HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

3 September 2008

HYCAMTIN 0.25 mg, capsules
Box of 10 (CIP: 384 876-5)
HYCAMTIN 1 mg, capsules
Box of 10 (CIP: 384 877-1)

Applicant: GLAXOSMITHKLINE

topotecan

List I

Marketing Authorisation (MA) date: 18 March 2008 (centralised procedure)

Reason for request: Inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals in the indication "Hycamtin capsules are indicated as monotherapy for the treatment of adult patients with relapsed small cell lung cancer (SCLC), for whom retreatment with the first line regimen is not considered appropriate".

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

topotecan

1.2. Indication

"Hycamtin capsules are indicated as monotherapy for the treatment of adult patients suffering from relapsed small cell lung cancer (SCLC), for whom retreatment with the first line regimen is not considered appropriate"

1.3. Dosage

"Hycamtin capsules should only be prescribed, and therapy supervised, by a physician experienced in the use of chemotherapy agents.

Initial dose
The recommended dose of Hycamtin capsules is 2.3 mg/m^2 of body surface area per day administered for five consecutive days, with three-week interval between the start of each course. If well tolerated, treatment may continue until disease progression.
Prior to administration of the first course of topotecan, patients must have a baseline neutrophil count of ≥1.5 x 10^9/l, a platelet count of ≥100 x 10^9/l and a haemoglobin level of ≥ 9 g/dl (after transfusion if necessary).

Subsequent doses
Topotecan should not be readministered unless the neutrophil count is ≥ 1 x 10^9/l, the platelet count is ≥100 x 10^9/l and the haemoglobin level is ≥9 g/dl (after transfusion if necessary)."

2 SIMILAR MEDICINAL PRODUCTS

2.1. 2008 ATC classification

L : ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01 : ANTINEOPLASIC AGENTS
L01X : OTHER ANTINEOPLASTIC AGENTS
L04AX : OTHER ANTINEOPLASTIC AGENTS
L01XX17 : Topotecan

2.2. Medicines in the same therapeutic category

2.2.1. Comparator drugs

HYCAMTIN 4 mg, soluble powder for concentrate for solution for infusion

2.3. Medicines with the same therapeutic aim

Cytotoxic agents indicated for small cell lung cancer used as monotherapy or in combination therapy, in particular
- etoposide (VEPESIDE SANDOZ) "small cell bronchial cancer"
- cisplatin (CISPLATYL) "bronchial cancers"
- carboplatin (CARBOPLATIEN DAKOTA) "small cell bronchial carcinoma"
- cyclophosphamide (ENDOXAN) "bronchial cancers, especially small cell forms"
- doxorubicin (ADRIBLASTINE) "lung cancers"

3 ANALYSIS OF AVAILABLE DATA

This request relates to the inclusion of the oral form of topotecan (Hycamtin) in the "small cell lung cancer" indication on the list of medicines reimbursed by National Insurance and approved for use by hospitals. The intravenous form of Hycamtin already appears on the list of medicines approved for use by hospitals for this indication and for two other indications (ovarian cancer and cervical cancer).
To provide support for this request, the company has submitted two randomised, open-label, phase III clinical studies conducted on patients with small cell lung cancer in a disseminated or localised form:

- Study 396, the objective of which was to demonstrate non-inferiority of the oral form versus the intravenous form of topotecan
- Study 478, the objective of which was to compare oral topotecan combined with symptomatic treatment versus adapted symptomatic treatment alone.

The Transparency Committee already examined these two studies when it was considering the request to extend the indication for intravenous Hycamtin to lung cancer (see the committee's opinion dated 21 June 2006). They are summarised below.

3.1. Efficacy

Study 396

A randomised, open-label, non-inferiority study comparing the efficacy of oral topotecan with that of intravenous topotecan in 304 patients suffering from relapsed small cell lung cancer responsive to first-line treatment.
The oral form was to be considered non-inferior to the intravenous form if the lower limit of the 95% confidence interval for the difference of the response rate criterion between the two forms of treatment (oral form minus intravenous form) was below 10%.

The primary endpoint was the overall response rate (complete[1] or partial[2]).

[1] Complete response was defined as the complete disappearance of all known assessable and measurable disease, determined by two measurements taken at least four weeks apart.
[2] Partial response was defined as a reduction of more than 50% in the total of the products of the maximum perpendicular widths and lengths for at least four weeks, with no simultaneous increases in the size of a known lesion (> 25%) and no new lesions or assessable increases in the disease over the same period.

