HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

13 May 2009

CAELYX 2 mg/ml, concentrate for solution for infusion
B/1 vial of 10 ml (20 mg) - CIP: 560 361-9
B/1 vial of 25 ml (50 mg) - CIP : 563 261-5

Applicant: SCHERING-PLOUGH

Doxorubicin hydrochloride in a pegylated liposomal formulation
ATC code: L01DB01

List I – For hospital use only

Medicine for hospital prescription only.
Prescription restricted to oncology or haematology specialists or doctors with cancer training.
Medicinal product requiring special supervision during treatment.

Date of European Marketing Authorisation: 21 June 1996 - corrections: 24 October 2000 - 10 January 2003 - 14 December 2007 (extension of indication in multiple myeloma)

Reason for request: Inclusion on the list of medicines approved for use by hospitals in the extension of indication “In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one previous treatment and who have already undergone or are unsuitable for bone marrow transplant”.

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Doxorubicin hydrochloride in a pegylated liposomal formulation

1.2. Indications

"CAELYX is indicated:

- **In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one previous treatment and who have already undergone or are unsuitable for bone marrow transplant.**
- For treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD_4 counts (< 200 CD_4 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).
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk."

1.3. Dosage

In the extension of indication:

"CAELYX is administered at 30 mg/m² on day 4 of the bortezomib 3 week regimen as a 1 hour infusion administered immediately after the bortezomib infusion.

The bortezomib regimen consists of 1.3 mg/m² on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2008)

L	:	Antineoplastic and immunomodulating agents
L01	:	Antineoplastic agents
L01D	:	Cytotoxic antibiotics and related substances
L01DB	:	Anthracyclines and related substances
L01DB01	:	Doxorubicin

2.2. Medicines in the same therapeutic category

None

2.3. Medicines with a similar therapeutic aim

- VELCADE (bortezomib)[1]
- REVLIMID (lenalidomide) in combination with dexamethasone[1]
- THALIDOMIDE CELGENE (thalidomide)
- ALKERAN (melphalan)
- ENDOXAN ASTA (cyclophosphamide)
- ONCOVIN (vincristine)
- BICNU (carmustine)
- INTRONA (interferon alfa-2b)

Corticosteroids (prednisone or dexamethasone) at high doses are used alone or in combination with cytotoxic agents.

[1] Medicines indicated in the treatment of multiple myeloma that has progressed in patients who have received at least one previous treatment.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The dossier contains a pivotal phase III study. Two other studies which evaluated pegylated liposomal doxorubicin (CAELYX) outside the current indication will therefore not be described: one with untreated multiple myeloma patients and the other with patients who received induction treatment prior to stem cell transplantation.

Study MMY-3001[2]The efficacy and tolerance of pegylated liposomal doxorubicin were evaluated in a randomised open study comparing the combination pegylated liposomal doxorubicin/bortezomib with bortezomib monotherapy in 646 patients with multiple myeloma after failure or relapse after at least one previous treatment.

Randomisation was stratified according to the level of β_2-microglobulin and the response to the previous treatment (failure or relapse). Patients should not have received bortezomib and not be refractory to anthracyclines (nor have received more than 240 mg/m^2 of doxorubicin or equivalent).

Primary endpoint: time to progression defined as being the time between randomisation and the occurrence of one of the following events: progression of the disease or death linked to progression of the disease.

Secondary endpoints:
- percentage of response (overall, complete and partial according to the EBMT criteria[3])
- overall survival (time between randomisation and death, irrespective of cause),
- progression-free survival (time between randomisation and the occurrence of one of the following events: progression of the disease or death, irrespective to the cause).

Treatments:
The patients in the 2 groups received bortezomib in a dose of 1.3 mg/m^2 i.v. on D1, D4, D8 and D11 every 3 weeks.
Patients in the pegylated liposomal doxorubicin/bortezomib group received anthracycline in a dose of 30 mg/m^2 i.v. on D4 of each cycle.

Results:
Three analyses are given in the dossier:
- an initial interim analysis scheduled in the protocol (time to progression from the occurrence of 50% of the events),
- an interim analysis (time to progression and survival) not scheduled in the protocol but made at the request of the FDA,
- another interim analysis (survival) not scheduled in the protocol but made at the request of the EMEA.

The median age of the patients was 61 years. All patients were in good general condition (ECOG 0: 44% and ECOG 1: 56%)[4].

