HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 October 2010

LEVACT 2.5 mg/ml, powder for concentrate for solution for drip
B/5 x 25 mg vials (CIP code: 577 863-2)
B/20 x 25 mg vials (CIP code: 577 864-9)
B/5 x 100 mg vials (CIP code: 577 865-5)

Applicant: MUNDIPHARMA

bendamustine
ATC code: L01AA09

List I

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

Date of Marketing Authorisation (decentralised procedure): 15.07.10

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

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

bendamustine

1.2. Background

Bendamustine hydrochloride is an antineoplastic alkylating agent.

1.3. Indications

" - First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

- Indolent non-Hodgkin's lymphoma as monotherapy treatment in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab-containing regimen.

- Front-line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment."

1.4. Posology

"Monotherapy for chronic lymphocytic leukaemia
100 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab
120 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks.

Multiple myeloma
120-150 mg/m^2 body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m^2 body area surface prednisone i.v. or per os on days 1 to 4; every 4 weeks."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

L	Antineoplastic and immunomodulating agents
L01	Antineoplastic agents
L01A	Alkylating agents and the like
L01AA	Nitrogen mustard analogues
L01AA09	Bendamustine

2.2. Medicines in the same therapeutic category

A. Chronic lymphocytic leukaemia

CHLORAMINOPHENE (chlorambucil)

B. Non-Hodgkin's lymphoma

None

C. Multiple myeloma

- ALKERAN (melphalan)
- ENDOXAN ASTA (cyclophosphamide)

2.3. Medicines with a similar therapeutic aim

A. Chronic lymphocytic leukaemia

- FLUDARA (fludarabine)
- MABTHERA (rituximab)
- MABCAMPATH (alemtuzumab), indicated when combination chemotherapy including fludarabine is not appropriate
- ARZERRA (ofatumumab) for patients who do not respond to fludarabine or alemtuzumab

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) combination chemotherapy regimens, etc.

B. Non-Hodgkin's lymphoma

ZEVALIN (ibritumomab tiuxetan), indicated particularly for B CD 20+ cells and follicular forms of NHL, and for patients who relapse following treatment with rituximab or do not respond to it.

Other treatments indicated for NHL (treatment line unspecified):

- ALKERAN (melphalan),
- CHLORAMINOPHENE (chlorambucil),
- ENDOXAN (cyclophosphamide),
- HOLOXAN (ifosfamide),
- MABTHERA (rituximab),
- ROFERON; INTRONA (interferon alfa)

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and CVP (cyclophosphamide, vincristine, prednisone) combination chemotherapy regimens, with or without doxorubicin (anthracycline),

C. Multiple myeloma

- BICNU (carmustine)
- CAELYX (pegylated liposomal doxorubicin)
- INTRONA (interferon alfa-2b)
- ONCOVIN (vincristine)
- REVLIMID (lenalidomide)
- THALIDOMIDE PHARMION (thalidomide)
- VELCADE (bortezomib)

High-dose corticosteroids (prednisone or dexamethasone) are used alone or in combination with cytotoxic agents.

3. ANALYSIS OF AVAILABLE DATA

Bendamustine was used in the German Democratic Republic from the 1970s and was granted marketing authorisation in Germany in 2003 for the treatment of chronic lymphocytic leukaemia, non-Hodgkin's lymphoma and multiple myeloma.
Bendamustine was approved in the United States for the treatment of chronic lymphocytic leukaemia in 2007 and for the treatment of non-Hodgkin's lymphoma in 2008.
It has been supplied on a named-patient basis under the temporary authorisation of use system in France since November 2005.
An application for European marketing authorisation under the decentralised procedure was submitted in November 2007 for the three indications which have been validated in Germany. Two of these indications (non-Hodgkin's lymphoma and multiple myeloma) have been reviewed by the EMA.

3.1. Chronic lymphocytic leukaemia

The dossier comprises:

- three phase I/II studies,
- two phase II studies, available only as summaries presented to conferences (Fisher, ASH 2009, summary 205; Fisher, ASH 2008, summary 330). They will not therefore be analysed in this document.
- a comparative phase III study (02CLLIII).

