HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

26 September 2007

UVADEX 20µg/ml, solution for modifying the blood fraction
Box of 12 x 10 ml vials (CIP: 570 392-4)

Applicant: THERAKOS EUROPE

Methoxsalen

ATC Code: L03AX:

Reserved for hospital use

Marketing authorisation (MA) date: 15 December 2006

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

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Methoxsalen

1.2. Background

UVADEX is an extracorporeal photochemotherapy (ECP or photopheresis) treatment administered exclusively using the UVAR TXS photopheresis system where the 3 phases of the treatment procedure take place in a closed loop: collection of leucocytes, photoactivation after administering UVADEX in the photoactivation bag and reinfusion in the patient by gravity.

1.3. Indication

UVADEX is used in combination with the UVAR TXS Photopheresis System in the palliative treatment of skin manifestations (plaques, extended patches, erythrodermia) of cutaneous T-cell lymphoma (CTCL), only in patients who have not responded to other forms of treatment.

1.4. Dosage

Do not inject directly in patients.

As part of the photopheresis method, the patient is connected to the UVAR XTS device using an interface of catheters.

Red blood cells are separated from white blood cells and plasma in the centrifuge bowl. Excess red blood cells and plasma are returned to the patient while the buffy coat (leucocyte-enriched blood) and a certain volume of plasma are collected in the photoactivation bag located at the side of the UVAR XTS device. The buffy coat collection cycle is repeated three to six times, depending on the size of the centrifuge bowl used in the UVAR XTS device.

During each photopheresis treatment with UVADEX, the dosage of UVADEX is calculated based on the treatment volume (displayed on the UVAR XTS device's screen), using the following formula:

Volume treated x 0.017 mL UVADEX for each treatment.

For example: volume treated = 240 mL x 0.017 = 4.1 mL UVADEX.

The prescribed quantity of UVADEX is injected into the recirculation bag before the photoactivation phase.

During photoactivation, the leucocyte-enriched blood is continually circulated in the photoactivation chamber (photoceptor) for a maximum of 90 minutes during which it is exposed to UVA rays (1-2 J/cm^2) emitted by two banks of UVA lamps.

Once the photoactivation cycle is complete, the photoactivated cells are reinfused in the patient by gravity.

The recommended time for reinfusion is between 15 and 20 minutes. The entire photopheresis procedure lasts between 2 and 3 hours.

Treatment must be administered to the patient for two consecutive days, every month for six months. Where patients do not respond satisfactorily to the treatment after eight sessions, the rate of administration may be adjusted to two consecutive days, every fortnight (15 days) for the subsequent three months.

The patient’s response is considered to be “satisfactory” if there is a 25% improvement in the skin score (see below), maintained for at least 4 weeks.

The skin score is calculated as follows: the severity of the skin lesions is determined for each of the 29 areas on the surface of the body (identical to those used to evaluate burn lesions), according to a scale from 0 to 4 as follows:

0 = normal skin

0.5 = normal appearance with diffuse red pimples

1 = mild rash and oedema; no desquamation or fissure

2 = moderate rash and oedema; no desquamation or fissure

3 = severe rash and desquamation and oedema; no fissure or ectropion

4 = the most severe; includes extremely severe rash and oedema, as well as desquamation; possibility of fissures and ectropions.

Each score in terms of severity must then be multiplied by the percentage of the body's surface corresponding to the area affected in order to obtain an area score. All the area scores are then added up to obtain a regional score. All the regional scores are then added up to obtain the overall skin score.

A 25% improvement is considered to be a clinically significant change. It is linked to the severity of the overall condition (extent to which the blood and lymph nodes are invaded by the malignant cells - T-lymphocytes). Any improvement observed in the disease's manifestations on the skin is accompanied by a parallel improvement in the systemic disease. To avoid confusing a slight improvement with a moderate, temporary reduction in skin lesions with a real improvement, all positive changes in terms of skin lesions must be maintained for at least four weeks to be considered clinically significant.

The number of photopheresis sessions must not exceed 20 in six months.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2007)

L	Antineoplastic and immunomodulating agents
L03	Immunostimulants
L03A	Cytokines and immunomodulating agents
L03AX	Other cytokines and immunomodulating agents

2.2. Medicines in the same therapeutic category

UVADEX is the only pharmaceutical product in its therapeutic category with an indication for the treatment of cutaneous T-cell lymphoma.

