HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
10 July 2013

PIXUVRI 29 mg, powder for concentrate for solution for infusion
Box of 1 vial (CIP: 583 972-4.

Applicant: NOVEX PHARMA

INN	pixantrone
ATC code (2012)	L01DB11 (anthracyclines and related substances)
Reason for the request	**Inclusion**
Lists concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy. "**

Actual Benefit	**The actual benefit of PIXUVRI is low.**
Improvement in Actual Benefit	**In view of the suboptimal level of demonstration of efficacy, but in view of the absence of alternative drug therapy validated as third- or fourth-line therapy for aggressive non-Hodgkin B-cell lymphomas, the Committee considers that based on the current data, PIXUVRI does not contribute any improvement in actual benefit (IAB V, non-existent) in the management of this disease.**
Therapeutic use	**PIXUVRI is a third- or fourth-line therapy for aggressive non-Hodgkin B-cell lymphoma in patients refractory to previous therapy including autologous transplantation unless this was not indicated.**
Committee recommendations	**The Committee will re-examine the proprietary medicinal product PIXUVRI two years after it has been placed on the market.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (centralised procedure)	Conditional Marketing Authorisation: 10 May 2012
Prescribing and dispensing conditions/ special status	List I Medicinal product reserved for hospital use. Prescription restricted to specialists in and departments of haematology. Medicine requiring special monitoring during treatment.
ATC Classification	2012 L Antineoplastic and immunomodulating agents L01 Antineoplastic agents L01D Cytotoxic antibiotics and related substances L01DB Anthracyclines and related substances L01DB11 pixantrone

02 BACKGROUND

The active ingredient of PIXUVRI is pixantrone base, which is a cytotoxic aza-anthracenedione. Pixantrone caused less cardiotoxicity in animal models than doxorubicin or mitoxantrone, probably as a result of its chemical structure.
PIXUVRI has orphan drug status and a "conditional" Marketing Authorisation issued on 10 May 2012 pending further data becoming available. The European Medicines Agency will re-assess any new information for this medicinal product at least once a year, and the SPC will be updated if necessary.

03 THERAPEUTIC INDICATIONS

"Pixuvri is indicated as monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy. "

04 DOSAGE

"Pixuvri must be administered by physicians who are familiar with the use of antineoplastic agents and have the facilities for regular monitoring of clinical, haematological, and biochemical parameters during and after treatment (see SPC).

Posology
The recommended dose is 50 mg/m^2 IV of pixantrone on days 1, 8, and 15 of each 28-day cycle for up to 6 cycles. However, the dose has to be adjusted before the start of each cycle based on nadir haematologic counts or maximum toxicity from the preceding cycle of therapy. The amount of Pixuvri in milligrammes that is to be administered to a patient should be determined on the basis of the patient's body surface area (BSA). The BSA should be determined using the institutional standard for BSA calculation and should use a weight measured on day 1 of every cycle.
Some caution is advised in obese patients as data on BSA-based dosing is very limited for this group.
Previous clinical trial experience was based on an 85 mg/m^2 dose of pixantrone dimaleate, equivalent to 50 mg/m^2 of pixantrone base. "

05 THERAPEUTIC NEED

As first-line therapy for aggressive non-Hodgkin B-cell lymphoma (NHL), chemotherapy regimens generally consist of cyclophosphamide, an anthracycline (doxorubicin), vincristine and corticosteroids (CHOP protocol). Addition of rituximab improved the percentage response and global survival.
20-50% of patients do not respond to first-line therapy (primary refractory disease) or they relapse at the end of treatment. In these patients, those with adequate performance status (no major organ dysfunction, age <65-70 years) are eligible for high-dose chemotherapy (intensification) with stem cell transplantation. Other patients receive chemotherapy without either intensification or autologous transplantation. At this stage of the disease, no chemotherapy (monotherapy or combination) is regarded as standard.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Various forms of chemotherapy are indicated in the treatment of non-Hodgkin lymphoma but at advanced stages of multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma, no drug has a Marketing Authorisation that is identical to that for PIXUVRI (pixantrone).