Only the phase III study is analysed below.

A. **Efficacy: study 02CLLIII**[1]

Open-label randomised study comparing the efficacy and tolerance of bendamustine with those of chlorambucil as first-line treatment of 319 patients suffering from chronic lymphocytic leukaemia, Binet stage B or C.

Inclusion criteria:
- chronic lymphocytic leukaemia, Binet stage B or C,
- patients aged under 75,
- patients who have not received any previous treatment for chronic lymphocytic leukaemia,
- WHO performance index ≤ 2,
- life expectancy of at least 3 months.

Treatments (up to 6 cycles in total):
- bendamustine group: 100 mg/m^2 IV on D1 and D2 every 4 weeks (n=162);
- chlorambucil group: 0.8 mg/kg per os on D1 and D15 every 4 weeks (n=157), a different administration regime to that used in France.

Primary endpoints:
- overall percentage response determined by the independent committee (see appendix 1);
- progression-free survival, defined as the time from randomisation to one of the following events: tumour progression, relapse after intercurrent remission or death from any cause.

The latter criterion was analysed only if a significant difference was observed in relation to the former primary endpoint.

[1] Knauf WU, Lissichkov T. et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia. J Clin Oncol 2009, 27:4378-4384

Secondary endpoints:
- time to progression, defined as the time from randomisation to one of the following events: tumour progression, relapse after intercurrent remission or death connected to chronic lymphocytic leukaemia;
- duration of remission, defined as the time from the best response observed and progression of the disease or death from any cause;
- overall survival, defined as the time from randomisation to death from any cause.

Results
The median age of patients was 63 in the bendamustine group (45-77) and 66 in the chlorambucil group (35-78). Two-thirds of the patients were in a good general condition, and almost a third in reasonable general condition.
Approximately 71% of patients had stage B chronic lymphocytic leukaemia.
This study specifically excluded patients for whom combination chemotherapy including fludarabine was not appropriate (in accordance with the indication text of the MA).

The results described below were obtained from a third intermediate analysis which was scheduled in the protocol (after recruitment of the 300th patient). The study was stopped in light of the results.

- Primary endpoints:
The overall response rate was 68% in the bendamustine group (including 31% total response) versus 31% (including 2% total response) in the chlorambucil group ($p<0.0001$[2]).
The median progression-free survival time was 21.5 months in the bendamustine group versus 8.3 months in the chlorambucil group ($p<0.0001$).
The values observed for these two criteria are probably overestimate given the suspension of the study during an intermediate analysis.

- Secondary endpoints:
The median time to progression assessed by the independent committee was 23.9 months in the bendamustine group and 8.3 months in the chlorambucil group ($p<0.001$).
The median remission time was 19 months in the bendamustine group and 6 months in the chlorambucil group ($p < 0.0001$).
No difference in overall median survival times was observed between the two groups (65.4 months in the chlorambucil group and not achieved in the bendamustine group).

The sub-group results will not be described, as the analyses were not provided for in the protocol.

B. Tolerance

Treatment was stopped because adverse events were reported in 9.3% (15/162) of patients in the bendamustine group and 3.2% (5/157) in the chlorambucil group.
The adverse events which frequently led to cessation of treatment were skin disorders (6 patients in the bendamustine group vs. 1 in the chlorambucil group), allergic reactions (6 patients vs. 2 patients), infections (3 patients vs. 2 patients) and haematological disorders (3 patients vs. 1 patient).

Grade 3-4 adverse events were more common in the bendamustine group: 52.8% (85/161) vs. 31.1% (47/151) in the chlorambucil group.

Grade 3-4 haematological adverse events were reported in 40.4% of patients in the bendamustine group versus 19.2% in the comparator group. Most of these were neutropenia (23% vs. 10.6%).
Grade 3-4 non-haematological adverse events were more common in the bendamustine group: 41% (66/161) vs. 17.2% (26/151) in the chlorambucil group.

[2] The value required for the intermediate analysis significance test was p=0.016.

The other serious adverse events reported more frequently in the bendamustine group were infections (8.7% grade 3-4 events vs. 3.3%) and hypersensitivity (1.2% grade 3-4 events vs. 0%).

