**DAUNOXOME 2 mg/ml, liposomal dispersion for injection**
B/1 vial of 50 ml (CIP: 34009 560 0636 0 0)

**Applicant:** NOVEX PHARMA

<table>
<thead>
<tr>
<th>INN</th>
<th>Daunorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code  (2012)</td>
<td>L01DB02 (Antineoplastic agents - anthracyclines and related substances)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Re-assessment of the IAB following joint referral from the Ministry of Health, the Social Security Directorate and the Directorate General for Health Services on 10 October 2013, in accordance with article R 163-19 of the French Social Security Code.</td>
</tr>
<tr>
<td>List concerned</td>
<td>Hospital use (French Public Health Code L.5123 2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>&quot;Treatment of Kaposi’s sarcoma with extensive or visceral skin and mucous membrane involvement in patients at an advanced stage of the HIV infection (CD4 &lt; 200/mm³)&quot;</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>Improvement in Actual Benefit</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Substantial only in patients at an advanced stage of the HIV infection (CD4 $&lt; 200$/mm$^3$) with Kaposi’s sarcoma with extensive or visceral skin and mucous membrane involvement who have an incomplete response to ARVs.</td>
<td>In patients at an advanced stage of the HIV infection (CD4 $&lt; 200$/mm$^3$) with Kaposi’s disease with extensive or visceral skin and mucous membrane involvement who have an incomplete response to ARVs, DAUNOXOME does not provide any improvement in actual benefit (IAB V, non-existent) compared with CAELYX.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>Recommendations</td>
</tr>
</tbody>
</table>
| In rare patients who have an incomplete response to ARVs, DAUNOXOME (daunorubicin), an anthracycline, is an alternative to doxorubicin (CAELYX), while an anthracycline is recommended, i.e. according to the above recommendations, in patients with:  
  - debilitating Kaposi’s disease with skin involvement to limit progression of lesions,  
  - advanced Kaposi’s disease particularly if there are visceral lesions;  
  - Kaposi’s disease in patients who have failed to respond to antiretrovirals.                                                                                                                                                                                                                                                                                                                                                                         | In patients at an advanced stage of the HIV infection (CD4 $< 200$/mm$^3$) with Kaposi’s disease with extensive or visceral skin and mucous membrane involvement who have an incomplete response to ARVs, DAUNOXOME does not provide any improvement in actual benefit (IAB V, non-existent) compared with CAELYX.                                                                                                                                                                                                                           |
01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national)  
Initial date: 20 August 1996  
The Marketing Authorisation was accompanied by a request for further studies (103-24) in AIDS-related Kaposi’s sarcoma with pulmonary involvement, which was published in 1998 (Tulpule et al.).

Prescribing and dispensing conditions/special status  
List I  
Medicine for hospital prescription  
Prescription restricted to certain specialists (doctors with cancer training, or specialists in haematology or medical oncology)  
Medicine requiring special monitoring during treatment

ATC Classification  
2012 L  
L01 Antineoplastic and immunomodulating agents  
L01D Antineoplastic agents  
L01DB Cytotoxic antibiotics and related substances  
L01DB02 Anthracyclines and related substances  
daunorubicin

02 BACKGROUND

As part of the work aimed at updating the list of chargeable medicinal products in addition to hospital services by the Hospitalisation council, and pursuant to article R 163-19 of the French Social Security Code, the Ministry of Health, the Social Security Directorate and the Directorate General for the Organisation of Care has applied to HAS for a ruling on the IAB of proprietary medicinal products, including the proprietary medicinal product DAUNOXOME 2 mg/ml, liposomal dispersion for injection, the subject of this opinion.

03 THERAPEUTIC INDICATION

“Treatment of Kaposi’s sarcoma with extensive or visceral skin and mucous membrane involvement in patients at an advanced stage of the HIV infection (CD4 < 200/mm³)”

04 DOSAGE

See SPC.

