HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 February 2009

FOSCAN 4 mg/mL, solution for injection
B/1 bottle containing 3.5 mL (CIP: 563 565-0)
B/1 bottle containing 5 mL (CIP: 563 596-7)

Applicant: BIOLITECH PHARMA LTD

temoporfin

List I
Medicinal product for hospital use only. Can only be prescribed by oncologists.

Date of European marketing authorisation (centralised procedure): 24 October 2001

Reason for request: re-assessment of actual clinical benefit and assessment of improvement in actual benefit.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
temoporfin

1.2. Background
Temoporfin is a photosensitising agent used in the photodynamic treatment of tumours. The pharmacological activity is initiated by photoactivation of temoporfin with non-thermal light at 652nm following intravenous administration.

1.3. Indication
"Foscan is indicated for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy. "

1.4. Dosage

"Foscan photodynamic therapy must only be administered in specialist oncology centres in which a multidisciplinary team assesses patient treatment and under the supervision of physicians experienced in photodynamic therapy.
Foscan is administered via an in-dwelling intravenous cannula in a large proximal limb vein, preferably in the antecubital fossa, as a single slow intravenous injection over not less than 6 minutes. The patency of the in-dwelling cannula should be tested before injection and every precaution taken against extravasation.
The dark purple colour of the solution, together with the amber vials makes a visual check for particulates impossible. Thus, an in-line filter must be used as a precautionary measure and is provided in the package. Do not flush with sodium chloride or any other aqueous solution.
The dose is 0.15 mg/kg body weight. Do not dilute Foscan.
Administer the required dose of Foscan by slow intravenous injection, over not less than 6 minutes.
96 hours after the administration of Foscan, the treatment site is to be illuminated with light at 652 nm from an approved laser source. Light must be delivered to the entire surface of the tumour using an approved microlens fibre-optic. Wherever possible, the illuminated area must extend beyond the tumour margin by a distance of 0.5cm.
Light must be administered not less than 90 hours and not more than 110 hours after Foscan injection.
The incident light dose is 20J/cm^2, delivered at an irradiance of 100mW/cm^2 to the tumour surface, implying an illumination time of approximately 200 seconds.
Each field is to be illuminated once only at each treatment. Multiple non-overlapping fields may be illuminated. Care must be taken to ensure that no area of tissue receives more than the specified light dose. Tissue outside the target area must be shielded completely to avoid photoactivation by scattered or reflected light.
A second course of treatment may be given at the discretion of the treating physician in patients where additional tumour necrosis and removal is deemed appropriate, The recommended minimum interval between treatments is 4 weeks. "

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

L Antineoplastic and immunomodulating agents
L01 Antineoplastic agents
L01X Other antineoplastic agents
L01XD Agents used in photodynamic therapy

2.2. Medicines in the same therapeutic category

2.2.1 Comparator medicines
None

2.3. Medicines with a similar therapeutic aim

Medicines used in palliative care, in particular corticosteroids and analgesics.

3. ANALYSIS OF AVAILABLE DATA

FOSCAN was granted European centralised marketing authorisation under exceptional circumstances for the following indication: "Foscan is indicated for the palliative treatment of patients with advanced head and neck squamous cell carcinoma failing prior therapies and unsuitable for radiotherapy, surgery or systemic chemotherapy".
The Transparency Committee evaluated this product in 2004, based on the pivotal 8B study, as summarised below, and concluded that the clinical benefit it provided was insufficient. In 2006, Foscan was included on the list of products approved for hospital use, following a ministerial decision.
Under the initial marketing authorisation, the applicant undertook to carry out a study with the aim of confirming palliative benefit for patients with advanced head and neck cancer, and to create a follow-up register of patients treated with Foscan, until the CHMP came to its conclusions concerning the results of the post-marketing study. For this reason, a non-comparative study (TEM-HNC-001) was carried out (between November 2002 and November 2006).
The CHMP, in its opinion dated 19 March 2008, took into account the fact that the applicant was fulfilling its specific obligations, along with the results of a re-assessment of the risk/benefit ratio, removed the restrictions on FOSCAN's marketing authorisation.
On the basis of this new study, the applicant requested re-assessment of the actual clinical benefit and an assessment of the improvement in actual clinical benefit.

3.1. Efficacy

A/ Summary of the results of the pivotal 8B study, assessed in 2004[1]

Non-comparative study to assess the clinical benefit of photoactivated FOSCAN (0.15 mg/kg) in 147 patients with head and neck cancer which was resistant to treatment or unsuitable for surgery, radiotherapy or chemotherapy.