Previously, 56% of the patients had received a stem cell transplant and about 66% of the patients had received at least 2 lines of treatment (91% of patients had relapsed and 9% had failed treatment). Almost all patients had received corticosteroids (99%) and an alkylating

[2] Orlowski R., Nagler A.et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007 Sep 1;25(25):3892-901.
[3] EBMT : European Group for Blood and Marrow Transplantation
[4] ECOG (*Eastern Cooperative Oncology Group*) scale: Grade 0 = Fully active; Grade 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

agent (91%), 41% of patients had received thalidomide or lenalidomide and about one third of patients were naïve to anthracycline treatment.

- Primary endpoint:

In the interim analysis scheduled in the protocol, the median time to progression (primary endpoint) was extended by 2.8 months with the combination pegylated liposomal doxorubicin/bortezomib by comparison with bortezomib alone: 9.3 months versus 6.5 months (HR = 1.82 ; 95% CI [1.41; 2.35]).

The results of subgroup analyses of the primary endpoint still favoured the combination pegylated liposomal doxorubicin/bortezomib when adjusted for prognostic factors (level of β_2-microglobulin, response to initial treatment, ECOG score, prior stem cell transplant, previous treatments with anthracyclines or immunomodulators).

Table 1: Results for the primary endpoint: time to progression (study MMY-3001)

	Scheduled interim analysis 28 April 2006		Interim analysis requested by the FDA 28 November 2006	
	PLD/bortezomib n = 324	Bortezomib n = 322	PLD/bortezomib n = 324	Bortezomib n = 322
Progression or death (%)	30.6	46.6	56.8	69.3
Median time to progression (days)	**282**	**197**	**271**	**209**
95% CI (months)	[250; 338] (9.3)	[170; 217] (6.5)	[246; 298] (8.9)	[185; 222] (6.9)
Hazard ratio 95%CI	1.82 [1.41; 2.35]		1.55 [1.27; 1.89]	
p	0.000004		0.0000013	

- Secondary endpoints:

- No difference was observed between the percentage of overall responses in the 2 groups (48% in the pegylated liposomal doxorubicin/bortezomib group, of which 43% partial response and 43% in the bortezomib group, of which 40% partial response).

- In the interim analysis scheduled in the protocol, overall survival did not differ between the 2 groups (HR = 0.68 ; 95% CI [0.415; 1.098]). Two other unscheduled analyses were made with longer follow-up. In the first, there was shown to be an impact on overall survival (HR = 0.71; 95% CI [0.507; 0.998]). However, this advantage was not observed in the second analysis (HR = 0.86 ; 95% CI [0.649; 1.127]).

The final analysis of overall survival (when 80% of the patients are dead) will be available in 2010.

Table 2: Results for the secondary endpoint: overall survival (study MMY-3001)

	Scheduled interim analysis 28 April 2006	Interim analysis requested by the FDA 28 November 2006	Interim analysis requested by the EMEA 10 August 2007
Median study follow-up (months)	3.9	10.9	18
Mortality (%)			
Total	67/646 (10%)	139/646 (22%)	206/646 (32%)
PLD/bortezomib	28/324 (8.6%)	58/324 (17.9%)	96/324 (29.6%)
Bortezomib	39/322 (12.1%)	81/322 (25.2%)	110/322 (34.2%)
Hazard ratio 95%CI	0.68 [0.415; 1.098]	0.71 [0.507; 0.998]	0.86 [0.649; 1.127]
p	0.113	0.0476	0.265

- Median progression-free survival (including deaths from all causes combined) evaluated in a secondary analysis was 11.2 months in the pegylated liposomal doxorubicin/bortezomib group and 7.3 months in the group with bortezomib alone (p = 0.000038).

The Committee notes that in each of the 2 groups, contrary to usual practice, bortezomib was not used in combination with corticosteroids.

In view of the open design of the study, the quality of life data were not taken into account.

3.2. Adverse effects

The percentage of patients who stopped treatment on account of an adverse event was 27% in the pegylated liposomal doxorubicin/bortezomib group and 20% in the group with bortezomib alone. The common adverse events which led to the administration of bortezomib and pegylated liposomal doxorubicin being stopped were: palmar-plantar erythrodysaesthesia, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopenia, decreased ejection fraction and fatigue.

The percentage of grade 3 or 4 adverse events was higher in the pegylated liposomal doxorubicin/bortezomib group (80%) than in the group with bortezomib alone (64%).

The commonest adverse events observed in the two groups were haematological (50%), gastrointestinal (73%), neurological (64%) and disorders of a general nature (64%).

Among the adverse effects reported with increased frequency in the pegylated liposomal doxorubicin/bortezomib group than in the group with bortezomib alone were:

- grades 3/4 neutropenia: 28% vs 14%
- grades 3/4 thrombopenia: 22% vs 14%
- nausea and vomiting: 40% and 28% vs 32% and 15%
- stomatitis: 16% vs 3%
- palmar-plantar erythrodysaesthesia: 16% vs 0%.

