TRANSPARENCY COMMITTEE

OPINION

28 March 2012

TARGETIN 75 mg, soft capsule
B/1 high-density polyethylene (HDPE) bottle of 100 capsules (CIP code: 365 747-9)

Applicant: CEPHALON FRANCE

Bexarotene
ATC code: L01XX25 (antineoplastic agent)

List I
Medicine requiring special monitoring during treatment.
Medicine for hospital prescription only, with prescription restricted to cancer treatment, haematology and clinical oncology specialists and departments.

Date of European Marketing Authorisation (centralised procedure): 29 March 2001 – revised on 11 December 2007

Proprietary medicinal product included on the list of medicines approved for hospital use and various public services since 22 June 2002 (Official Gazette of 22 June 2002).

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance following the decision by the Directorate-General for Health to delete this proprietary medicinal product from the list of medicines that can be dispensed to outpatients by hospital/retail pharmacies.

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

1.1. Active ingredient

Bexarotene

1.2. Indication

“Treatment of skin manifestations of advanced-stage cutaneous T-cell lymphoma (CTCL) patients refractory to at least one systemic treatment.”

1.3. Dosage

“Bexarotene therapy should only be initiated and maintained by physicians experienced in the treatment of patients with CTCL. The recommended initial dose is 300 mg/m²/day. TARGRETIN capsules should be taken as a single oral daily dose with a meal (see section 4.5). The initial dose is calculated according to the patient’s body surface area (see SPC).

Dose modification guidelines: the 300 mg/m²/day dose level may be adjusted to 200 mg/m²/day then to 100 mg/m²/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, the dosage may be carefully readjusted upward. With appropriate clinical monitoring, individual patients may benefit from doses above 300 mg/m²/day. Doses greater than 650 mg/m²/day have not been evaluated in patients with CTCL. In clinical trials, bexarotene was administered for up to 118 weeks to patients with CTCL.

Use in children and adolescents: the clinical safety and effectiveness of bexarotene in the paediatric population (below 18 years of age) have not been studied and this medicinal product should not be used in a paediatric population until further data become available.

Use in the elderly: of the total number of patients with CTCL in clinical studies, 61% were 60 years or older, while 30% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to bexarotene cannot be ruled out. The standard dose should be used in the elderly.

Renal insufficiency: no formal studies have been conducted in patients with renal insufficiency. Clinical pharmacokinetic data indicate that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients, the estimated renal clearance of bexarotene was less than 1 ml/minute. In view of the limited data, patients with renal insufficiency should be monitored carefully while on bexarotene therapy.”
2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC 2011 Classification

L: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS
L01: ANTINEOPLASTIC AGENTS
L01X: OTHER ANTINEOPLASTIC AGENTS
L01XX: OTHER ANTINEOPLASTIC AGENTS
L01XX25: Bexarotene

2.2. Medicines in the same therapeutic category

2.2.1. Comparator medicines
None

2.3. Medicines with a similar therapeutic aim

Other treatments with a similar therapeutic aim that have marketing authorisation in advanced-stage cutaneous T-cell lymphoma are:

- ROFERON A (interferon alfa-2a) - Roche
  The wording of the indication of the marketing authorisation for this proprietary medicinal product is much broader than that of TARGRETIN, as its use is not limited to patients refractory to treatment: “Treatment of cutaneous T-cell lymphoma. Interferon alfa-2a (ROFERON-A) may be active in patients with progressive cutaneous T-cell lymphoma and who are refractory to, or unsuitable for conventional therapy.”
  The AB of ROFERON A is substantial, with a modest efficacy/safety ratio in oncological and haematological indications (renewal of inclusion, TC Opinion of 15 February 2006). This proprietary medicinal product is included on the list of medicines refundable by National Insurance and approved for hospital use.