05 THERAPEUTIC NEED1,2,3

Kaposi’s disease (KD), formerly known as Kaposi’s sarcoma (KS), is today no longer considered a cancer.

If it exists in forms that are independent of the AIDS virus infection, it develops especially in individuals infected both with HIV and HHV8. It is based on a mesenchymal proliferative process

1 Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d’experts. RAPPORT 2013.
3 www.sidainfoplus.fr
concerning the cells of the blood and lymphatic systems, induced by viral growth factors, particularly interleukin 6 from human herpes virus type 8 (HHV8)

Its early expression is mostly cutaneous. It is a chronic disease, which causes often disseminated tumours for which the screening is based on close examination of the skin and mucous membranes. It is associated with an exceptional mortality.

Therapeutic management
Management of KD has changed since the advent of HIV; indeed, at the onset of the disease, KD often represented one of the first diagnostic signs of HIV. Thus, the management of this disease was based on systemic chemotherapy. With the development of ARVs and the early management of patients, the incidence of KD has considerably reduced.

Thus, in one antiretroviral-naive patient, the antiretroviral treatment is from now on the basic treatment for KD with a complete response in the vast majority of patients over time (6 to 12 months).

In debilitating KD with skin involvement, the immediate addition of local adjuvant treatments may be discussed with an oncodermatologist: laser, cryotherapy or retinoic acid as a topical gel or radiotherapy.

Systemic chemotherapy with liposomal doxorubicin or liposomal daunorubicin lasting 2 to 3 months may be discussed to limit the progression of lesions in the context of immune reconstitution inflammatory syndrome (IRIS).

In the case of advanced KD, particularly if there are visceral lesions (particularly pulmonary) or in the face of a simultaneous severe flare-up of immune reconstitution, initiating systemic chemotherapy alongside the antiretroviral treatment is recommended after discussion at an interdisciplinary consultation meeting (ICM). This may also be proposed if KD occurs in a patient who has failed to respond to antiretrovirals. Liposomal doxorubicin administered at a dose of 20 mg/m² every 2 to 3 weeks is to be preferred; liposomal daunorubicin may be proposed as an alternative at a dose of 40 to 60 mg/m² every 2 weeks.

In the event that anthracyclines have failed (about 50% of patients in the studies performed before the year 2000), one might propose the use of taxanes, paclitaxel or docetaxel, which have shown efficacy of around 60% in this situation. In Europe, only paclitaxel, at a dose of 100 mg/m² every 15 days, has a Marketing Authorisation in this indication.
06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

The clinically relevant comparators are the other anthracyclines, indicated in the management of Kaposi's sarcoma.

<table>
<thead>
<tr>
<th>NAME (INN)</th>
<th>Indication</th>
<th>Date of opinion</th>
<th>AB IAB (Wording)</th>
<th>Reimbursement Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAELYX (liposomal doxorubicin)</td>
<td>For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (&lt; 200 CD4 lymphocytes/mm$^3$) and extensive mucocutaneous or visceral disease. Caelyx may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).</td>
<td>19/02/1997</td>
<td>Substantial AB IAB V compared with DAUNOXOME (simultaneous development)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

The management of Kaposi's sarcoma is also based on:
- antiretroviral treatment (first-line treatments),
- local treatment: retinoic acid as a topical gel,
- chemotherapy: vinblastine (VELBE), taxanes (paclitaxel (TAXOL) or docetaxel (off-label use)).

06.2 Other health technologies

Local adjuvant therapies may be proposed: laser, cryotherapy, radiotherapy.