C. Conclusion

The efficacy and tolerance of bendamustine administered at a dose of 100 mg/m^2 IV on D1 and D2 every 4 weeks were assessed in an open-label randomised study versus chlorambucil administered at a dose of 0.8 mg/kg per os on D1 and D15 every 4 weeks. The study was conducted on 319 patients with chronic lymphocytic leukaemia, Binet stage B or C, who had not previously undergone treatment.
The median age of patients was 63 in the bendamustine group and 66 in the chlorambucil group. Two-thirds of the patients were in a good general condition (WHO performance index 0), and a third were in reasonable general condition. This study specifically excluded patients "for whom combination chemotherapy including fludarabine was not appropriate" (in accordance with the indication text of the MA).
The results available are those of a third intermediate analysis, scheduled in the protocol, following which the study was stopped.
The percentage of overall response (primary efficacy endpoint) was higher in the bendamustine group (68%, including 31% total response) than in the chlorambucil group (31%, including 2% total response), p<0.0001.
The median progression-free survival time (second primary efficacy endpoint) was longer in the bendamustine group than in the chlorambucil group (21.5 months versus 8.3 months, p<0.0001) i.e. a gain of 13.2 months. The values observed for these two criteria are probably overestimates given the suspension of the study after an intermediate analysis.
At the time of the intermediate analysis there was no difference between the two groups in respect of median overall survival.
Grade 3-4 adverse events were more common in the bendamustine group than in the chlorambucil group (52.8% vs. 31.1%), especially haematological adverse events (40.4% vs. 19.2%, of which neutropenia accounted for 23% vs. 10.6%) and infections (8.7% vs. 3.3%).

3.2. Non-Hodgkin's lymphoma

Only data relating to the MA indication was taken into consideration. The data was obtained from three non-comparative studies: two phase II studies (SDX105-01 and 2007002) and one phase III study (SDX105-03).
Data relating to assessment of the efficacy of bendamustine as first-line treatment (rituximab-bendamustine vs. R-CHOP) is therefore not taken into account (StiL study, abstract ASH 2009).

The non-comparative phase II study SDX105-01 assessed the efficacy and tolerance of bendamustine administered at a dose of 120 mg/m^2/d IV on D1 and D2 every 21 days for at least 6 cycles in a heterogeneous population of patients with indolent or transformed B-cell non-Hodgkin's lymphoma who had previously undergone treatment. The patients had to be refractory to retuximab. They were considered to be refractory to rituximab if:
- they did not develop a complete or partial response or show progression during six months of treatment;
- they had a history of rituximab intolerance.

The efficacy results related to 76 patients, 61 of whom had indolent non-Hodgkin's lymphoma (80%) and 15 had transformed lymphoma (20%). The median age of the patients was 63.
The median number of prior courses of rituximab treatment received by the patients was 2. Only 45 of the 76 patients (59%) included were refractory to rituximab.
The overall percentage response in the study population as a whole (see appendix 2) was 76.3% (58/76), of which 14% was total response with a median duration of response of five months.

This data does not allow any conclusions to be drawn because of the heterogeneous nature of the population included, the broad definition of refractory, and the lack of standardisation for tumour assessment.

The non-comparative phase II study 2007002 assessed the efficacy and tolerance of bendamustine administered at a dose of 120 mg/m^2/d IV on D1 and D2 every 21 days for 3 to 6 cycles to patients with low-grade B-cell non-Hodgkin's lymphoma (NHL) or histologically confirmed mantle cell lymphoma (MCL) in relapse.
Patients were required:
- not to have been in partial remission with prior chemotherapy or immunotherapy, or to have relapsed after complete remission,
- not to have responded to prior treatment.