- UVADEX (methoxsalen) - Therakos Europe
  This proprietary medicinal product, used in conjunction with the UVAR system, is indicated in the palliative treatment of cutaneous manifestations (extensive patches or plaques, erythroderma in cutaneous T-cell lymphomas/CTCL), solely in patients who have failed to respond to other forms of treatment.
  The AB of UVADEX is substantial, with a high efficacy/safety ratio and level V IAB in the management of the disease (inclusion, TC Opinion of 26 September 2007). This proprietary medicinal product is approved for hospital use.
3 REVIEW OF PREVIOUS EVALUATIONS

Opinion of 3 April 2002: Inclusion on the list of medicines approved for use by hospitals

“Actual benefit:
Advanced-stage cutaneous T-cell lymphomas (CTCL) those are life-threatening for the patient. The efficacy/safety ratio of this medicinal product in this indication is modest. This medicinal product is a second-line therapy. There are treatment alternatives. The actual benefit is moderate.”

“Improvement in actual benefit (IAB):
In the absence of comparative data, the Committee is unable to assess the level of improvement in actual benefit.”

Opinion of 4 July 2007: Re-evaluation of the AB and IAB following the submission of new data

“Actual benefit:
Advanced-stage cutaneous T-cell lymphomas (CTCL) those are life-threatening. The efficacy/safety ratio of this medicinal product is modest. This medicinal product is a second-line therapy. There are treatment alternatives. The actual benefit of this proprietary medicinal product is moderate.”

“Improvement in actual benefit (IAB):
The Committee considers that TARGRETIN remains an additional treatment option for the management of skin manifestations of advanced-stage cutaneous T-cell lymphomas (CTCL) refractory to at least one systemic treatment. It offers no improvement in actual benefit (level V).”
The dossier submitted by the pharmaceutical company comprises:
- two non-comparative studies: one carried out in early-stage cutaneous T-cell lymphoma (CTCL) (L1069-23), which is off-label use and hence is not described, and the other in advanced-stage disease refractory to treatment (L1069-24), which had been previously examined and included in the earlier Opinions issued by the Committee;
- the periodic safety update report covering the period from 1 January 2007 to 30 August 2011.

In its dossier, the company also cited:
- an ORELY survey\(^1\), for which the data are not presented and are referred to in the company dossier as currently undergoing analysis;
- a retrospective survey\(^2\) carried out in the UK with the aim of describing the experience of dermatologists and evaluating the efficacy and safety of bexarotene in 66 patients with mycosis fungoides or Sézary syndrome, of whom 19 had early-stage cutaneous T-cell lymphoma;
- two publications concerning folliculotropic mycosis fungoides (a variant of mycosis fungoides): a retrospective series of 20 cases\(^3\) and a retrospective and subsequently prospective series of eight patients\(^4\), who cannot be taken into consideration because of the low level of evidence and because inclusion was not limited to advanced-stage disease (off-label use);
- four publications on the pathophysiological mechanism of hyperlipidaemia induced by:
  - bexarotene used off-label in thyroid cancer\(^5\) and lung cancer\(^6,7\) patients, in animals\(^8\) or in vitro\(^7\);  
  - isotretinoin in healthy volunteers\(^9\);
- three publications on studies describing off-label use in lung cancer.\(^10,11,12\)

The additional literature data search supplied by the company (for the period from July 2007, date of the most recent Opinion, to January 2012), which was carried out by the HAS literature search service, identified only retrospective studies with very small patient populations (< 15 patients) and studies in conditions not covered by the marketing authorisation (early-stage disease).

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\(^1\) Longitudinal survey of factors predictive of response to and safety of retinoids in cutaneous T-cell lymphomas initiated in 2008 by the company


\(^5\) De Vries-Van Der Weij J, De Haan W, Hu L et al. Bexarotene induces dyslipidemia by increased very low density lipoprotein production and cholesteryl ester transfer protein-mediated reduction of high-density lipoprotein. Endocrinology, 2009; 150: 2 368-75


\(^8\) Laloyer F, Fievet C, Lestavel S et al. The RXR agonist bexarotene improves cholesterol homeostasis and inhibits atherosclerosis progression in a mouse model of mixed dyslipidemia. Arterioscler Thromb Vasc Biol, 2006; 26: 2 731-7


\(^12\) Govindan R, Crowley J, Schwartzberg L et al. Phase II trial of bexarotene capsules in patients with advanced non-small-cell lung cancer after failure of two or more previous therapies. J Clin Oncol. 2006 Oct 20; 24(30): 4848-54
In total, the only study described is the one in advanced-stage disease refractory to treatment (L1069-24) that had been previously examined and included in the earlier Opinions issued by the Committee. Publications with a low level of evidence (because of their retrospective nature and small patient populations) and/or which describe off-label use and/or were published prior to the previous Transparency Committee Opinion in July 2007 are therefore not examined further in this Opinion.

