temsirolimus dosing regimens with single-drug chemotherapy in 162 adults with relapsed and/or refractory mantle cell lymphoma.

**Inclusion criteria:**
- mantle cell lymphoma confirmed by histology, immunophenotyping and analysis of cyclin D1;
- adults who have undergone 2 to 7 previous treatments, of which at least one was an alkylating agent or an anthracycline and rituximab and possibly a haematopoietic stem cell transplant;
- Karnofsky index ≥ 60%;
- life expectancy of at least 3 months.

**Treatments (administered until disease progression, development of unacceptable toxicity or for a maximum of 2 years):**
- temsirolimus 175/75 i.v.: TORISEL 175 mg once weekly for 3 weeks, then 75 mg once weekly (n = 54);
- temsirolimus 175/25 i.v.: TORISEL 175 mg once weekly for 3 weeks, then 25 mg once weekly (n = 54);
- single-agent chemotherapy (i.v. or oral administration) as chosen by the investigator, mainly fludarabine, chlorambucil, gemcitabine, cyclophosphamide, cladribine, etoposide, prednisone and dexamethasone (n = 54). Other drugs could be used with the agreement of the sponsor.

**Primary endpoint:** progression-free survival, defined as the length of time between randomization and the first of the following events: tumour progression or death, irrespective of cause (in the four months following the most recent assessment) and evaluated by an independent committee (oncologists and radiologists).

**Secondary endpoints:**
- overall survival, defined as the interval between the date of randomisation and death, irrespective of cause,
- objective response rates in percent (complete and partial responses), evaluated by an independent committee and by the investigators according to the published criteria of the International Workshop for non-Hodgkin’s lymphoma\(^2\).

**Results**

The median age of the patients was 67 years (39-88 years). The majority of the patients were men (81.5%). Stage IV (disseminated disease) was present in over 80% of patients and 85% had a Karnofsky index > 80%.

The diagnosis of mantle cell lymphoma was confirmed in 84% of patients. The median time between diagnosis and randomisation was 42 months. Three-quarters of patients had a typical histological grade and 8% had a blastoid component. The architecture was diffuse in 40% of cases and nodular in 24%.

The patients had undergone a median of 3.5 previous treatment regimens (3 for the temsirolimus 175/75 and 175/25 groups and 4 for the single-agent chemotherapy group).


About 70% of patients had undergone between 2 and 4 previous treatments (including chemotherapy and immunotherapy) and about one third of patients had had radiotherapy and one third a haematopoietic stem cell transplant.

In the group given single-agent chemotherapy as chosen by the investigator, the treatments most often given were gemcitabine i.v. (22 patients = 41.5%) and fludarabine (i.v.: 12 patients = 22.6% or oral: 2 patients = 3.8%).

The median progression-free survival (primary endpoint) was 4.8 months in the temsirolimus 175/75 group, 3.4 months in the temsirolimus 175/25 group and 1.9 months in the single-agent chemotherapy group.

The median progression-free survival did not differ between temsirolimus 175/25 and single-agent chemotherapy. A median absolute increase in progression-free survival of 2.9 months was observed between the temsirolimus 175/75 group and the single-agent chemotherapy group (HR = 0.44 [0.25-0.78]; p = 0.0009). The temsirolimus dosage with a maintenance dose of 75 mg was the one specified in the Marketing Authorisation.

Secondary endpoints:
No differences were observed in median overall survival:
- between temsirolimus 175/75 (10.9 months) and single-agent chemotherapy (5.8 months), HR = 0.62 [0.37-1.05];
- between temsirolimus 175/25 (8.5 months) and single-agent chemotherapy (5.8 months), HR = 0.80 [0.48-1.33].

According to an analysis carried out by the independent committee, the objective response rate in the temsirolimus 175/75 group was 22.2% (of which 1.9% showed a complete response), compared with 1.9% in the single-agent chemotherapy group (p = 0.0019). However, the analysis based on the evaluation by the investigators did not show any difference between the two groups (see Table 1).