Table 1: Results for the primary endpoint

Response	ITT Population		Per protocol population	
	Oral Topotecan N=153	**IV Topotecan N=151**	**Oral Topotecan N=148**	**IV Topotecan N=148**
Responders				
CR (%)	2 (1.3)	0	2 (1.4)	0
PR (%)	26 (17.0)	33 (21.9)	26 (17.6)	32 (21.6)
Overall response (%)	28 (18.3)	33 (21.9)	28 (18.9)	32 (21.6)
[95% CI]	[12.2 - 24.4]	[15.3 - 28.5]	[12.6 - 25.2]	[15.0 - 28.3]
Difference (oral-IV)	-3.6 (-12.6 – 5.5)		-2.7 (-11.9 – 6.5)	
Stabilisation **(%)**	27 (17.6)	35 (23.2)	25 (16.9)	35 (23.6)
Non-responders				
Progression (%)	78 (51.0)	65 (43.0)	78 (52.7)	64 (43.2)
Non-assessable (%)	20 (13.1)	18 (11.9)	17 (11.5)	17 (11.5)

CR: complete response - PR: partial response

In ITT, the response rate for oral topotecan and intravenous topotecan were 18.3% and 21.9% respectively.
Non-inferiority between the intravenous form and the oral form was not established, as the lower limit of the 95% confidence interval of the difference between the two treatments was 12.6%, above the limit set at 10%.

Study 478

A randomised, open-label study comparing oral topotecan combined with an adapted symptomatic treatment (Active Symptom Control, ASC) to a symptomatic treatment alone in 141 patients with relapsed small cell lung cancer for whom retreatment with the first-line therapy was not possible.

The patients included had to be over the age of 18, have a performance status (ECOG scale) of $\leq$ 2, have previously received one chemotherapy regimen only and be "resistant" to this chemotherapy, i.e., they had to have a 45- to 90-day time lapse between the first line of treatment and the onset of disease progression, and have either a localised or disseminated form of the disease. Following an amendment, the definition of "resistant patient" was left up to the investigator's judgment, with the lower limit of 45 days retained to prevent refractory patients from being recruited.

Patients with cerebral metastases were included only if they were asymptomatic during neurological examination and if they were not taking corticosteroids to control their symptoms.

Inclusion in this study was stratified according to performance status, presence or absence of hepatic metastases, gender and time to progression (≤ 60 days or > 60 days).

Topotecan was administered orally at a dose of 2.3 mg/m^2/day for five days every 21 days.

The duration of treatment was left up to the investigator's discretion. It was recommended that all patients in the topotecan arm have at least four cycles of treatment. Patients who stopped oral topotecan continued with adapted symptomatic treatment for as long as necessary.

The primary endpoint was overall survival, defined as the time lapse from randomisation to death, regardless of the cause.

The secondary endpoints were:
- the objective response rate defined as the percentage of patients with a complete or partial response.
- the time to progression (non-comparative, recorded only in the oral topotecan arm), defined as the time from randomisation to the first documented sign of progression of the disease or death linked to progression of the disease. Progression of the disease was defined as an increase of > 25% in any measurable lesion, the reappearance of measurable disease, net aggravation of the assessable disease, the appearance of any new lesions (including cerebral metastases even if a non-cerebral response was present), or significant worsening of any situation presumed to be associated with the malignancy.
- the Patient Symptom Assessment – used to evaluate nine symptoms (shortness of breath, coughing, chest pain, haemoptysis, loss of appetite, sleep disturbances, hoarseness, fatigue and interference with activities of daily living) on inclusion and at the end of each cycle of treatment.
- the quality of life (Global Health Score: EuroQol EQ-5D)

The number of subjects needed to demonstrate superiority in terms of overall survival had been calculated as 110 patients per group for an expected median survival of 12 weeks with adapted symptomatic treatment and 20 weeks with oral topotecan combined with adapted symptomatic treatment, an alpha risk of 5% and a power of 90%. Inclusion stopped when the 141st patient was randomised because of the difficulties in recruiting patients for this study. The power of the study was therefore only 80%.

Results

Baseline patient characteristics:
- The average patient age was 60 in the group receiving oral topotecan combined with adapted symptomatic treatment and 59 in the group receiving adapted symptomatic treatment alone.
- The median time to progression after first-line treatment was 84 days in the group receiving oral topotecan combined with adapted symptomatic treatment and 90 days in the group receiving adapted symptomatic treatment alone.
- Almost a third of the patients in each group had a localised tumour, and about two-thirds of the patients had a performance score of 1 or less.

The median survival time (primary endpoint) was three months longer in the group receiving oral topotecan combined with adapted symptomatic treatment than in the group receiving adapted symptomatic treatment alone (25.9 weeks compared to 13.9 weeks, p = 0.0104).

In the sub-group of patients with a time to progression after the first chemotherapy regimen of > 60 days, there was no significant difference between the two groups with respect to the overall median survival rate: 27.7 weeks in the group receiving oral topotecan combined with adapted symptomatic treatment versus 14.4 weeks in the group receiving adapted symptomatic treatment alone (p = 0.0975).

In the sub-group of patients with a time to progression after the first chemotherapy regimen of ≤ 60 days, the overall median survival rate was 23.3 weeks in the group receiving oral topotecan combined with adapted symptomatic treatment versus 13.2 weeks in the group receiving adapted symptomatic treatment alone (p = 0.0357).