There is another extracorporeal photochemotherapy method, known as the Vilber Lourmat method, implemented in an open system, which uses methoxsalen as a photosensitising agent. In this use methoxsalen has the status of a related therapeutic product.

2.3. Medicines with a similar therapeutic aim

Other medicinal products or treatments with a similar therapeutic aim are:
- Interferon alpha-2a (ROFERON-A):
- Bexarotene (TARGRETIN)
- Chlormethine (CARYOLYSINE)
- Methoxsalen (MELADININE) used as part of PUVA therapy: irradiation of the body using UVA rays after taking a photosensitising agent.
- Systemic single-agent chemotherapy: especially methotrexate
- Polychemotherapy: CHOP regimen in particular [cyclophosphamide (ENDOXAN), alkylating agent, hydroxyadriamycin, vincristin sulphate (ONCOVIN), prednisone (CORTANCYL)].

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The laboratory submitted in support of its request a phase III study (study CTCL-03), which evaluated the efficacy and safety of ECP with methoxsalen (UVADEX) as a photosensitising agent administered *ex vivo* and the UVAR system (predecessor to the UVAR XTS model currently used and for which UVADEX has its MA).

Supplementary data:

- 2 studies (CTCL-01 and CLCL-02) carried out using the UVAR system with methoxsalen administered orally
- 4 case series treated using ECP with UVADEX
- 4 case series treated using ECP with UVADEX or methoxsalen administered orally without distinguishing between the two scenarios.

Only those studies where methoxsalen was administered according to the conditions recommended by the UVADEX MA (*ex vivo*) are described below. Two case series involving a very small number of patients (n = 12) are not included.

Main study: CTCL-03

Objective: to evaluate the clinical effect on the skin manifestations of CTCL (advanced stage) of ECP using the UVAR system and a sterile solution of methoxsalen (UVADEX) administered *ex vivo* directly into the target cells.

Design: non-comparative, multicentre study.

Inclusion criteria

Patients aged 18 to 80 years, with CTCL skin lesions. CTCL diagnosis had to be based on one of the following 4 criteria:

- at least one skin biopsy indicating an abnormal histological model consistent with a diagnosis of CTCL
- a skin biopsy indicating an abnormal immunological phenotype or screening (antibodies BE2, OKT1, OKT3, OKT8)
- a lymph node biopsy whose histological and chromosome (karyotype) analyses were consistent with a diagnosis of CTCL
- progression of the disease during the previous year: increase in the condition's scope or skin score observed by patients or their doctor.

Patients treated with photosensitising agents were able to be included in the study, providing that they discontinued their treatment before receiving ECP treatment with methoxsalen. Similarly, patients had to discontinue any treatment with oral prednisone at least 30 days before being included in the study.

Additionally, patients had to be able to withstand the phase where a large extracorporeal volume was taken discontinuously (problem for cardiac or anaemic patients).

Main non-inclusion criteria:

- prior treatment with ECP using the UVAR system
- idiosyncratic or hypersensitive reactions to methoxsalen derivatives

- clinical condition affecting the liver, spleen or other viscera, the bone marrow, CTCL skin tumours caused by CTCL without erythrodermia or skin tumours 5 mm in diameter or wide
- recent deterioration (in the last 3 months) in renal function with a creatinine clearance rate > 3.0 mg/dL
- history of a liver condition.

Number of patients to be included: the number of subjects to be included was calculated to be able to demonstrate a success rate of 40% (success was defined by a reduction of at least 25% in the skin score, maintained for at least 4 weeks). As a result, a minimum of 42 patients were required to be able to achieve this lower limit. The plan had therefore been to include at least 42 patients at 10 centres.

Treatment

Two treatment regimens were possible:

- **"Normal" treatment**
  A cycle of two sessions of ECP during two consecutive days, repeated every four weeks for six months (i.e. seven treatment cycles). Patients were followed up for 6 months.
- **"Accelerated" treatment**
  If the skin score after 3 months had increased in relation to the baseline score (during the fourth treatment cycle), the cycle frequency was increased to twice a month: a patient was able to receive a maximum of 10 treatment cycles.

  After the first 6 months, if the skin score had dropped, the patient returned to the "normal" regimen, i.e. follow-up for 6 months. If the score did not drop, patients could continue with the "accelerated" treatment for another 6 months and receive up to 20 treatment cycles.

Concomitant treatments
Topical steroids were authorised during the study only on the palm of the hands and soles of the feet. Patients with skin tumours exceeding 1.5 cm in diameter were able to have one or more of the following treatments: localised, superficial radiotherapy, surgical excision, cryotherapy. Photosensitising agents could be administered after the ECP session.