Table 1: Efficacy results for objective response (secondary endpoint)

<table>
<thead>
<tr>
<th>In ITT n [%]</th>
<th>Temsirolimus 175/75 [N = 54]</th>
<th>Temsirolimus 175/25 [N = 54]</th>
<th>Single-agent chemotherapy as chosen by the investigator [N = 54]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response 95% CI p</td>
<td>12 (22.2) (11.1; 33.3) 0.0019</td>
<td>3 (5.6) (0; 11.7) NS</td>
<td>1 (1.9) (0; 5.4) /</td>
</tr>
<tr>
<td>Response could not be assessed</td>
<td>14 (25.9)</td>
<td>11 (20.4)</td>
<td>14 (25.9)</td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (20.4)</td>
<td>3 (5.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disease stable</td>
<td>16 (29.6)</td>
<td>17 (31.5)</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Progression</td>
<td>12 (22.2)</td>
<td>23 (42.6)</td>
<td>28 (51.9)</td>
</tr>
</tbody>
</table>

| Objective response 95% CI p | 7 (13) (4; 21.9) NS | 8 (14.8) (5.3; 24.3) 0.0314 | 1 (1.9) (0; 5.9) / |
| Response could not be assessed | 17 (31.5) | 15 (27.8) | 7 (13.) |
| Complete response | 2 (3.7) | 1 (1.9) | 0 (0) |
| Partial response | 5 (9.3) | 7 (13.0) | 1 (1.9) |
| Disease stable | 19 (35.2) | 18 (33.3) | 16 (29.6) |
| Progression | 11 (20.4) | 13 (24.1) | 30 (55.6) |

The results for time to response, duration of response, time to treatment failure and time to progression are not reported, as they are exploratory analyses.
3.2. Adverse effects

The safety data in the indication mantle cell lymphoma are taken from study 3066K1-305-WW (108 patients treated with temsirolimus).

Discontinuation of treatment due to adverse effects was reported in 22.2% of patients in the temsirolimus 175/75 group, 16.7% in the temsirolimus 175/25 group and in 11.3% in the single-agent chemotherapy group.

The number of deaths linked to adverse events was higher in the temsirolimus groups (175/75: 2; 175/25: 3; single-agent chemotherapy: 0). One patient in the temsirolimus 175/75 group and one in the temsirolimus 175/25 group died from adverse events judged to be treatment-related.

Serious adverse events were observed more frequently in the temsirolimus groups than in the single-agent chemotherapy group (see Table 2). The serious adverse events most commonly seen in the temsirolimus groups were general, respiratory and gastrointestinal in nature.

Grade 3 and 4 adverse events occurred more often in the temsirolimus 175/75 group than in the single-agent chemotherapy group (88.9% vs. 67.9%), the most frequent being in particular: thrombocytopenia (59.3% vs. 35.8%), anaemia (20.4% vs. 17%), neutropenia (14.8% vs. 26.4%), hypokalaemia (7.4% vs. 0%), mucositis (5.6% vs. 0%).

<table>
<thead>
<tr>
<th>Number of patients having had at least one adverse event:</th>
<th>Temsirolimus 175/75 [N = 54]</th>
<th>Temsirolimus 175/25 [N = 54]</th>
<th>Single-agent chemotherapy as chosen by the investigator [N = 53]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>51 (94.4%)</td>
<td>52 (96.3%)</td>
<td>48 (90.6%)</td>
</tr>
<tr>
<td>Grade 3 or 4 adverse event</td>
<td>48 (88.9%)</td>
<td>43 (79.6%)</td>
<td>36 (67.9%)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>28 (51.9%)</td>
<td>27 (50.0%)</td>
<td>13 (24.5%)</td>
</tr>
<tr>
<td>Adverse event resulting in discontinuation of treatment</td>
<td>18 (33.3%)</td>
<td>12 (22.2%)</td>
<td>6 (11.3%)</td>
</tr>
</tbody>
</table>

The adverse events most frequently reported in the temsirolimus 175/75 group were haematological (91% vs. 77% in the single-agent chemotherapy group), general (89% vs. 62%), gastrointestinal (83% vs. 47%), respiratory (67% vs. 49%), metabolic (65% vs. 43%) and cutaneous (65% vs. 38%).