4.1. Efficacy

Review of the data evaluated in the Transparency Committee Opinions of 2002 and 2007:
Non-comparative phase II/III study (L1069-24) of patients with advanced-stage cutaneous T-cell lymphoma refractory to at least one systemic treatment.

Inclusion criteria:
- patients over 18 years with biopsy-confirmed stage IIB to IVB CTCL warranting systemic treatment;
- refractory to at least one systemic cytotoxic treatment;
  A patient was considered refractory to previous systemic treatment if he/she had failed to show an improvement in response of at least 50% or if the disease had progressed during treatment despite an initial response having been achieved.
- a performance status/Karnofsky score ≥ 60.

Treatment:
The initial study protocol, finalised in July 1996, specified an initial dosage of 650 mg/m²/day, to be taken orally. Following subsequent amendments to the protocol, this dosage was reduced to 300 mg/m²/day for safety reasons (amendment of 15 September 1997). This is the dosage specified in the marketing authorisation. The duration of treatment was at least 16 weeks (mean duration of treatment not given).

Primary efficacy endpoint:
The overall tumour response was the sum of the complete clinical response rate\(^{13}\) and the partial response rate.\(^{14}\)

In the absence of a standard criterion, the evaluation was based on the signs (skin lesions, lymph node and visceral involvement) and symptoms of the disease based on:
- a clinical overall evaluation carried out by the doctor,
- a composite score defined and evaluated by the company. This score takes account of more than five lesion indices assessed at each visit on a scale from 0 to 8 (0: absence of lesion, 8 = severe lesion) and taking into account erythema, induration of the skin and affected skin surface area.

Results:
Of the 93 patients with biopsy-confirmed advanced-stage disease (stages IIB, III, IVA, IVB) for whom systemic treatment could be considered, 61 patients received bexarotene monotherapy at the dosage of 300 mg/m²/day recommended in the marketing authorisation and 32 patients were treated at a dosage greater than 300 mg/m²/day (results not presented for this group).

The median age of the patients was 60 years. The median number of systemic treatments the patients had previously received was two. The most commonly administered previous treatments were interferon (59%), methotrexate (38%), combination chemotherapy (25%), systemic corticoids (25%) and photopheresis (22%).

\(^{13}\) defined as the absence of manifestations (skin, lymph node, visceral)
\(^{14}\) defined as a reduction of more than 50% in skin, lymph node or visceral manifestations
The results of this non-comparative study are given only for the 61 patients initially treated with 300 mg/m²/day (dosage specified in the marketing authorisation):

- based on the clinical overall evaluation: the overall tumour response rate was 51% (31/61) and the complete clinical response rate was 3% (2/61).
- based on the composite score: the overall tumour response rate was 31% (19/61) and the complete clinical response rate was 7% (4/61).

4.2. Adverse effects

The safety data obtained in the clinical studies were available for 152 patients with CTCL, of whom 109 were treated with the recommended dose of 300 mg/m²/day. Discontinuation of treatment on account of adverse effects occurred in 24 out of 152 patients.

The adverse effects reported most often were:
- hypertriglyceridaemia (74%) with risk of pancreatitis
- hypothyroidism (29%), which generally developed four to eight weeks after the start of treatment. This may be asymptomatic. It responds to treatment with thyroxine and ceases after stopping the medicinal product.
- hypercholesterolaemia (28%)
- headache (27%)
- leucopenia (20%)
- pruritus (20%)
- asthenia (19%)
- rash (16%)
- exfoliative dermatitis (15%)
- pain (12%).