Conclusion

There is no clinically relevant comparator medicine available with a Marketing Authorisation.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO Start date	Population
AUSTRIA	YES	From obtaining Marketing Authorisation
FINLAND		
DENMARK		Marketing Authorisation Population
SWEDEN		
ENGLAND	Not reimbursed	No assessment by NICE

08 ANALYSIS OF AVAILABLE DATA

In support of its application for inclusion, the applicant submitted a clinical dossier containing:

- a phase 2 trial (PIX-203), in which PIXUVRI was used at different doses from those of the Marketing Authorisation, and it will therefore not be taken into account.
- a phase 2 trial, AZA-II-01 (PIX201), in patients with a different profile from that given in the Marketing Authorisation indication (the patients studied in this trial could previously have received 0-3 forms of treatment). It will not be taken into account.
- a phase 3 trial (PIX301), which will be analysed below.

08.1 Efficacy

Phase 3 trial PIX301,[1] a randomised (1:1) open trial that evaluated the efficacy and safety of PIXUVRI compared with investigator's choice of monochemotherapy in patients with relapsed or refractory non-Hodgkin lymphoma (NHL), who had received two or more prior therapies.

The primary efficacy endpoint was the proportion of patients with a complete response (CR, see Appendix) or complete response, unconfirmed (CRu, see Appendix) according to 1999 IWG-NHL criteria.
Tumour response was evaluated by a blinded independent assessment panel.

The secondary endpoints included:
- progression-free survival, defined as the time between start of treatment and disease progression or death,
- global survival, defined as the time between start of treatment and death from any cause,
- proportion of response lasting at least 4 months
- duration of response, defined as the time between initial response and disease progression or death from any cause,
- proportion of global response, defined as a complete response (CR) or complete response, unconfirmed (CRu) or a partial response (PR) according to 1999 IWG-NHL criteria (see Appendix).

Inclusion criteria included:
1. Aggressive NHL (*de novo* or transformed) confirmed histologically according to the WHO/REAL classification. The types of lymphoma allowing the patient to be included in the trial were:
   - grade 3 follicular lymphoma
   - transformed indolent lymphoma (permitted areas of folliculitis)
   - diffuse large B-cell lymphoma
   - mediastinal large B-cell lymphoma
   - primary effusion lymphoma (including disease previously called immunoblastic lymphoma)
   - peripheral T-cell lymphoma not otherwise specified (includes diffuse mixed-cell lymphoma)
   - anaplastic large-cell lymphoma and primary T-/null-cell type
2. Patients' prior therapy had to have included rituximab in countries where it was regarded as recommended therapy, and if the neoplastic cells expressed CD20.
3. At least one measurable objective lesion revealed by CT, helical CT or MRI that could be monitored as the target lesion to determine response. Patients whose involvement was limited to skin lesions, palpable lymph nodes, spleen or bone marrow were not eligible.