Treatment duration: 12 months, in two periods: an initial 6-month period of treatment, then a 6-month follow-up period.

Primary endpoint: progression of skin score[1].

[1] Skin score: severity score of 0 (normal skin) to 4 (very severe condition) measured for each of the 29 areas of the body and weighted by the surface area and by adding all the regional scores in order to obtain the overall score. An improvement in the score of at least 25%, maintained for a period of at least 4 weeks, was considered to be a successful treatment. The difference between the baseline score and final score was considered to be clinically relevant if the lower limit of the confidence interval of the percentage of responders was higher than 25%.

The treatment was defined as successful if the skin score was reduced by 25% in relation to the baseline score and maintained for 4 weeks. The treatment was considered to be effective if the lower limit of the 95% confidence interval for the proportion of patients who successfully responded to the treatment was at least 25%.

The response was assessed among the following populations:

- Intention-to-treat (ITT) population: all the patients included who had received at least one ECP treatment with methoxsalen, i.e. 51 patients:
  - response after 6 months
  - overall response at end of study.
- Population treated for 6 months: all the patients who completed the treatment period, i.e. 35 patients
  - response after 6 months.

Results

Most of the patients included in the study were in the advanced stages of CTCL, which were resistant to treatment: 30 (59%) were at stage T4, 20 (39%) at stage T2 and a single patient was at stage T1. They had been non-responsive to other treatments for CTCL. The various treatments received previously by the patients are indicated in Table 1.

Table 1: Treatment previously received by patients

Treatment	Number of patients (%)
Topical/systemic corticosteroids	30 (59%)
PUVA therapy	14 (27%)
Methotrexate/chemotherapy	11 (22%)
Nitrogen mustard (CARYOLYSINE)	4 (8%)
Radiotherapy (total body irradiation)	3 (2%)
Other	3 (2%)

To avoid temporary changes in the lesions' appearance being confused with a genuine improvement, any positive change in the skin lesions had to be maintained for at least 4 consecutive weeks to be considered as being clinically significant.

In order to standardise how the skin score is measured, the investigators had all attended training and practice sessions during which it was established that they could measure the skin score reliably.

As a result, a reduction in the skin score of at least 25% for a minimum of 4 weeks was considered to be a criterion for success and clinically significant. This success criterion was chosen in consultation with the Food and Drug Administration (FDA), taking into account a maximum rate of spontaneous remission of 10% (even if at these advanced stages of CTCL, such a high rate is very unlikely) and a minimum improvement resulting from the treatment of 15%.

Primary endpoint results (see Table 2)

Table 2: Progression of skin score (at least a 25% improvement for a minimum of 4 weeks)

	Responders	95% CI	Non-responders
ITT patients (n = 51)			
After 6 months	17 (33%)	[21; 48]	34 (67%)
Total response	19 (37%)	[24; 52]	32 (63%)
Patients who took the treatment for 6 months (n = 35)			
After 6 months	15 (43%)	[26; 61]	20 (57%)

Among patients who had received at least one treatment (51 patients), 33% achieved a decrease in their skin score of more than 25% during the 6 months after the treatment started, which was maintained for more than 25 days.

After 12 months (6 months of treatment and 6 months of follow-up), 37% of patients who had received at least one treatment achieved a decrease in their skin score of more than 25% at some time during the study, which was maintained for more than 25 days.

Among those who received the entire course of treatment (35 patients) for 6 months, 43% achieved a decrease in their skin score of more than 25% during the 6 months after the treatment started, which was maintained for more than 25 days.

Supplementary data: series of patients treated with methoxsalen administered *ex vivo*

Crovetti et al, 2000

Thirty-three patients with CTCL (24 with mycosis fungoides from stage IIB to IVA and 9 with Sezary syndrome), having had no success with other treatments, were treated with ECP using methoxsalen (*ex vivo*), in combination with the UVAR or UVAR XTS system.

Two treatment regimens were used:

- Two treatment sessions during two consecutive days; this cycle was repeated every four weeks for six months.
- The treatment cycle was repeated every 2 weeks for 3 months, then every 4 weeks for the following 3 months. This regimen was intended for the most severely affected patients (generalised erythrodermia and/or negative prognosis factors).