**Conclusion**

The clinically relevant comparator is liposomal doxorubicin (CAELYX), the other liposomal anthracycline indicated in the treatment of Kaposi's sarcoma.
07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

<table>
<thead>
<tr>
<th>Country</th>
<th>REIMBURSEMENT</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Yes</td>
<td>19/03/1996</td>
</tr>
<tr>
<td>Austria</td>
<td></td>
<td>29/03/1996</td>
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<tr>
<td>Denmark</td>
<td></td>
<td>19/03/1996</td>
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<tr>
<td>Finland</td>
<td></td>
<td>05/02/1996</td>
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<tr>
<td>Ireland</td>
<td></td>
<td>19/03/1996</td>
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<tr>
<td>Italy</td>
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<td>09/07/1997</td>
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<tr>
<td>Norway</td>
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<td>15/04/1997</td>
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<td>Portugal</td>
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<td>30/03/1996</td>
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<tr>
<td>United Kingdom</td>
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<td>12/10/1995</td>
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<tr>
<td>Brazil</td>
<td></td>
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<tr>
<td>United States</td>
<td></td>
<td>08/04/1996</td>
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</table>

08 SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>20 November 1996</th>
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</thead>
<tbody>
<tr>
<td>Inclusion for hospital use</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Treatment of Kaposi's sarcoma with extensive skin and mucous membrane or</td>
</tr>
<tr>
<td>visceral involvement in patients at an advanced stage of the HIV infection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Actual Benefit (wording)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi's sarcoma is a serious disease, responsible for significant morbidity and aesthetic and psychological harm. In its advanced forms (extensive or visceral Kaposi's sarcoma) and in patients whose CD4 count is lower than 200/mm³, DAUNOXOME has shown its efficacy and an acceptable safety. The only alternative treatment is multidrug cytotoxic chemotherapy. The role of this proprietary medicinal product in the therapeutic strategy of this infection is notable.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improvement in Actual Benefit (wording)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAUNOXOME provides a moderate improvement in actual benefit (level III) in terms of safety and ease of use compared with the currently recommended therapeutic strategy.</td>
</tr>
</tbody>
</table>
09 ANALYSIS OF AVAILABLE DATA

The company has reported two new studies which evaluated the benefit of DAUNOXOME (daunorubicin) in the treatment of Kaposi's disease:

- The study by Cooley et al. 2007, a randomised clinical trial, which compared the efficacy of liposomal daunorubicin with liposomal doxorubicin in terms of clinical benefit (improvement of symptoms) in 79 patients, treated between 1996 and 2000.
- The study by Rosenthal et al 2002, a phase IV retrospective study, which evaluated the efficacy of daunorubicin in a cohort of French patients treated between September 1996 and September 1997.

The latest periodic safety update report (PSUR) covering the period from 25 May 2011 to 24 May 2012 has also been provided.

09.1 Efficacy

9.1.1 Reminder of initial data (TC opinion of 20/11/1996)

"The clinical file includes in particular eight phase II studies (open-label efficacy study) bringing together 135 patients and one phase III randomised, open-label study comparing DAUNOXOME (40 mg/m\(^2\)) with ABV chemotherapy (adriamycin 10 mg/m\(^2\), bleomycin 15 U, vincristine 1 mg).

The phase III study brings together 232 patients presenting the following prognostic factors at inclusion: CD4 < 100/mm\(^3\), with visceral involvement, Karnofsky score < 80, and initial treatment with AZT.

The response rates are the same in both groups. No significant difference is observed in terms of the Karnofsky score, weight change or quality of life.

In terms of safety, DAUNOXOME has fewer adverse effects than the ABV group, as far as alopecia and the occurrence of neuropathies are concerned.

In terms of haematological safety, there is no significant difference between the two groups.

On a cardiac level, safety is good.

Overall, the efficacy of DAUNOXOME seems equivalent to multidrug chemotherapy including adriamycin, bleomycin and vincristine with good safety at the cardiac level and fewer adverse effects as far as alopecia and neuropathies are concerned".

9.1.2 Study by Cooley 20074

Method: comparative, prospective, randomised (3:1), double-blind study of liposomal daunorubicin (40 mg/m\(^2\) every 2 weeks, six cycles) versus liposomal doxorubicin (20 mg/m\(^2\) every 2 weeks, six cycles) evaluating the efficacy of these two treatments compared with the initial state in terms of response rate (clinical benefit) in 79 patients with Kaposi's disease.