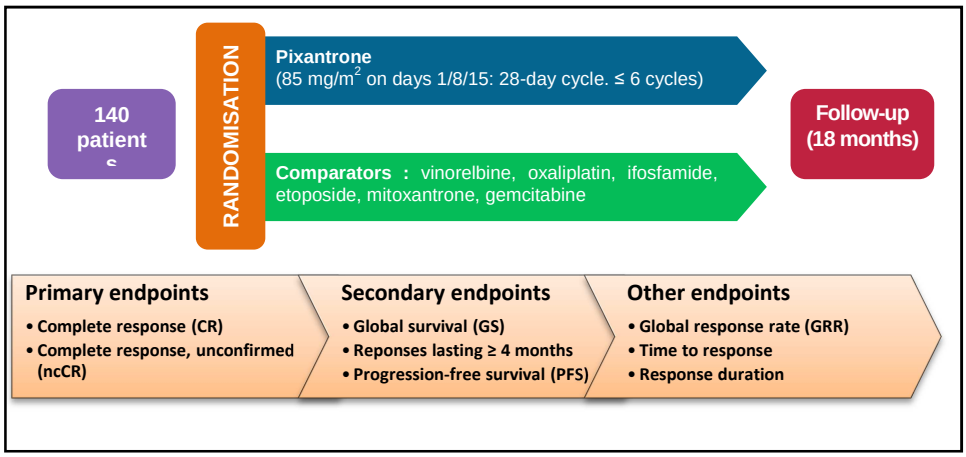
[1] Cancer. 2008; 113: 3192-3198.
Pettengell R, Coiffier B, Narayanan G, Hurtado de Mendoza F, Digumarti R, Gomez H, Zinzani PL, Schiller G, Rizzieri D, Boland G, Cernohous P, Wang L, Kuepfer C, Gorbachevsky I, Singer J. Pixantrone dimaleate versus other chemotherapeutic agents as single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: a phase 3, multicentre, open-label, randomised trial. Lancet Oncol. 2012; 13: 696-706. Epub 2012 May 30.

4. Relapse (with signs of disease progression) after at least two prior chemotherapy regimens, including one first-line therapy with a standard protocol containing an anthracycline, such as CHOP or equivalent, and at least one further polychemotherapy regimen. High-dose chemotherapy or radiochemotherapy followed by autologous stem cell transplantation was not counted as a prior therapy. Allogenic stem cell transplantation was not counted as a prior therapy. Patients who had previously received allogenic stem cell transplantation had to have not had severe or active graft-versus-host disease requiring immunosuppressant therapy.
5. Patients had to have been sensitive to the most recent regimen containing an anthracycline or anthracenedione. Sensitivity was defined as a response (PR or confirmed or unconfirmed CR, see Appendix) to an anthracycline or anthracenedione lasting ≥ 6 months, followed by relapse.
6. Age ≥ 18 years
7. ECOG performance status score ≤ 2
9. Hb ≥ 8 g/dL, neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 50 x10^9/L; in the event of bone marrow involvement, neutrophil count > 0.5 x 10^9/L, platelet count >10 x 10^9/L.
10. Serum bilirubin 1.5 x site's upper limit of normal (ULN), creatinine 1.5 x ULN, alkaline phosphatase 2 x ULN and AST or ALT 2 x site's ULN. In the event of lymphoma-related liver involvement, AST or ALT values could be 5 x site's ULN.
12. LVEF ≥ 50% determined by multigated nuclear imaging (MUGA),

Treatments:
- Pixantrone (PIXUVRI) 85 mg/m^2 IV infusion on days 1, 8 and 15 of each 4-week cycle for 6 cycles.
- Investigator's choice of monochemotherapy from a list of medicinal products recognised as being effective in treating NHL, i.e. vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine (United States) for a maximum of 6 cycles or rituximab (United States).

General study plan

Figure 1: Trial PIX301 - general plan and main criteria



The pixantrone dose is expressed as pixantrone dimaleate

After treatment had finished, patients were followed up for 18 months. The primary analysis was scheduled for end of treatment, and the final analysis of survival was scheduled for two years after the last patient had been enrolled in the trial.

Results:
A total of 140 patients were randomised. Median age of patients was 60 years in the PIXUVRI group and 58 years in the monochemotherapy group.
Approximately 80% of patients were in a good general state of health (ECOG performance status score of 0-1). Seventy-six percent (76%) of all patients in the trial had stage 3/4 disease according to the Ann Arbor classification, 74% had a score ≥ 2 for the international prognostic index (IPI) and 60% had received at least three prior chemotherapy regimens.

◗ Results for primary efficacy endpoint

Percentage complete response (CR, see Appendix) or complete response, unconfirmed (CRu, see Appendix) evaluated by an independent assessment panel was 20.0% in the PIXUVRI group compared with 5.7% in the monochemotherapy group, p = 0.021.