Other data:
The SPC of TORISEL states that the loading dose of 175 mg is associated with a significant incidence of adverse events and required dose reductions or a longer interval between infusions in the majority of patients. As a consequence, the company is carrying out a study comparing the efficacy and safety of the currently approved dosing regimen (175/75 mg) with that minus the loading dose (75 mg).

3.3. Conclusion

The efficacy and safety of TORISEL have been evaluated in an open randomised study in 162 adults with mantle cell lymphoma unresponsive to at least two lines of treatment.

The objective of the study was to compare two i.v. temsirolimus dosing regimens (175 mg once weekly for three weeks followed by once-weekly doses of 75 or 25 mg, depending on group) with single-agent chemotherapy as chosen by the investigator.

About 70% of patients had undergone between 2 and 4 previous treatments and about one third of patients had had radiotherapy and one third a haematopoietic stem cell transplant.

The single-agent chemotherapies most commonly chosen by the investigator were gemcitabine (41.5%) and fludarabine (26.4%).
The median progression-free survival (primary endpoint) was 4.8 months in the temsirolimus 175/75 group, 3.4 months in the temsirolimus 175/25 group and 1.9 months in the single-agent chemotherapy group. A median absolute increase in progression-free survival of 2.9 months was observed between the temsirolimus 175/75 group and the single-agent chemotherapy group (HR = 0.44 [0.25-0.78]; p = 0.0009).

The median overall survival did not differ between temsirolimus 175/75 (10.9 months) and single-agent chemotherapy (5.8 months) or between temsirolimus 175/25 (8.5 months) and single-agent chemotherapy (5.8 months).

The objective response rate, as established by an independent committee, was statistically higher in the temsirolimus 175/75 group (22.2%, of which 1.9% showed a complete response) than in the single-agent chemotherapy group (1.9%).

Grade 3 and 4 adverse events occurred more often in the temsirolimus 175/75 group than in the single-agent chemotherapy group (88.9% vs. 67.9%), grade 3 and 4 thrombocytopenia in particular (59.3% vs. 35.8%).

The adverse events most frequently reported in the temsirolimus 175/75 group were haematological (91% vs. 77% in the single-agent chemotherapy group), general (89% vs. 62%), gastrointestinal (83% vs. 47%), respiratory (67% vs. 49%), metabolic (65% vs. 43%) and cutaneous (65% vs. 38%).

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4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Mantle cell lymphoma, characterised by rapid progression, resistance to treatment, and repeated recurrence, is the most aggressive form of indolent non-Hodgkin's lymphoma. This proprietary product is intended as curative therapy.

The efficacy/adverse effects ratio for the 175/75 mg dosage is average.

Public health benefit:

The public health burden of non-Hodgkin's lymphoma in the population of patients requiring treatment with TORISEL (relapsed or refractory mantle cell lymphoma) is low, given the limited number of patients concerned. Improving the management of this disease is a public health need (Cancer Plan/GTNDO\(^3\) priority) that is only partly covered by existing therapies.

On the basis of the available study data [in particular the low efficacy of TORISEL as regards progression-free survival (increase of 3 months), contribution to overall survival yet to be demonstrated, absence of quality of life data], the expected impact on morbidity/mortality and quality of life can only be low.

Consequently, and given the limited size of the population concerned, it is not expected that TORISEL will benefit public health in this indication.

It is intended for third-line or subsequent therapy.

At this stage of the disease, there are few alternative drug therapies.

The actual benefit of TORISEL administered at a dose of 175 mg once weekly for three weeks followed by weekly doses of 75 mg is substantial.