This study, which evaluated patients treated between 1996 and 2000, is based on therapeutic strategies that do not conform with the recommendations in force since it was performed in patients who were not receiving optimal ARV treatment.

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This study was not designed to compare the two treatments with each other, daunorubicin having been used in this study only as a control arm.

**Inclusion criteria:** patients with AIDS-related Kaposi's sarcoma requiring systemic chemotherapy (whatever the previous treatments) with:

- A life expectancy of at least 120 days,
- At least five skin and mucous membrane lesions,
- At least one of the following symptoms:
  - Oedema associated with Kaposi's sarcoma in the extremities, genital area or face, with an impact on function,
  - Pulmonary Kaposi's sarcoma,6
  - Gastrointestinal Kaposi's sarcoma,6
  - Pain associated with moderate or severe Kaposi's sarcoma despite the use of analgesics,
  - Lesions associated with Kaposi's sarcoma which, in the patient's view, are disfiguring and associated with an impaired self-image or impairment of daily activities.
- A left ventricular ejection fraction $\geq 50\%$,
- A Karnofsky performance score $\geq 40\%$,
- Haemoglobin $\geq 9$ g/dl, neutrophils $\geq 1200/mm^3$, platelets $\geq 75,000/mm^3$,
- Bilirubin < 2 ULN, creatinine < 2 ULN.

**Non-inclusion criteria, in particular:** patients treated for Kaposi's sarcoma in the 14 days prior to entering the study with one of the two study products, cardiac disease with an impact on function, opportunistic infection in the 4 weeks prior to entering the study, and respiratory failure not linked to Kaposi's sarcoma (oxygen saturation < 90%).

**Treatment:**

- Daunorubicin 40 mg/m$^2$ every 2 weeks, six cycles, n=19,
- Doxorubicin 20 mg/m$^2$ every 2 weeks, six cycles, n=60.

**Primary efficacy endpoints:** proportion of patients with a clinical benefit observed at the end of the six cycles of treatment compared with the initial state (Kaplan Meier analysis). Clinical benefit was defined by:

- an improvement over at least 28 days in at least one of the five categories of symptoms linked to Kaposi's sarcoma, in the absence of disease progression or severe toxicity linked to the treatment,

Or

- an improvement over at least 28 days in at least one of the Five categories of symptoms linked to Kaposi's sarcoma, in the absence of disease progression or severe toxicity linked to the treatment, with no worsening of other categories of symptoms and with no intensification of the medical treatment throughout this period (conservative approach).

**RESULTS:**

After six cycles of treatment, a clinical benefit was observed in 48/60 (80%) patients in the doxorubicin group for a median duration of 62 days [28; 107]. With the conservative approach, a clinical benefit was observed in 22/60 (36.7%) patients for a median duration of 42 days [28; 106].

After six cycles of treatment, a clinical benefit was observed in 12/19 (63.2%) patients in the daunorubicin (DAUNOXOME) group for a median duration of 55 days [28; 84]. With the conservative approach, a clinical benefit was observed in 3/19 (15.8%) patients. In these patients, 6 Symptomatic and evaluable, documented by bronchoscopy in the 3 months prior to entering the study, measurable using radiography or tomography and not associated with any other manifestation of AIDS.
the median duration could not be calculated to the extent that the Kaplan Meier test estimated at each point was greater than 50%.

Given the methodology of this study, the purely descriptive results observed are difficult to interpret.

9.1.3 Study by Rosenthal

This retrospective, descriptive analysis aimed to evaluate the efficacy and safety of daunorubicin in the treatment of HIV patients with Kaposi's sarcoma.

The patients included in this analysis (n=94) were French patients with Kaposi's disease proven histologically and treated with at least one cycle of daunorubicin in 13 university hospitals. This study, which analysed patients treated between September 1996 and September 1997, is based on therapeutic strategies that do not conform with the recommendations in force since it was performed in patients who were not receiving optimal ARV treatment.