Table 1: PIX301 – Efficacy analysis: percentage CR/CRu

	Pixantrone (n = 70)	**Comparator (n = 70)**
End of treatment (date of main analysis)		
CR/CRu, n (%)	14 (20.0%)	4 (5.7%)
95% CI	(11.4%, 31.3%)	(1.6%, 14.0%)
	p = 0.021	
End of study		
CR/CRu, n (%)	17 (24.3%)	5 (7.1%)
95% CI	(14.8%, 36.0%)	(2.4%, 15.9%)
	p = 0.009	

◗ Results for secondary endpoints

- the global response rate was 37.1% in the pixantrone group compared with 14.3% in the monochemotherapy group, p = 0.003.
- median progression-free survival was 5.3 months in the pixantrone group and 2.6 months in the comparison group (p = 0.005).

There was no difference between the two groups for:
- global survival: 10.2 months compared with 7.6 months (p=0.251). Data for patients still alive were collected at 24 months for this analysis.

- proportion of global response (CR/CRu/PR, see Appendix) lasting ≥ 4 months: 17.1% compared with 8.6%, p = 0.206).
- median duration of objective responses (CR/CRu/PR: 7 months compared with 4.5 months, p = 0.226.
- median duration of CR/CRu: median = 9.6 months compared with 4.0 months, p = 0,081.

There are no quality of life data.

◗ Results of subgroup analyses:

Treatment results were influenced by the number of prior treatment regimens. The benefit of PIXUVRI treatment has not been established in patients when used as fifth-line or greater chemotherapy in patients who are refractory to their last therapy. There are limited data for patients previously treated with rituximab (38 patients in the PIXUVRI group and 39 patients in the monochemotherapy group) and they do not allow any conclusions to be drawn.

Table 1: PIX301 – Summary of analyses by line of treatment and previous exposure to rituximab (ITT, n = 140, evaluation by independent panel)

Subgroup	CR/CRu (PIX *vs.* comparator)	GRR (PIX *vs.* comparator)	PFS (PIX *vs.* comparator)	Global survival (PIX *vs.* comparator)
Prior rituximab therapy				
All	15.8% (6/38) *vs.* 7.7% (3/39) p = 0.310	31.6% (12/38) *vs.* 17.9% (7/39) p = 0.194	RR = 0.83 (0.51, 1.34) p = 0.438	RR = 0.95 (0.57, 1.59) p = 0.843
3rd line	30.0% (3/10) *vs.* 0.0% (0/9) p = 0.211	50.0% (5/10) *vs.* 0.0% (0/9) p = 0.033	5.7 *vs.* 2.8 months RR = 0.28 (0.08, 0.94) p = 0.029	--
4th line	20.0% (3/15) *vs.* 6.3% (1/16) p = 0.333	40.0% (6/15) *vs.* 18.8% (3/16) p = 0.252	3.3 *vs.* 2.8 months RR = 1.44 (0.66, 3.15) p = 0.360	--
3rd or 4th line	24.0% (6/25) *vs.* 4.0% (1/25) p = 0.098	44.0% (11/25) *vs.* 12.0% (3/25) p = 0.025	4.3 *vs.* 2.8 months RR = 0.83 (0.46, 1.50) p = 0.529	10.2 *vs.* 6.1 months RR = 0.90 (0.47, 1.75) p = 0.765
≥5th line	7.7% (1/13) *vs.* 21.4% (3/14) NS	7.7% (1/13) *vs.* 28.6% (4/14) NS	--	--
No prior rituximab therapy**				
All	25.0% (8/32) *vs.* 3.2% (1/31) p = 0.026	43.8% (14/32) *vs.* 9.7% (3/31) p = 0.004	RR = 0.40 (0.23, 0.69) p = 0.001	RR = 0.63 (0.34, 1.17) p = 0.142
3rd line	37.5% (6/16) *vs.* 6.7% (1/15) p = 0.083	56.3% (9/16) *vs.* 13.3% (2/15) p = 0.023	6.1 *vs.* 1.9 months RR = 0.36 (0.16, 0.80) p = 0.009	--
4th line	22.2% (2/9) *vs.* 0.0% (0/9) p = 0.471	44.4% (4/9) *vs.* 11.1% (1/9) p = 0.294	6.5 *vs.* 3.4 months RR = 0.25 (0.08, 0.77) p = 0.010	--