Since market launch, no new safety issues have come to light according to data from the PSUR covering the period from 1 January 2007 to 30 August 2011. The “Undesirable effects” section of the SPC is unchanged since the last Transparency Committee Opinion.

Lastly, some amendments to the SPC have been made since the last Opinion in July 2007. These concern section 4.5 “Interactions”, which now states: “Caution is advised in case of combination with CYP3A4 substrates with a narrow therapeutic margin i.e. immunosuppressive agents (cyclosporine, tacrolimus, sirolimus) as well as CYP3A4-metabolised cytotoxics, i.e. cyclophosphamide, etoposide, finasteride, ifosfamide, tamoxifen, vinca alkaloids.” (revision of 11 December 2007).

In addition, a phase IV institutional study is planned with the aim of estimating the frequency of disorders of carbohydrate metabolism in patients with hypertriglyceridaemia induced by bexarotene prescribed for cutaneous T cell lymphoma.
4.3. Conclusion

This application for inclusion on the list of medicines refundable by National Insurance follows on from the decision by the Directorate-General for Health to delete this proprietary medicinal product from the list of medicines that can be dispensed to outpatients by hospital/retail pharmacies.

Oral bexarotene is evaluated in this context on the basis of data already examined by the Transparency Committee in 2002 and 2007 that were obtained in a non-comparative study of 93 patients (median age 60 years) with advanced-stage cutaneous T-cell lymphoma refractory to at least one systemic treatment (median 2), which included interferon (59%), methotrexate (38%), combination chemotherapy (25%), systemic corticoids (25%) and photopheresis (22%). The results of this non-comparative study come from the subgroup of 61 patients who received bexarotene monotherapy at an initial dosage of 300/mg/m²/day, corresponding to the dosage approved by the marketing authorisation.

The overall tumour response rate was 51% (31/61) based on the clinical overall evaluation, of which 3% (2/61) showed a complete clinical response, and 31% (19/61), of which 7% (4/61) showed a complete clinical response based on the composite score.

The adverse events most commonly reported were lipid disorders (hypertriglyceridaemia [79%] and hypercholesterolaemia [28%]), thyroid disorders (hypothyroidism [29%]) and leucopenia (20%), which necessitate close monitoring particularly of thyroid and lipid function and of the white blood cell count.

All in all, it is difficult to evaluate the effect of oral bexarotene, in view of the methodology that was employed (analysis of a subgroup in a non-comparative study); its safety profile is characterised by the occurrence of lipid disorders in about two-thirds of cases and hypothyroidism in almost a third of cases.

5 MEDICINAL PRODUCT USAGE DATA

5.1. IMS data

This proprietary medicinal product, which is for hospital prescription only, with prescription restricted to haematology and clinical oncology specialists and departments, does not appear in the prescribing panels available to us.

5.2. GERS data

According to GERS data (moving annual total November 2011), 354,300 capsules have been sold to hospitals. Given the variable duration of treatment, it is not possible to estimate the number of patients treated.
6.1. **Actual benefit**

Cutaneous T-cell lymphomas are malignant lymphocyte proliferations localised initially in the skin. They comprise for the most part mycosis fungoides and Sézary syndrome. Mycosis fungoides is considered a low-grade lymphoma, progressing only slowly in the early stages of the disease and with a poor prognosis in its advanced stages; Sézary syndrome is considered an aggressive lymphoma with a poor prognosis.

This proprietary medicinal product is a specific treatment for cutaneous T-cell lymphomas and is intended as palliative therapy.

This medicinal product is a second-line therapy or beyond in advanced stages of the disease in patients refractory to at least one systemic treatment.

The efficacy/safety ratio for this medicinal product is modest.

There are treatment alternatives.

The actual benefit of TARGRETIN is substantial in the treatment of skin manifestations of advanced-stage cutaneous T-cell lymphomas (CTCL) refractory to at least one systemic treatment.