- Primary endpoint: change at 12-16 weeks in 5 major symptoms (pain, swallowing, chewing, disfigurement and speech) evaluated using the University of Washington Head and Neck Questionnaire.
- Secondary endpoint: tumour response at 12-16 weeks; survival at 1 year

University of Washington scale:
- pain (0 - 4, none - severe pain not controlled by medication)
- swallowing (0 - 3; no problem - I cannot swallow)
- Eating-chewing (0 - 2; no problem - I cannot even chew soft solids)
- Disfigurement (0 - 4; no problem - I cannot be with people due to my appearance)
- Speech (0 - 4; no problem - I cannot be understood)

Tumour response scale (WHO)
- complete response: disappearance of all known disease, determined by two observations not less than 4 weeks apart
- partial response: reduction of at least 50% in the size of lesions, determined by two observations not less than 4 weeks apart

1 Four efficacy studies were presented in the initial dossier. Three were not examined, as the population of patients included did not correspond to the indication.

Symptom relief:
Efficacy analysis on the primary endpoint (change in symptoms) was done for 128 of the 147 patients included in this study.

28 of the 128 patients analysed reported improvement in symptoms on the University of Washington scale. In half of cases, disappearance of all symptoms or a reduction of at least two points was reported.
For 19 other patients, analysis related to prevention of complications. The results of this analysis have not been provided.

Tumour response:

- Tumour mass reduction by tumour depth:

% tumour mass reduction	All lesions N = 102	< 10 mm N = 52	10 to <20 mm N = 31	>20 mm N = 19
100	44 (43%)	31 (60%)	9 (29%)	4 (21%)
>50	59 (58%)	39 (73%)	15 (48%)	5 (26%)
>25	66 (65%)	39 (75%)	18 (58%)	9 (47%)

- Tumour mass reduction by completeness of illumination:
Completeness of illumination was determined by using the surface area of each lesion and the illumination spot diameter. If the illumination spot area was greater or equal to the tumour area, illumination was categorised as complete.

% tumour mass reduction	All lesions N = 102	Complete illumination N = 82	Incomplete illumination N = 20
100	44 (43%)	41 (50%)	3 (15%)
>50	59 (58%)	51 (62%)	8 (40%)
>25	66 (65%)	55 (67%)	11 (55%)

Tumour response was observed in 37/147 (25%) of the patients after the first treatment course.
Of the 43 patients who were considered by the investigators to have received the maximum benefit from FOSCAN (completely illuminated, non-externalising lesions with a depth of < 10 mm), complete response was observed in 10 patients, with a response duration of 145 days.
Median survival was 487 days for patients with objective tumour response, and 214 for non-responders.

3.2. Adverse effects

According to the summary of product characteristics, all patients who receive FOSCAN will become temporarily photosensitive.
Of the 855 patients in the register, 170 reported 176 occurrences of photosensitivity, including 19 severe reactions. Overall incidence of serious phototoxicity was 1.6%.
Most toxicity associated with this therapy are transient local effects seen in the region of illumination and occasionally in surrounding tissues.

Very common:
- injection site pain (12%):
- haemorrhage NOS, pain in face, mouth necrosis, dysphagia, face oedema

Common:

- burning sensation and injection site reaction
- oedema, trismus, swallowing difficult, localised infection, fever, mouth ulceration, skin necrosis
- burning, blistering, redness, hyperpigmentation, photosensitivity reaction, sunburn
- vomiting, anaemia, nausea, vertigo

Conclusions of pivotal study:

The study under consideration here had many methodological shortcomings, and there was a lack of clarity in the presentation of the results. The patients who were included are not representative of the target population. The number of responders is low, and the extent of the effect is difficult to assess. The product only appears to be effective on shallow tumours that are accessible to complete illumination, and which are regular in shape.
Overall safety is poor, and all patients experienced photosensitivity reaction.
The use of FOSCAN is severely limited because of the requirement for complex photoprotection of the patient for 3 weeks, while the mean duration of response does not exceed 145 days in the 7% of patients (10/147) who experienced complete response.

B/ New data:

Study TEM-HNC-001
Non-comparative study involving 43 patients with head and neck cancer resistant to treatment or unsuitable for surgery, radiotherapy or chemotherapy. Included patients were required to have tumours with a depth of < 10 mm that were accessible to complete illumination by fibre-optic laser.

The primary endpoint was objective tumour response (complete response[2], partial response[3]).