Cardiac (10% vs 7%) and renal (9% vs 7%) adverse events and grade 3-4 peripheral neuropathy (4% vs 9%) were observed with similar frequency in the pegylated liposomal doxorubicin/bortezomib group and in the group with bortezomib alone.

3.3. Conclusion

The efficacy and tolerance of pegylated liposomal doxorubicin were evaluated in a randomised open phase III study comparing the combination pegylated liposomal doxorubicin/bortezomib with bortezomib monotherapy in patients with multiple myeloma after the failure of or a relapse after at least one previous treatment.

The results of a scheduled interim analysis showed an improvement in median time to progression (primary endpoint) of 2.8 months in favour of the pegylated liposomal doxorubicin/bortezomib group: 9.3 months in the pegylated liposomal doxorubicin/bortezomib group versus 6.5 months in the group with bortezomib alone (HR = 1.82; 95% CI [1.41; 2.35]).

Overall survival did not differ between the 2 groups (interim analysis scheduled in the protocol: HR = 0,68 ; 95% CI [0.415; 1.098]).

The percentage of grade 3 or 4 adverse events was higher in the pegylated liposomal doxorubicin/bortezomib group (80%) than in the group with bortezomib alone (64%).

In addition to the neurological toxicity linked to bortezomib, the combination pegylated liposomal doxorubicin/bortezomib induced haematological toxicity, in particular grades 3-4 neutropenia and thrombopenia, in less than one third of cases.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Multiple myeloma is a haemopathy that is almost always fatal, with a short median survival time (3-5 years).

The medicinal product is intended as palliative therapy.

Public health benefit:
The public health burden of multiple myeloma can be regarded as moderate. That corresponding to the more restricted population covered by the indication is low.

An improvement in the management of multiple myeloma is a public health need.

In view of the clinical data available and the usual treatment strategies, the possible impact expected for the medicinal product CAELYX in combination with VELCADE is hard to quantify (absence of data on overall survival and quality of life) and it may at best only be small.

Consequently, the medicinal product CAELYX is not expected to offer any public health benefit in this indication.

The efficacy/adverse effects ratio is moderate.

This medicinal product is a second-line or later treatment, when bone marrow transplantation has already been performed or cannot be considered.

There are alternative drug therapies.

The actual benefit is substantial.

4.2. Improvement in actual benefit (IAB)

The combination of CAELYX with bortezomib does not provide any improvement in actual benefit (IAB V) as compared to bortezomib alone in the treatment of multiple myeloma that has progressed after at least one previous treatment and where bone marrow transplantation is not possible.

This combination is an additional therapeutic option in the treatment strategy.

4.3. Therapeutic use

The management of patients with multiple myeloma depends on whether or not they are eligible for bone marrow transplantation. There is no consensus on the optimal sequence of treatment.

Traditionally, second-line treatments have comprised mainly alkylating agents, anthracyclines, corticosteroids, interferon and thalidomide.

The use of lenalidomide and bortezomib has extended the range of treatment options.

According to American recommendation[5] NCCN 2009, bortezomib in monotherapy or in combination with pegylated liposomal doxorubicin and lenalidomide combined with dexamethasone have a higher level of evidence than traditional treatments (level 1). In practice, the treatments are used in combination.

In the event of a late relapse (after > 6 months), it is acknowledged that the initial treatment may be effective again. If that is not the case (an early relapse), other medicines are selected and account is taken of the patient's condition and particularly his/her renal function.

The combination pegylated liposomal doxorubicin/bortezomib is a new option in the treatment of myeloma after the failure of or a relapse after at least one line of treatment in patients who have not previously received bortezomib.

4.4. Target population

The target population for CAELYX in combination with bortezomib consists of patients receiving second-line or later treatment for multiple myeloma who are not eligible for bone marrow transplantation.

According to data from the Health Monitoring Institute (InVS)[6], the incidence of multiple myeloma and immunoproliferative disorders in France rose from 3565 new cases a year in 2000 to 4516 in 2005.

Bearing in mind that a second-line treatment is used in about 60%[7] of cases, the incident target population for CAELYX would be of the order of 2700 patients a year in this extension of indication.

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 extension of indication and at the dosages in the Marketing Authorisation.

[5] National Comprehensive Cancer Network (NCCN 2009) http://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf
[6] Evolution de l'incidence et de la mortalité par cancer en France de 1980 à 2005 ; Fiche Myélome Multiple et Maladies Immunoprolifératives INVS 30/01/2008 : http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/donnees_localisation/myelome/myelome.pdf
[7] Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc 2004;79:867-874.