The efficacy results related to 69 patients, 58 of whom had low-grade B-cell non-Hodgkin's lymphoma and 11 had mantle cell lymphoma. The median age of patients with non-Hodgkin's lymphoma was 58.5 and that of patients with mantle cell lymphoma was 70.
The median number of lines of treatment previously received was 2 for patients with non-Hodgkin's lymphoma and 4 for patients with mantle cell lymphoma. A total of 29 out of the 69 patients included were refractory to rituximab (sub-group matching the MA population).
The overall response percentage (primary efficacy endpoint) for the study population as a whole was 91.3% (63/69), of whom 66.7% achieved a complete response. The overall response percentage in the sub-group of patients with non-Hodgkin's lymphoma was 89.7%.
The heterogeneous nature of the study population and the lack of efficacy results specifically for the 29 patients with non-Hodgkin's lymphoma who were refractory to rituximab (matching the MA population) mean that the data from this study is not usable.

A. Efficacy: study SDX105-03[3]

Phase III non-comparative study assessing the efficacy of bendamustine in patients with indolent non-Hodgkin's lymphoma refractory to treatment with rituximab as monotherapy or as part of combination therapy.

Inclusion criteria:
- patients aged over 18 with indolent non-Hodgkin's lymphoma in relapse after up to three cycles of chemotherapy,
- refractory to rituximab: patients were considered refractory to rituximab if:
    - they had not presented an objective response after a full cycle of rituximab alone or as part of combination chemotherapy, or if the disease had progressed during treatment or within six months of treatment with rituximab;
    - if the disease had progressed during maintenance treatment or within six months after administration of the first dose.
- (WHO) performance index ≤ 2,
- life expectancy of at least 3 months.

Treatment: 120 mg/m^2 I.V. of bendamustine on D1 and D2 every 21 days for 6 to 8 treatment cycles.

Primary co-endpoints (see appendix 2):
- overall response percentage (complete response, unconfirmed complete response and partial response) and
- duration of response to treatment.

Response was assessed by an independent committee on the basis of clinical, radiological and biochemical data.

Secondary endpoint: progression-free survival.

[3] Kahl B., Bartlett N. et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell Non-Hodgkin Lymphoma Cancer 2010 ;116 :106-14

Results:
The efficacy results related to 100 patients. 62 of these had follicular lymphoma (in most cases grade 1 or 2) and 21 had lymphocytic lymphoma / B-cell chronic lymphocytic leukaemia.
Approximately three-quarters of patients were in stage III or IV according to the Ann Arbor classification system. The median age of the patients was 60.
Approximately a third of the patients (29%) had low-risk follicular lymphoma, 42% had intermediate-risk lymphoma and a third (29%) had high-risk lymphoma, according to the FLIPI scale[4].
In total, 50% of the patients were in good general condition and 45% in reasonable general condition. The average number of previous treatment lines was 3.6. The most common protocols were rituximab-CHOP (37 patients), CVP (19 patients) and R-CVP (19 patients). 58% of patients were refractory to rituximab administered as monotherapy or maintenance treatment, 26% were refractory to rituximab administered as part of combination chemotherapy, and 13% were refractory to rituximab administered as monotherapy and as part of combination chemotherapy.

The overall response percentage was 75%, including 14% complete response, and a median duration of response of 40 weeks.
Median progression-free survival was 40 weeks. No figures are available for overall median survival times.

The sub-group results, particularly those based on diagnosis or prior treatment, will not be described, as the analyses were not provided for in the protocol.

Additional information:
During the MA procedure the pharmaceutical firm undertook to conduct a study comparing bendamustine to a treatment of the investigator's choice.

B. Tolerance : study SDX105-03

31% (31/100) of patients stopped treatment because of adverse events. The adverse events which frequently led to treatment cessation were thrombocytopenia (9%), fatigue (6%) and neutropenia (4%).

Almost 40% of patients had at least one serious adverse event. The most common serious adverse events were febrile neutropenia (6%) and pneumonia (5%).

C. Conclusion

The efficacy and tolerance of bendamustine administered at a dose of 120 mg/m^2 I.V. on D1 and D2 every 21 days were assessed in a phase III non-comparative study of 100 patients with indolent or progressing non-Hodgkin's lymphoma during or within six months after prior treatment with rituximab administered alone or in combination.
The overall response percentage was 75%, including 14% complete response, and a median duration of response of 40 weeks (primary efficacy endpoints). Median progression-free survival was 40 weeks. No figures are available for overall median survival times.
31% (31/100) of patients stopped treatment because of adverse events. The adverse events which frequently led to treatment cessation were thrombocytopenia (9%), fatigue (6%) and neutropenia (4%).