Secondary endpoints:
The time to progression in the group receiving oral topotecan combined with adapted symptomatic treatment was 16.3 weeks.
A statistically significant difference in favour of the oral topotecan combined with adapted symptomatic treatment group was observed for four of the nine symptoms assessed (shortness of breath, chest pain, sleep disturbances and fatigue).

3.2. Adverse effects

The main toxicities associated with oral topotecan were haematological in nature. In the group receiving oral topotecan combined with adapted symptomatic treatment, the frequency of haematological toxicity was the same as what already had been established for IV topotecan: 61.2% of patients had grade 3-4 neutropenia, 40.6% of patients had grade 3-4 leukopenia, 37.7% of patients had grade 3-4 thrombopenia and 24.6% of patients had grade 3-4 anaemia.
The most commonly reported adverse events in the group receiving oral topotecan combined with adapted symptomatic treatment were nausea (32.9%), vomiting (22.9%) and diarrhoea (21.4%). The most commonly reported adverse events in the group receiving only adapted symptomatic treatment were dyspnoea (14.9%) and cough (11.9%).

3.3. Conclusion

The assessment of the efficacy and tolerance of oral topotecan is based on a randomised, open-label, phase III study comparing oral topotecan combined with adapted symptomatic treatment to adapted symptomatic treatment alone in 141 patients with relapsed small cell lung cancer for whom retreatment with the first-line regimen was not appropriate (early relapse occurring after less than 90 days). A three-month improvement in the median survival time (primary endpoint) was observed for oral topotecan combined with adapted symptomatic treatment compared to adapted symptomatic treatment alone (25.9 weeks versus 13.9 weeks, p = 0.0104).
The main toxicities associated with oral topotecan treatment were haematological in nature (61.2% of patients had grade 3-4 neutropenia and 37.7% of patients had grade 3-4 thrombopenia).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Small cell lung cancer is life-threatening;
The product is intended for curative treatment;
The efficacy/safety ratio is moderate;
This proprietary drug is intended for second-line therapy;
There are alternative medicines available.

Public health benefit:
Small cell lung cancer causes a substantial public health burden. However, the burden represented by the sub-population of relapse patients who cannot receive the first-line treatment again is moderate because of the small number of patients affected.
Improving the management of lung cancer is a public health need that falls within the scope of identified priorities (GTNDO[3] for the management of cancer).
In light of the data available (modest increase in median survival times with oral Hycamtin compared to palliative treatment alone), the expected additional impact on the morbimortality of these patients can only be very limited.
In addition, it can only be assumed that the proprietary Hycamtin capsules will offer an additional response to the identified public health need.
Consequently, Hycamtin is not expected to provide a public health benefit.

The actual benefit of this medicinal product is substantial.

4.2. Improvement in actual benefit

Hycamtin capsules confer a minor IAB (level IV) compared to palliative treatment alone.

4.3. Therapeutic use

The current, standard first-line treatment for small cell lung cancer is the combination of platinum salts and etoposide. However, it is known that most patients relapse within a year of diagnosis. "Responsive" patients are those who responded to the first-line treatment and who did not have a relapse for at least three months[4]. These patients may benefit from receiving the same chemotherapy again. In contrast, another form of chemotherapy can be considered for patients described as "resistant". The outcomes of drugs used as second-line treatment showed response rates ranging from 6 to 70% and a median survival time of 4 to 9 months in non-comparative studies[5].
Oral topotecan represents a new option in the second-line treatment of patients suffering from small cell lung cancer.

[3] GTNDO: *Groupe Technique National de Définition des Objectifs* [National Technical Objective Definition Group] (DGS-2003)

[4] David M Jackman, Bruce E Johnson. Small cell lung cancer. Lancet 2005; 366:1385-1396

[5] Simon M, Argiris A, Murren JR. Progress in the therapy of small cell lung cancer. Critical reviews in oncology/hematology 2004; 49(2):119-133.

4.4. Target Population

In 2002[6], there were 27,500 new cases of bronchial cancer diagnosed in France. Between 15% and 20% of these were small cell cancers.
The experts agree that approximately one quarter to one third of these patients are likely to need a second line of chemotherapy.
This means that the target population for Hycamtin capsules in the relapsed small cell bronchial cancer indication for whom reintroduction of the first line of therapy is not appropriate is estimated at between 1,000 and 1,800 patients a year.

4.5. Transparency Committee recommendations

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

4.5.1. Packaging
The packaging is appropriate for the prescription conditions.

4.5.2. Reimbursement rate: 100%

6 Remontet L, Estève J, Bouvier AM et al. Estimations nationales : Tendance de l'incidence et de la mortalité par cancer en France entre 1978 et 2000 [National estimates: incidence and mortality trends for cancer in France between 1978 and 2000]. BEH 2003; 41-42: 190-3