PIX = PIXUVRI
Comparator = monochemotherapy
*Treatment line = number of previous treatment lines + treatment in the PIX301 trial. Third-line means two previous regimens plus the trial therapy. Fourth-line means three previous regimens plus the trial therapy.
Response percentages include all responses up to the end of the PIX301 trial.
The p values derived from a two-sided Fisher's exact test are shown for comparisons of response rates, and the p values derived from a log-rank test are shown for Kaplan-Meier analyses. A 95% confidence interval is given for relative risks.
**Only one patient not previously treated with rituximab was treated as ≥ 5th line. This patient from the PIXUVRI group had a partial response.

08.2 Adverse effects

42.6% of patients in the PIXUVRI group compared with 37.3% of patients in the monochemotherapy group stopped treatment because of adverse effects. The most common adverse effects in the PIXUVRI group were:

- neutropenia 10.3% vs.1.5%,
- cardiac disorders (7.4% vs. 1.5%, including heart failure recorded in 2.9% of the PIXUVRI group compared with 1.5% in the comparator group)
- asthenia: 7.4% compared with no cases in the comparator group

The incidence of grade 3 or 4 undesirable events was higher in the PIXUVRI group than in the monochemotherapy group: neutropenia (50% vs. 23%), leukocytopenia (25% vs. 10.4%), asthenia (23.5% vs. 13.4%), infection (42.6% vs. 28.4%), decreased left ventricular ejection fraction (19.1% vs. 10.4%), anorexia (11.8% vs. 6%), cough (22.1% vs. 4.5%).

08.3 Summary & discussion

The PIX301 randomised (1:1) open trial compared PIXUVRI with investigator's choice of monochemotherapy in 140 patients with relapsed or refractory non-Hodgkin lymphoma (NHL), who had received two or more prior therapies.
The investigator's choice of monochemotherapy could be a drug from a list of drugs recognised as being effective in treating NHL, i.e. vinorelbine, oxaliplatin, ifosfamide, etoposide, mitoxantrone, gemcitabine (United States) or rituximab (United States).
A total of 140 patients were randomised. Median age of patients was 60 years in the PIXUVRI group and 58 years in the monochemotherapy group.
For all patients in the trial, 76% had stage 3/4 disease according to the Ann Arbor classification, 74% had a score ≥ 2 for the international prognostic index (IPI) and 60% had received at least three prior chemotherapy regimens.
The primary efficacy endpoint evaluated by an independent panel was the proportion of patients with a complete response (CR) or complete response, unconfirmed (CRu) according to 1999 IWG-NHL criteria (see Appendix).

The percentage of complete response (CR) or complete response, unconfirmed (CRu) was 20.0% in the PIXUVRI group compared with 5.7% in the monochemotherapy group, p = 0.021.
PIXUVRI was superior to monochemotherapy in terms of percentage global response (37.1% vs. 14.3%, p = 0.003) and median progression-free survival (5.3 months vs. 2.6 months, p = 0.005). However, there was no difference between the two groups for global survival (10.2 months vs.7.6 months, p = 0.251), proportion of global response (CR/CRu/PR) lasting ≥ 4 months (17.1% vs. 8.6%, p = 0.206) and median duration of objective responses (7 months vs. 4.5 months; p = 0.226)
A subgroup analysis suggested that the treatment effect was influenced by the number of prior treatment lines. The benefit of PIXUVRI has not been established in patients refractory to fifth-line or greater treatment. Furthermore, there are limited data for patients previously treated with rituximab (38 patients in the PIXUVRI group and 39 patients in the monochemotherapy group). Given that in Europe, most patients who have had multiple relapses or who are refractory to treatment have already received rituximab recommended for first-line therapy onwards, the contribution of PIXUVRI in this population has yet to be confirmed.
There are no quality of life data.