For each patient, the data were collected at inclusion, after each cycle of daunorubicin and at the end of the analysis (first trimester 1998).

Characteristics at inclusion:
- 80% of patients had received cytotoxic treatment before the first cycle of daunorubicin,
- The mean CD4+ count was 114/µl,
- 90% received antiretroviral treatment (HAART).

Treatments:
Daunorubicin was administered as monotherapy in 70% of patients with total cycle number of 1422, a mean cycle number of 16.1 [1; 68] and a dose of 40 mg/m2/ every 2 weeks in 77% of patients (dosage in the Marketing Authorisation).

Endpoints and results:
The endpoint was the response rate evaluated in line with the AIDS Clinical Trials group criteria.7

Thus, low response rates were observed:
- a complete response was observed in 11.5% of patients,
- partial response in 26.5%,
- stabilisation in 29%
- progression in 26.5%

09.2 Adverse effects

9.2.1 Data from clinical studies

In the Cooley study, instances where treatment was discontinued or interrupted or where doses were reduced due to adverse effects were observed in 41/69 (68.3%) patients taking doxorubicin and 12/19 (63.2%) patients taking daunorubicin (DAUNOXOME) due mainly to haematological toxicity (32.1% versus 15.8%).

The most commonly observed adverse effects (>15%) were:
- neutropenia: 30% versus 15.8%,
- nausea: 28.3% versus 26.3%,
- asthenia: 16.7% compared with 15.8%

9.2.2 PSUR data

During the period from 1st June 2011 to 24 May 2012 covered by the latest periodic safety update report (PSUR), 6533 vials of DAUNOXOME were sold, including 580 in France.

During this period, 47 cases were identified, including 42 in the literature. The most commonly observed adverse effects were: neutropenia and thrombocytopenia (14 cases), hypothyroidism (6 cases) and hepatic toxicity (5 cases).

In total, 20 cases of fatal progression were also reported without a direct link with daunorubicin being established.

9.2.3 SPC data

According to the SPC, the adverse effects considered as being at least possibly due to treatment with DAUNOXOME and observed very frequently (> 10%) are:

- infection,
- headaches, dyspnoea, alopecia,
- gastrointestinal conditions: stomatitis, mucosal ulceration, nausea, vomiting, diarrhoea, abdominal pain.
- haematological disorders: myelosuppression, agranulocytosis, neutropenia, febrile neutropenia, leukopenia, pancytopenia, thrombocytopenia and anaemia. As with other DNA-damaging antineoplastic agents, cases of myelodysplastic syndrome and acute myeloid leukaemia were observed after combined treatment including daunorubicin. With topoisomerase II inhibitors, a higher incidence than expected of secondary leukaemia presenting as de novo AML2, AML3, AML4 was reported. Such forms may have a short period of latency (from 1 to 3 years). These forms require an early diagnosis and suitable treatment.
- general disorders: asthenia, fatigue, fever, shivers, reactions linked to infusion.
Summary & discussion

New data justifying the clinical benefit of DAUNOXOME (daunorubicin) in the treatment of Kaposi's sarcoma is based on a study which evaluated the benefit of daunorubicin (control arm) and doxorubicin (Cooley 2007) and a retrospective study (Rosenthal 2002). Available data at the time of the first request for inclusion in 1996 were also included.

Primary efficacy data
Reminder of the conclusions of the previous opinion in 1996: “Overall, the efficacy of DAUNOXOME seems equivalent to multidrug chemotherapy including adriamycin, bleomycin and vincristine with good safety at the cardiac level and fewer adverse effects as far as alopecia and neuropathies are concerned”.