1. Follicular Lymphoma International Prognostic Index, which includes five prognostic factors (age >60; stage III-IV according to the Ann Arbor classification system; number of lymph node sites affected $\geq$5; haemoglobin >12 g/dl; LDH > normal)
2.

3.3. Multiple myeloma

A comparative phase III study[5] was presented as part of the submission.

A. Efficacy

The phase III, open-label, randomised study (study 94PB01) assessed LEVACT in combination with prednisolone (BP) versus the combination of melphalan and prednisolone (MP), as first-line treatment for patients with multiple myeloma.

Inclusion criteria:
- patients aged 18 to 80 years,
- myeloma confirmed by histocytology tests, stage II in progression or stage III according to the Durie-Salmon classification,
- no prior chemotherapy or radiotherapy,
- Karnofski index ≥ 60 %,
- life expectancy more than 3 months.

Treatments (cycles repeated every 4 weeks):
- bendamustine-prednisolone (BP) group: 150 mg/m^2 I.V. bendamustine on D1 and D2, and 60 mg/m^2 prednisolone I.V. or per os from D1 to D4 (n=68);
- melphalan-prednisolone (MP) group: 15 mg/m^2 I.V. melphalan on D1 and D2, and 60 mg/m^2 prednisolone I.V. or per os from D1 to D4 (n=63).

The Committee emphasises that standard treatment is currently based on melphalan-prednisolone-thalidomide or melphalan-prednisolone-bortezomib combinations.

Primary efficacy endpoint: time to treatment failure, defined as the time from randomisation to one of the following events: progression of the disease during treatment or within three months after the cessation of treatment, death linked to treatment or cessation/change of treatment.
At the request of the EMA, progression-free survival, defined as the time from randomisation to progression of the tumour or death from any cause, was assessed retrospectively.

Among the secondary endpoints:
- overall response percentage (see appendix 3);
- length of remission, defined as the time from obtaining a better remission to progression of the disease;
- overall survival, defined as the time from randomisation to death;
- quality of life.

Results:
The study protocol provided for 120 patients per group. The study was stopped prematurely because recruitment was too slow. Consequently, the data available was obtained from an analysis conducted on 131 patients (68 in the bendamustine-prednisolone group and 63 in the melphalan-prednisolone group).
This study specifically excluded patients over 65 who were not eligible for autologous stem cell transplant and who had neuropathy at the time of diagnosis, which meant that they could not be treated with thalidomide or bortezomib (according to the indication wording of the MA).
The median age of the patients was 62. Almost 37% of patients (48/131) were over 60. 41% of them were over 65. Approximately 15% of patients were in stage II and 85% were in stage III.

[5] Poenisch W, Mitrou PS *et al.* Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to treatment with melphalan and prednisone – a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). J Cancer Res Clin Oncol 2006; 132: 205-212

- *Primary endpoint:*

The median time to treatment failure was 14 months in the BP group versus 9 months in the MP group (p=0.016).
An exploratory analysis showed that there was no difference between the two groups in terms of median progression-free survival time (15 months in the BP group versus 12 months in the MP group).

- *Secondary endpoints:*

- There was no difference between the two groups in terms of the overall response percentage: 75%, including 32.4% complete response, in the BP group and 68.2%, including 11.1% complete response, in the MP group.
- The median duration of remission was 18 months in the BP group versus 12 months in the MP group (p=0.018).
- There was no difference between the groups in terms of median overall survival time (BP group 35 months vs. MP group 33 months).

- *Sub-group analyses*:

- An analysis scheduled in the protocol showed a difference in favour of bendamustine in the sub-group of patients aged 60 or over (43 patients in the BP group and 40 in the MP group) in respect of median time to treatment failure (BP=14 months vs. MP=9 months; p=0.005) and median progression-free survival time (BP=18 months vs. MP=11 months; p=0.007).
- A post-hoc analysis requested by the EMA found a similar result in the sub-group of patients aged over 65 (29 patients in the BP group and 25 in the MP group) (time to treatment failure: BP=13 months vs. MP=9 months; p= 0.011 and median progression-free survival time BP=18 months vs. MP=11 months; p=0.017).