6 patients received ECP using methoxsalen (*ex vivo*) in combination with interferon alpha. The clinical response was evaluated after 3 and 6 months of treatment as follows:

- Complete response (CR): erythrodermia and/or skin lesions disappeared; no adenopathy.
- Partial response (PR): reduction in skin lesions of between 50 and 99%, no increase in size of lesions, no new lesions.
- Minimum response (MR): reduction in skin lesions of 25 to 49%.
- Disease progression (DP) increase in skin lesions of at least more than 25%, new lesions or new adenopathy appear.

Results
Thirty patients received at least 3 cycles of ECP with UVADEX and were evaluated. A favourable clinical response (PR + CR) was achieved in 16 of the 21 patients with mycosis fungoides and in 6 of the 9 patients with Sezary syndrome. Their median survival from the start of the treatment was 18 months (4 to 58 months). In total, 16 of the 30 patients responded.

Evans et al, 2001
This case series involved 23 patients with Sezary syndrome who received treatment every month (2 sessions on 2 consecutive days) with ECP (UVAR system + UVADEX) for at least 6 months and no more than 1 year. The skin score was measured at the time of inclusion and then 3, 6, 9 and 12 months after initiating the treatment. The responders were the patients who had a reduction in the skin score of at least 25% in relation to the baseline score.

Results
Out of the 23 patients treated for 6 months, 8 responded to the treatment after 6 months. Out of the 12 patients treated with ECP for 12 months, 8 responded to the treatment after 12 months. In total, 13 of the 23 patients responded after 3, 6, 9 and 12 months. The reduction in the skin score was significant ($p = 0.001$). This reduction was also significantly correlated with a reduction in the proportion of Sezary cells ($p = 0.03$). None of the parameters examined (age, gender, previous treatments, presence of tumours etc.) were correlated with the response.

3.2. Adverse effefcts

The adverse effects currently observed (>1-10%) during the clinical studies were hypotension, nausea and vomiting, infections and complications linked to the treatment procedure (transient fever and complicated vascular access).

3.3. Conclusion

The efficacy and safety of ECP using UVADEX, combined with the UVAR system, were mainly evaluated in a non-comparative phase III study, involving patients with advanced CTCL (stages T2 to T4) who failed to respond to other treatments.

The primary endpoint was the overall skin score (total of regional scores where 0 = normal skin and 4 = very severe condition, weighted by the surface of each area of the body). Responders were defined by a minimum 25% improvement in the score, maintained for at least 4 weeks. The difference between the baseline score and final score was considered to be clinically relevant if the lower limit of the confidence interval for the rate of responders was higher than 25%.

In the case of patients who received at least one treatment, there were 17 responders out of 51 (33%: $CI_{95\%}$ =[21; 48]) after 6 months. After 12 months, including 6 months of treatment and 6 months of follow-up, 19 out of the 51 patients were responders (37%: $CI_{95\%}$ = [24; 52]).
Among those who received the entire course of treatment 15 out of 35 were responders (43%: $CI_{95\%}$ = [26; 61]). Only this effect is clinically relevant in terms of the clinical relevance threshold defined in the protocol.

Two case series which involved a very small number of patients were submitted and indicated an improvement in skin manifestations. In the Crovetti study (2000), 16 out of the 30 patients with mycosis fungoides (stage IIB to IVA) or Sezary syndrome were responders (with a minimum 50% improvement). In the Evans (2001) study on 23 patients with Sezary syndrome, 13 achieved an improvement in their skin score of at least 25%.

The phase III study and case series highlighted an important effect on improving skin manifestations in patients with CTCL at a severe, advanced stage and resistant to other treatments. In the Crovetti study where the rates of complete responses were individualised, a third of patients achieved a complete response (skin symptoms disappeared and no adenopathy). However, the results of these studies must be interpreted with caution insofar as they are not comparative.

In all the clinical studies, ECP using methoxsalen *ex vivo* was well tolerated. The adverse effects currently observed (>1-10%) during the studies were hypotension, nausea and vomiting, infections and complications linked to the treatment procedure (transient fever and complicated vascular access).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Cutaneous T-cell lymphoma (CTCL) is a non-Hodgkin lymphoma defined as a proliferation of T-lymphocytes starting with the skin, without any infiltration of the lymph nodes, bone marrow or other organs in the 6 months following diagnosis. It accounts for 65% of primary cutaneous lymphomas. CTCL has multiple clinical manifestations, including mycosis fungoides (initial skin condition which evolves slowly towards a tumour stage with extracutaneous infiltration) and Sezary syndrome (a severe, systemic skin condition), which are the two most common forms. The advanced stages entail numerous complications, especially bacterial and viral infections due to immunosuppression and hepatosplenomegaly.