The main grade 3 or 4 adverse events that were more common in the PIXUVRI group than in the monochemotherapy group were neutropenia (50% vs. 23%), infection (42.6% vs. 28.4%), asthenia (23.5% vs. 13.4%), anorexia (11.8% vs. 6%), cough (22.1% vs. 4.5%), skin discolouration (10.3% vs. 0%), decreased left ventricular ejection fraction (19.1% vs. 10.4%), and heart failure (2.9% vs. 1.5%).

The Transparency Committee highlights the following points:

- slightly more than half (55%) of the patients had previously been treated with rituximab, while it has been recommended for more than a decade as first-line treatment combined with

chemotherapy (the Marketing Authorisation for MABTHERA (rituximab) being issued on 21 March 2002),

- only 15% of patients in the trial had undergone stem cell transplantation after previous relapses. The median age of the patients in the study was compatible with stem cell therapy (60 years in the PIXUVRI group and 58 years in the monochemotherapy group), and in the majority of cases their general health was good (approximately 80% of patients had a performance status score of 0-1).

Overall, the Committee considers that the available data raise the issue of transferability of the results of this trial into clinical practice, and therefore considers that the level of demonstration of efficacy of PIXUVRI in this indication is suboptimal.

08.4 Programme of studies

Within the context of granting a conditional Marketing Authorisation, the Marketing Authorisation holder should carry out the following measures, according to the schedule given:

Description	Date
Carry out a randomised controlled phase 3 trial (PIX306) with pixantrone-rituximab compared with gemcitabine-rituximab in patients with aggressive non-Hodgkin B-cell lymphoma who have not responded to first-line therapy with R-CHOP, who are not eligible for autologous stem cell transplantation (ASCT) (second-line) or in whom an ASCT has failed (third- or fourth-line).	30 June 2015

09 THERAPEUTIC USE

As first-line therapy for aggressive non-Hodgkin B-cell lymphoma (NHL), chemotherapy regimens generally consist of cyclophosphamide, an anthracycline (doxorubicin), vincristine and corticosteroids (CHOP protocol). Addition of rituximab improved the percentage response and global survival.

20-50% of patients do not respond to first-line therapy (primary refractory disease) or relapse at the end of treatment. These patients may be offered salvage therapy (second-line chemotherapy). If they respond to this salvage therapy, patients are classed as chemosensitive and they may be offered consolidation therapy in the form of intensification for eligible patients. The major criteria for eligibility for high-dose chemotherapy (intensification) with stem cell transplantation are: chemosensitive disease, adequate performance status (no major organ dysfunction) and age <65 to 70 years.

Other patients who are not eligible for autologous stem cell transplantation because of their age but who have chemosensitive disease, do not receive any other treatment and are monitored; those who have not responded to second-line salvage therapy may be eligible for third-line chemotherapy such as pixantrone. At this stage of the disease, no chemotherapy (monotherapy or combination) is regarded as standard. PIXUVRI is a third- or fourth-line therapy for aggressive non-Hodgkin B-cell lymphoma in patients refractory to previous therapy, including autologous transplantation, unless this is not indicated.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Non-Hodgkin lymphoma is a serious and life-threatening disease.
◗ This proprietary medicinal product is intended as a curative therapy, specifically for non-Hodgkin lymphoma.
◗ The efficacy/adverse effects ratio is moderate.