In the Cooley study, in which two treatment arms were evaluated compared with the initial state (liposomal daunorubicin (DAUNOXOME, 40 mg/m² every 2 weeks, six cycles) and liposomal doxorubicin (20 mg/m² every 2 weeks, six cycles)) and which was performed in 69 patients with Kaposi's sarcoma, the following was observed after six cycles of treatment:
- a clinical benefit in 48/60 (80%) patients in the doxorubicin group for a median duration of 62 days [28; 107]. With the conservative approach, a clinical benefit was observed in 22/60 (36.7%) patients for a median duration of 42 days [28; 106].
- a clinical benefit in 12/19 (63.2%) patients in the daunorubicin (DAUNOXOME) group for a median duration of 55 days [28; 84]. With the conservative approach, a clinical benefit was observed in 3/19 (15.8%) patients. In these patients, the median duration could not be calculated to the extent that the Kaplan Meier test estimated at each point was greater than 50%.

Given the methodology of this study, the purely descriptive results observed are difficult to interpret.

In the retrospective, descriptive analysis by Rosenthal, which evaluated the benefit of daunorubicin in 94 French patients, a complete response was observed in 11.5% of patients, a partial response in 26.5%, stabilisation in 29%, and progression in 26.5%. Given the methodology of this analysis, these results are difficult to interpret.

Primary safety data:
In the clinical studies and the latest PSUR, the most commonly observed adverse effects were neutropenia and thrombocytopenia.

According to the SPC, the adverse effects considered as being at least possibly due to treatment with DAUNOXOME and observed very frequently (> 10%) are:
- infections,
- headaches, dyspnoea, alopecia,
- gastrointestinal conditions: stomatitis, mucosal ulceration, nausea, vomiting, diarrhoea, abdominal pain.
- haematological disorders: myelosuppression, agranulocytosis, neutropenia, febrile neutropenia, leukopenia, pancytopenia, thrombocytopenia and anaemia.
- general disorders: asthenia, fatigue, fever, shivers, reactions linked to infusion.

Discussion:
Given the methodological weaknesses of the studies, the available data do not allow DAUNOXOME to be positioned against doxorubicin, especially as the populations studied do not correspond to the patients currently treated, i.e. those who are receiving optimal ARV treatment.

Moreover, given the fact that:
- the antiretroviral treatment is the basic treatment for KD with an almost complete response in the vast majority of patients over time (3 to 6 months),
- and the downward trend in the annual incidence of Kaposi's disease (KD) in France (incidence of 1.1 (95 % CI: 0.7-1.4) for 1000 patients in 2011), the role of DAUNOXOME in the management of this disease seems very limited.

09.4 Planned studies

The company has mentioned several studies that are either in progress or which are to come concerning the treatment of acute myeloblastic leukaemia (AML) and acute lymphoblastic leukaemia (ALL) and adds that the request for indication extension in children's AML could be envisaged.

010 Therapeutic use

**Therapeutic management**

In one antiretroviral naive patient, the antiretroviral treatment is the basic treatment for KD with a complete response in the vast majority of patients over time (6 to 12 months).

In debilitating KD with skin involvement, the immediate addition of local adjuvant treatments may be discussed with an oncodermatologist: laser, cryotherapy or retinoic acid as a topical gel or radiotherapy.

Systemic chemotherapy with liposomal doxorubicin (CAELYX) or liposomal daunorubicin (DAUNOXOME) lasting 2 to 3 months may be discussed to limit the progression of lesions in the context of IRIS.

In the case of advanced KD, particularly if there are visceral lesions (particularly pulmonary) or in the face of a simultaneous severe flare-up of immune reconstitution, initiating systemic chemotherapy, alongside the antiretroviral treatment, is recommended after discussion at an ICM. This may also be proposed if KD occurs in a patient who has failed to respond to antiretrovirals:

- liposomal doxorubicin (CAELYX) 20 mg/m² every 2 to 3 weeks, to be preferred over the adriamycin-vincristine-bleomycin combination, given its superior efficacy and safety, particularly cardiac.

- liposomal daunorubicin (DAUNOXOME) may be proposed as an alternative at a dose of 40 to 60 mg/m² every 2 weeks.