The secondary endpoints were percentage of complete response, duration of tumour response, time to disease progression, quality of life, overall survival, ECOG performance index, weight, patient global assessment of treatment benefit, and tolerability.

FOSCAN was given in a 0.15 mg dose intravenously, with diode laser illumination of the tumour 96 hours later (light dose 20J/cm2, fluence rate 100 mW/cm2, wave length 652 nm).
At the end of treatment, patients were assessed twice a week for the first 4 months, and then every month until the 10th month.

2 Complete response was defined as disappearance of all known disease, determined by two observations not less than 4 weeks apart
3 Partial response was defined as reduction of at least 50% in the size of lesions, determined by two observations not less than 4 weeks apart

Inclusion criteria:

- aged ≥18
- ECOG performance index of 0, 1 or 2
- advanced squamous cell head and neck carcinoma, confirmed on cytology (buccal, oropharynx, larynx)
- documented failure of previous treatments
- documented decision made by a multidisciplinary team, or equivalent, that curative therapy involving radiotherapy, surgery or chemotherapy is not possible
- presence of a single discrete locally accessible tumour
- depth of tumour does not exceed 10 mm, demonstrated on magnetic resonance imaging (MRI). Patients for whom MRI is contraindicated can undergo CT scan.
- tumour clearly visible and accessible without restrictions to illumination with a microlens fibre-optic
- documented treatment plan showing that the tumour can be completely and adequately illuminated with 3 light spots at most, with minimal overlapping
- patients with limited metastatic disease were accepted on condition that, in the view of the investigator, the extent of their disease would not cause them to leave the study prematurely.

Results:

Efficacy analysis involved 39 of the 43 patients included who received treatment.
The median age of patients was 59.5 years. More than half of the lesions were in the oral cavity (21 of 39 analysed). Around one third had lesions in the oropharyngeal region (11 of 39).
All patients had previously undergone surgery, 37 had received radiotherapy (associated with surgery or chemotherapy) and 13 had received chemotherapy associated with surgery and radiotherapy.

Objective tumour response (primary endpoint) was observed in 21 of the 39 patients analysed: 19 had complete response and 2 had partial response.
Median response duration was 131 weeks for complete response and 123 weeks for partial response.
At 4 months, one third of patients (13 of 39) had failed treatment: 7 patients had disease progression, and 5 had died.
At 10 months, around half of patients had failed treatment: 14 patients had disease progression, and 7 had died.
Median progression-free survival was 131 weeks for responders.
Estimated survival at 10 months was 91% for responders.

During the study, 20 patients had a steady ECOG performance score, 15 patients saw an improvement in ECOG from 1 to 0, and 3 had a deterioration from 0 to 1.
Quality of life assessment, using the EORTC QLQ-C30 or EORTC QLQ-H&N35 questionnaires, was difficult to interpret, firstly because of the comparison by the patient of their condition before and after treatment without comparator, and secondly because of the limited number of patients assessed (8 patients at 10 months, of the 31 selected at inclusion for questionnaire EORTC QLQ-C30 and 4 of 25 for EORTC QLQ-H&N35).

Safety data from study TEM-HNC-001:

The most common treatment-linked adverse effects were phototoxicity (41%), tumour site pain (21%), non-specific pain (13%) and dysphagia (13%).
Phototoxicity reactions (22 events) were reported in 16 patients; 14 patients had grade 3 or 4 reactions, of whom 2 had oral necrosis.
In three quarters of cases (74%), phototoxicity reactions were observed in the two weeks following administration of FOSCAN.

Conclusion:

Re-assessment of the FOSCAN dossier was based on a new non-comparative study (TEM-HNC-001) involving 43 patients with head and neck cancer who had failed prior therapies and were unsuitable for curative therapy with radiotherapy, surgery or systemic chemotherapy. Included patients were required to have tumours with a depth of < 10 mm that were accessible to complete illumination by fibre-optic laser.
Objective tumour response (primary endpoint) was observed in 21 of the 39 patients analysed: 19 had complete response and 2 had partial response.
Median response duration was 131 weeks for complete response and 123 weeks for partial response.
At 10 months, around half of patients had failed treatment: 14 patients had disease progression, and 7 had died.
During the study, 20 patients had a steady ECOG performance score, 15 patients saw an improvement in ECOG from 1 to 0, and 3 had an impairement from 0 to 1.
Quality of life assessment, using the EORTC QLQ-C30 or EORTC QLQ-H&N35 questionnaires, was difficult to interpret, firstly because of the comparison by the patient of their condition before and after treatment without comparator, and secondly because of the limited number of patients assessed (8 patients at 10 months, of the 31 selected at inclusion for questionnaire EORTC QLQ-C30 and 4 of 25 for EORTC QLQ-H&N35).