◗ Public health benefit:
Non-Hodgkin's lymphoma (NHL) is a serious, life-threatening clinical condition. The public health burden in the population of patients matching the claimed indication (multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma (NHL)) is low in view of the small number of patients affected.
Improvement in the management of this disease is a public health need that is an established priority (Cancer Plan 2009-2013). This priority is only partially covered by existing therapies.
The available clinical trial data, notably one comparative study against a reference therapy, show improvement in complete response rate and progression-free survival (gain of 2.7 months). However, in the absence of improvement in terms of global survival or quality of life, PIXUVRI is not expected to provide any additional impact in terms of morbidity, mortality or quality of life. Furthermore, it is not certain that it will be possible to transfer the trial results into clinical practice (the profile of patients treated and treatment strategy were different from those of normal practice).
Therefore, it would not be expected that the proprietary medicinal product PIXUVRI would provide any additional response to meeting an identified public health need.
No impact on the organisation of healthcare is expected (no data).
Consequently, it is not expected that the proprietary medicinal product PIXUVRI will benefit public health in this indication.

◗ At this stage of the disease, there is no alternative drug therapy that has been validated by a Marketing Authorisation in these patients.
◗ PIXUVRI is a third- or fourth-line therapy for aggressive non-Hodgkin B-cell lymphoma.

Taking account of these points, the Committee considers that the actual benefit of PIXUVRI is low.

010.2 Improvement in actual benefit (IAB)

In view of the suboptimal level of demonstration of efficacy, but in view of the absence of alternative drug therapy validated as third- or fourth-line therapy for aggressive non-Hodgkin B-cell lymphoma, the Committee considers that based on the current data, PIXUVRI does not provide any improvement in actual benefit (IAB V, non existent) in the management of this disease.

010.3 Target population

The target population is patients with multiply relapsed or refractory aggressive non-Hodgkin B-cell lymphoma who have relapsed for the second or third time (after two or three treatment lines).
Projections made by the *Health Monitoring Institute (InVS)* for 2010 and 2011 (worldwide distribution normalised for age) showed 10 777 new diagnoses of NHL in 2010 and 11 631 in 2011 (55% of them in men), with an annual incidence of 12.5 per 100 000 men and 8.3 per 100 000 women.
Aggressive NHL accounts for 50-60% of cases of NHL, which would correspond to 5800-7000 patients per year based on the 2011 projections.
Aggressive non-Hodgkin B-cell lymphoma is potentially curable with currently-available therapies. However, although the cure rate for aggressive non-Hodgkin lymphoma is approximately 50-60% with a standard first-line regimen, at least 30% of patients usually relapse within two years (1740-2100 patients a year).
These patients receive salvage therapy followed, if feasible (age, comorbidities), by high-dose chemotherapy with autologous stem cell transplantation. Although the risk of relapse is lower than if these patients received intensification chemotherapy, almost 90% of them (1600-1900 patients a year) have a second relapse. Nevertheless, depending on their general state of health (performance status score 3-4) and comorbidities, it could seem risky or even harmful to propose a third- or fourth-line treatment, which means that the target population will probably be between 1000 and 1500.
This is the population of patients eligible for treatment with pixantrone.

The total estimated target population for PIXUVRI is between 1000 and 1500 patients a year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends inclusion on the list of medicines approved for use by hospitals as third- or fourth-line therapy for aggressive B-cell non-Hodgkin lymphoma.

The Committee will re-examine the medicinal product PIXUVRI two years after it has been placed on the market.

APPENDIX: definition of responses according to 1999 IWG-NHL criteria

Complete response (CR):
- no clinical symptoms or radiographic signs and normalisation of biochemical values;
- regression of lymph nodes and lymphatic masses;
- reduction in size of spleen and other organs (e.g. liver, kidneys)
- normalisation of bone marrow, if originally involved.

Complete response, unconfirmed (CRu): 1 and 3 of the above criteria, and at least one of the following criteria:
- regression of residual lymphatic mass;
- undetermined bone marrow involvement.

Partial response (PR):
- ≥ 50% reduction in the sum of the largest diameters of the six largest lymph nodes or lymphatic masses;
- no increase in size of other lymph nodes, liver or spleen;
- at least 50% regression of spleen and liver involvement;
- apart from spleen and liver involvement, involvement of other organs is regarded as evaluable rather than measurable;
- no new sites involved.

Disease progression:
- lymph node size increased by ≥ 50%;
- appearance of new lesion during or at the end of treatment.