In its advanced stages, CTCL leads to a marked deterioration in the quality of life and is life-threatening.

This medicinal product is intended to provide palliative treatment.

Public health benefit

The advanced forms of cutaneous T-cell lymphoma (CTCL) represent a small public health burden, given their rarity.

Improving its management lies within the scope of an identified public health priority (cancer plan, rare diseases plan, palliative care). Existing systemic treatments (and in particular, the open-system photopheresis method, known as the Vilber Lourmat method) are already providing a solution to the need for palliative treatments for skin manifestations in the case of advanced CTCL.

It is not possible to evaluate from the data available the impact of UVADEX used with the UVAR XTS device (closed-system photopheresis) on the morbidity and quality of life in relation to current palliative therapeutic management of skin manifestations in the case of advanced CTCL.

Consequently, UVADEX used with the UVAR XTS device is not expected to have an impact on public health.

The efficacy/adverse effects ratio is high.

This medicinal product is a second-line treatment in the advanced stages of the disease where there has been no response to other forms of treatment (PUVA therapy, systemic corticosteroids, chlormethine, interferon alpha, methotrexate).

There are alternative treatments.

The actual benefit of UVADEX is substantial.

4.2. Improvement in actual benefit

In view of the absence of comparative data, the Transparency Committee concludes that UVADEX does not offer any improvement in actual benefit (IAB V) with regard to the current management of patients with advanced cutaneous T-cell lymphoma (plaques, extended patches, erythrodermia) who have not responded to other forms of treatment. UVADEX is an additional means of treatment.

4.3. Therapeutic use

4.3.1. Treatment strategy

In the early stages of the disease, if there is no extracutaneous condition, the treatment is local and usually involves the use of topical steroids, PUVA therapy with methoxsalen being used as a photosensitising agent (MELADININE), as well as the application of chlormethine (CARYOLYSINE) or carmustine (BiCNU). If this is unsuccessful, the patient may receive as second-line treatment interferon alpha 2A (ROFERON-A), on its own or in combination with PUVA therapy, a retinoid (bexarotene: TARGRETIN), a low dose of methotrexate or be treated using total body irradiation with maintenance from chlormethine.

In the advanced stages where the condition is systemic (infiltration of the nodes, appearance of tumours, erythrodermia), systemic treatment is required, either on its own or in combination with a local treatment. There is currently no comparative data available making it possible to favour one form of treatment over another. A group of experts in France had suggested treatments for the different stages of the disease[2]. Polychemotherapy remains a treatment of final resort due to its toxicity.

Systemic treatments:
- interferon alpha
- bexarotene
- low dose of methotrexate
- liposomal doxorubicin
- chlorambucil ± prednisone
- photopheresis
- polychemotherapy (in the case of visceral involvement)

Local treatments:
- corticosteroids
- chlormethine
- carmustine
- PUVA therapy
- irradiation

4.3.2. Medicinal product's therapeutic use

UVADEX is a second-line treatment in the advanced stages of the disease (presence of plaques, extended patches, erythrodermia with or without node involvement and with or without Sezary cells), if other forms of treatment are unsuccessful.

[2] Bachelez et al. Algorithme thérapeutique lymphomes T cutanés. Propositions du groupe d'experts. Ann Dermatol Venerol, 2005 ;132:5S43-4

4.4. Target population

Based on epidemiological data from the US (source: Orphanet), the annual incidence of cutaneous lymphoma is estimated at 1 case in 100,000. The incidence of mycosis fungoides may be estimated at 0.36 cases per 100,000 and that of Sezary syndrome at the much smaller figure of 0.4 cases per 1,000,000. Extrapolating these figures to the French population (INED 2007), the annual incidence of mycosis fungoides may be estimated at 230 cases per year and that of Sezary syndrome at 25 cases per year.

Advanced mycosis fungoides (T2 to T4) would seem to account for around a third of the cases (specialist opinion) or about 75 patients per year. In the case of Sezary syndromes, which are already at a severe stage, a total of 100 patients a year would be at the severe stage of the disease. Approximately 20% would be resistant to at least one treatment (specialist opinion), which means that the target population for UVADEX can be estimated it at around 20 patients 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 indications and dosages of the MA.

Packaging: Appropriate to the conditions of prescription.