This new study was carried out on a very limited selection of patients, in line with the results of the pivotal study (08b) which was assessed by the committee in 2004 (with tumours that were accessible to complete illumination and no more than 10 mm in depth). However, as was the case for the pivotal study, the lack of comparison with supportive care means that it is impossible to make a precise assessment of the effect of this therapy.
The majority of adverse effects reported during this study were mild to moderate, with the exception of oral necrosis. The most common treatment-linked adverse effects were phototoxicity (41%), tumour site pain (21%) and dysphagia (13%).

The committee would have liked to see a comparative approach, with or without randomisation, and regrets that there were no open-label studies. The heterogeneous nature of patients included in this study should also be emphasised, as should the lack of a centralised committee to determine whether disease was incurable (by surgery or radiotherapy) and to evaluate the endpoints.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Advanced squamous cell carcinomas of the head and neck are life-threatening conditions;
These products are intended to provide palliative treatment;
The efficacy/safety ratio for these products is low;
This is a last-resort treatment;
There are no other alternative medications;

Public health benefit:

The public health burden of head and neck cancers is high. Patients with advanced squamous cell carcinoma for which they are receiving palliative treatment and who could benefit from FOSCAN represent a small public health burden, because of the restricted numbers involved.

Prevention of head and neck cancers and improvement in their management are public health needs.

In view of the available data (non-comparative study, and no comparison with supportive care), it can be considered that this product has no additional impact in terms of morbidity, mortality and quality of life.

FOSCAN does not therefore appear likely to provide a response to an identified public health need.

Consequently, FOSCAN is not expected to benefit public health in this indication.

Given the methodological shortcomings of efficacy studies involving these products, the committee considers that the actual clinical benefit provided by FOSCAN is low.

4.2. Improvement in actual benefit

FOSCAN provides no improvement in actual benefit (level V) in comparison with current management.

4.3. Therapeutic use

The current standard treatment for inoperable head and neck tumours in France is a combination of radiotherapy and platinum-based chemotherapy with or without 5-fluorouracil.
If these therapies fail, there is no validated alternative. Methotrexate is the single modality chemotherapy that can be used in practice, with response rates of the order of 25-30% and median survival of less than 6-8 months in most series.
For patients with advanced disease, who cannot undergo surgery, radiotherapy or chemotherapy and who meet the following criteria: non-externalising tumour less than 10 mm in depth and accessible to illumination with laser via fibre-optic, FOSCAN is a new therapeutic option.

4.4. Target Population

The number of new cases of head and neck cancers in France was estimated at around 12,270[4] in 2005.
In more than 95% of cases[5], these cancers are squamous cell carcinomas. (11657)
60% of cases are locally advanced[6], [7], or around 6994 cases per year.
According to experts, 50% of these patients could benefit from surgery. The remaining 50% (3497 patients) are candidates for radiotherapy + chemotherapy.
According to experts, less than a third of patients with a recurrence of progressive disease can benefit from rescue surgery, because of the risk of complications and/or intolerable after-effects.
Considering that the remaining 2/3 will fail radiotherapy + chemotherapy at some point, the number of patients in the indication in the marketing authorisation for FOSCAN is estimated at 2330 patients per year.
Given the following:
- Foscan's place in therapeutic use (non-externalising tumours less than 10 mm in depth that are accessible to illumination by laser delivered via fibre-optic) means that the percentage of patients who can receive it make up 29% of cases (43 of the 147 patients in the pivotal study).
- around half of patients are ineligible because of general poor health, poor predicted survival, or a social/family situation that means the photosensitivity precautions cannot be adhered to.

Hence the estimated target population for Foscan is approximately 300 patients per year.

4.3. Transparency 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 this indication of the MA.

4 Presentation of latest cancer incidence and mortality data for France, and trends over the last 25 years (1980-2005) - Press conference, 21 February 2008. INVS/Hôpitaux de Lyon/FRANCIM/INCA
5http://www.ligue-cancer.asso.fr (2003)
6 State of the art management of locally advanced head and neck cancer. Br J Cancer 2005; 92: 1341-1348
7 Edwards S.Kim, Current opinion oncology, 2002, 14 :334-42.