6.2. **Improvement in actual benefit (IAB)**

In view of:
- the low level of evidence of the efficacy data already evaluated, which come from a subgroup of a non-comparative study, and toxicity characterised by hyperlipidaemia and hypothyroidism (see section 4.3 Conclusion),
- the absence of any new comparative data since the previous Committee Opinions (3 April 2002 and 4 July 2007) permitting assessment of the therapeutic benefit of this proprietary medicinal product in current management,

the Committee considers that, in the context of the application for inclusion on the list of medicines that can be dispensed to outpatients by retail pharmacies, this proprietary medicinal product remains an additional therapeutic option and that it does not offer any improvement in actual benefit (level V) in the management of skin manifestations of advanced-stage cutaneous T-cell lymphomas refractory to at least one systemic treatment.

6.3. **Therapeutic use**

The choice of treatment depends on the type of cutaneous T-cell lymphoma and the stage of the disease.\(^\text{15}\) No curative treatment is currently available, except for allogeneic haematopoietic stem cell transplantation, which can only be proposed in some rare situations of treatment failure in advanced disease and in young patients. Enduring responses have been observed, but experience is limited.

The early stages of the disease (IA, IB, IIA), if there is no extracutaneous involvement, are generally suitable for topical treatment including topical corticoids, application of chloromethine (CARYOLYSINE), or carmustine (BiCNU) if this is poorly tolerated or contraindicated or if the patient does not respond to topical CARYOLYSINE, phototherapy and radiotherapy.

\(^\text{15}\) Olsen E, Vonderheid E, Pimpinelli N Revisions to the staging and classification of mycosis fungoides and Sesary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organisation of Research and Treatment of cancer (EORTC) Blood 2007;110:1713-22
In the advanced stages (IIB to IVB), the efficacy data for the treatments employed have a low level of evidence and there are no comparative data favouring one form of treatment over another.

Radiotherapy is used when the number of tumours is small, otherwise systemic treatment, sometimes in combination with topical treatment, is necessary. Standard first-line systemic treatments are interferon alfa and low-dose methotrexate. In patients who fail to respond, other single-agent chemotherapies (such as liposomal doxorubicin, gemcitabine, chlorambucil ± prednisone) and photopheresis can be proposed. Combination chemotherapy (CHOP regimen in particular), considered in highly progressive forms and disseminated lesions, does not prolong survival and therefore remains a last-resort option on account of its toxicity; the remission achieved is most often partial and transitory.

In advanced-stage cutaneous T-cell lymphoma, it should be noted that both the guidelines of the French cutaneous lymphoma study group and the US guidelines (based on phase II studies, expert opinions and a small number of case studies) suggest oral bexarotene as a first-line treatment option contrary to the EORTIC consensus conference, which recommends it as a second-line treatment (in accordance with the marketing authorisation).

**Therapeutic use of TARGRETIN:**

In the treatment of skin manifestations of cutaneous T-cell lymphomas, oral bexarotene (TARGRETIN) can be considered an alternative second-line therapy or beyond in advanced-stage disease that is not highly progressive.

### 6.4. Target population

Epidemiological data on cutaneous T-cell lymphomas are scarce and no usable new data have been published since the previous Transparency Committee Opinion. The annual incidence of cutaneous lymphomas is estimated at 0.36 cases in 100,000. In the previous Transparency Committee Opinion, the prevalence in France had been estimated at 3200 cases and the annual incidence at 223 cases. According to experts, advanced-stage disease (IIB to IVB) has up to now accounted for 15 to 20% of cases (i.e. approximately 480-640 patients), with approximately 50% being refractory to at least one treatment (i.e. approximately 240-320 patients). The target population of TARGRETIN can therefore be estimated at 240 to 320 patients per year.

### 6.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance in the indication and at the dosage in the Marketing Authorisation. As regards the application for inclusion on the list of medicines that can be dispensed to outpatients by retail pharmacies, the Transparency Committee requests that the pharmaceutical company supplies an information document approved by the competent authorities to be provided to community-based pharmacists dispensing this anticancer drug in retail pharmacies.

#### 6.5.1. Packaging: Appropriate for the prescription conditions

#### 6.5.2. Reimbursement rate: 100%

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17 Non-Hodgkin’s lymphoma NCCN 2011