4.2. Improvement in actual benefit (IAB)

On the basis of the available data, the Committee considers that TORISEL offers a minor improvement in actual benefit (IAB level IV) in the management of adults with mantle cell lymphoma unresponsive to at least two previous treatments.

4.3. Therapeutic use

In non-Hodgkin's lymphoma (NHL), certain histological forms justify a particular therapeutic strategy\(^4\), in particular mantle cell lymphoma, which has a poor prognosis associated with the rapid progression typical of aggressive NHL, resistance to treatment, and repeated recurrence characteristic of indolent NHL. Some 60 to 70% of cases are assessed as stage IV (disseminated disease). A point to note is the frequency of extranodal cases, affecting in particular the bone marrow, gastrointestinal tract and liver.

There is no consensus on the therapeutic management of mantle cell lymphoma.

As first-line therapy in the rare stages I and II, chemotherapy followed by radiotherapy is normally indicated in order to achieve long remission\(^5\).

In the advanced stages there is no curative therapy, except for allogeneic bone marrow transplantation, though its use is restricted by patients' age\(^6\).

With the conventional chemotherapies that are normally used, cure cannot be expected. The most commonly used are CHOP\(^7\) or the nucleoside analogues fludarabine (plus cyclophosphamide) or cladribine (plus mitoxantrone), normally in association with anti-CD20

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\(^3\) GTNDO: Groupe Technique National de Définition des Objectifs [National group of experts defining French public health objectives]. DGS [Ministry of Health] 2003

\(^4\) Doctors' guide to chronic conditions: Nodal non-Hodgkin's lymphoma in adults, September 2009


\(^6\) Dreyling: Current treatment standards and emerging strategies in mantle cell lymphoma, ASH 2009

\(^7\) CHOP: cyclophosphamide, doxorubicine, vincristine, prednisone
immunotherapy (rituximab). Although response rates for R-CHOP are close to 90%, with some 40% achieving full remission\(^8\), relapse is inevitable. This is why, in the youngest patients and in the absence of comorbidities, when induction therapy has resulted in complete remission or a very good partial remission, intensification of treatment followed by an autologous stem cell transplant may be proposed.

In the event of relapse in young patients in whom treatment has not yet been intensified, a transplant may be considered. In elderly patients, immunotheraphy based on rituximab, fludarabine, and cyclophosphamide may be an alternative as a temporary treatment regimen. Monotherapy with VELCADE (bortezomib) was approved in the USA in 2006\(^9\) for use in patients who have undergone at least one previous therapy.

Based on the data currently available, TORISEL represents a new option in the management of adults with mantle cell lymphoma unresponsive to at least two previous treatments.

4.4. Target population

The target population of TORISEL is patients with relapsed and/or refractory mantle cell lymphoma, i.e. unresponsive to at least two previous treatments (in accordance with the inclusion criteria of the pivot study).

The incidence of malignant non-Hodgkin’s lymphoma in 2005 was 10,224 cases\(^10\). Mantle cell lymphoma accounts for some 5 to 10% of cases of non-Hodgkin’s lymphoma\(^11\), i.e. 500 to 1000 persons.

Almost all patients with relapsed and/or refractory mantle cell lymphoma eventually become resistant to first-line treatment\(^12\). According to experts, some 75% of patients are candidates for subsequent treatment.

The target population can therefore be estimated at approximately 375 to 750 adults per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the extension of the indication and at the dosage of the Marketing Authorisation pending the results of the study evaluating the need for a temsirolimus loading dose.

The Committee will reassess TORISEL in the light of the results of this study and in the context of the updated therapeutic use.


\(^9\) http://www.cancer.gov/cancertopics/druginfo/fda-bortezomib#Anchor-Mantl-63645

\(^10\) InVS, HCL, Francim, INCa: Presentation of the most recent data on cancer incidence and mortality in France and trends over the past 25 years (1980-2005)

\(^11\) Doctors’ guide to chronic conditions: Nodal non-Hodgkin's lymphoma in adults, September 2009