In case of failure with anthracyclines (around 50% of patients), taxanes (paclitaxel-TAXOL or docetaxel (off-label use)) must be proposed.

**Role of DAUNOXOME in the therapeutic strategy:**

In one antiretroviral naive patient, the antiretroviral treatment is the basic treatment for KD with a complete response in the vast majority of patients over time (6 to 12 months).

In rare patients who have an incomplete response to ARVs, DAUNOXOME (daunorubicin), an anthracycline, is an alternative to doxorubicin (CAELYX), while an anthracycline is recommended, i.e. according to the above recommendations, in patients with:

- debilitating Kaposi's disease with skin involvement to limit progression of lesions,
- advanced Kaposi's disease particularly if there are visceral lesions;
- Kaposi's disease in patients who have failed to respond to antiretrovirals.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

011.1 Actual benefit

- Kaposi’s disease is responsible for substantial morbidity and a marked deterioration in quality of life.

- DAUNOXOME 2 mg/ml, liposomal dispersion for injection (daunorubicin) is intended as curative therapy.

- In the management of Kaposi's disease, the therapeutic needs are theoretically covered by the use of ARV treatments at optimal doses that allow the vast majority of patients to obtain a complete response in 6 to 12 months. In rare patients who have an incomplete response to ARVs, i.e. presenting lesions with extensive skin or visceral involvement, the efficacy/adverse effects ratio of DAUNOXOME is high.

- There are treatment alternatives, particularly doxorubicin (CAELYX), another anthracycline indicated in the treatment of Kaposi’s disease.

- DAUNOXOME is a second-line treatment which may be proposed in debilitating KD with skin involvement to limit the progression of lesions; advanced KD, particularly if there are visceral lesions; or in patients who failed to respond to antiretroviral drugs.

**Public health benefit:**

In terms of public health, the burden induced by the HIV infection is substantial. That represented by Kaposi’s disease is low due to the restricted number of patients affected. The need is already covered by existing treatments, i.e. ARV treatments. Given the data available, it is not expected that the proprietary medicinal product DAUNOXOME will have an impact on morbidity/mortality and quality of life. Because of the rarity of cases requiring treatment with anthracyclines in particular, DAUNOXOME does not have any impact on public health.

Consequently, the Committee considers that the actual benefit of DAUNOXOME 2 mg/ml, liposomal dispersion for injection is substantial only in patients at an advanced stage of the HIV infection (CD4 < 200/mm$^3$) with Kaposi’s sarcoma with extensive skin and mucous membrane or visceral involvement who have an incomplete response to ARVs.

The Committee recommends maintaining inclusion on the list of medicines approved for hospital use, only in patients “at an advanced stage of the HIV infection (CD4 < 200/mm$^3$) with Kaposi’s disease with extensive skin and mucous membrane or visceral involvement who have an incomplete response to ARVs”; and at the dosages in the Marketing Authorisation.

**Proposed reimbursement rate: 65%**
011.2 Improvement in actual benefit (IAB)

In patients at an advanced stage of the HIV infection (CD4 < 200/mm$^3$) with Kaposi's disease with extensive skin and mucous membrane or visceral involvement who have an incomplete response to ARVs, DAUNOXOME (daunorubicin) does not provide any improvement in actual benefit (IAB V, non-existent) compared with CAELYX (doxorubicin).

011.3 Target population

The target population of DAUNOXOME corresponds to patients with Kaposi's disease with extensive skin and mucous membrane or visceral involvement, at an advanced stage of the HIV infection (CD4+ < 200/mm$^3$).

It can be estimated on the basis of the following information:
In terms of annual incidence, Kaposi's sarcoma is estimated at 1.1 per 1000 persons-years in 2011. The HIV population is estimated at around 150,000.
The proportion of patients who are candidates for cytostatic chemotherapy represents around 50% of cases.

Estimate:
On this basis, the target population for DAUNOXOME would be a maximum of 90 patients a year.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

➤ Packaging
Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.