In view of the open design of the study and the fact that data was available for less than a third of patients, the quality of life data was not taken into account.

B. Tolerance

Treatment cessation for adverse events was reported for 3% of patients in the BP group and no patients in the MP group.
Grade 3-4 haematological adverse events were similar in both groups (BP group vs. MP group): leukopenia (40% vs. 31%) and thrombocytopenia (13.2% vs. 14.4%).
Grade 3 nausea and vomiting was more common in the BP group than in the MP group (12% vs. 0%).
Grade 3-4 infections were reported in 12% of patients in each group.

C. Conclusion

The efficacy and tolerance of bendamustine in combination with prednisolone (BP) were compared with the melphalan + prednisolone (MP) combination in an open-label, randomised phase III study conducted on treatment-naïve patients suffering from stage II progressing multiple myeloma or stage III multiple myeloma according to the Durie-Salmon classification system.
As this study was terminated prematurely because of excessively slow recruitment, the data available came from an analysis carried out on 131 patients. This study did not specifically include patients over 65 who were not eligible for autologous stem cell transplant and who had neuropathy at the time of diagnosis, which meant that they could not be treated with thalidomide or bortezomib, according to the indication wording of the MA.
The median time to treatment failure (primary efficacy endpoint) was longer with the bendamustine + prednisolone combination than with melphalan + prednisolone (14 months versus 9 months; p = 0.016). The duration of remission was 18 months in the BP group versus 12 months in the MP group (p=0.018).
However, no difference was observed between the BP and MP groups with respect to:

- median progression-free survival time subjected to retrospective analysis: 15 months vs. 12 months, NS
- overall median survival time: 35 months vs. 33 months, NS

- overall response percentage: 75% including 32.4% complete response vs. 68.2% including 11.1% complete response; NS.

A post-hoc analysis carried out on the sub-group of patients aged over 65 (age group referred to in the indication wording of the MA), a difference in favour of bendamustine was observed in respect of the median time to treatment failure (13 months vs. 9 months; p=0.011) and median progression-free survival time (18 months vs. 11 months; p=0.017).

The events observed more frequently in the BP group than the MP group were grade 3 nausea and vomiting (12% versus 0%) and leukopenia (40% vs. 31%). Grade 3-4 infections (12% vs. 12%) and thrombocytopenia (13.2% vs. 14.4%) were found to be similar in frequency in both groups.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

A. Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (Binet stages B and C), characterised by the proliferation and accumulation of a malignant clone of mature B-line lymphocytes in bone marrow, blood and lymph organs, is a life-threatening condition.

This proprietary product is intended as curative therapy;

The efficacy/adverse effects ratio is high;

Public health benefit:

Chronic lymphocytic leukaemia (CLL) constitutes a moderate public health burden.
Improving its therapeutic management is a public health need falling within the scope of the fight against cancer.
The data available indicates that LEVACT should have an impact on progression-free survival. However, it is impossible to assess this impact in view of the insignificant difference in terms of overall survival compared to the benchmark, and the lack of quality of life data.
LEVACT offers only a partial response to the identified public health need.
Consequently, LEVACT is not expected to have an impact on public health in this indication.

It is a first-line treatment when combination chemotherapy including fludarabine is not suitable;

Alternative medicinal products exist;

The actual benefit is substantial.

B. Non-Hodgkin's lymphoma

Indolent or low-malignancy grade non-Hodgkin's lymphomas, the most common histological form of which is follicular lymphoma, are conditions which progress slowly and are life-threatening.

This proprietary product is intended as curative therapy;

The efficacy/adverse effects ratio is high;

Public health benefit:

Indolent non-Hodgkin's lymphomas are serious clinical conditions which threaten the patient's life but often develop slowly. The public health burden in the population of patients matching the claimed indication is low in view of the small number of patients affected.

Improving the management of this disease is a public health need (Cancer Plan priority) that is only partly covered by existing therapies.

In view of the data available, LEVACT is likely to have an impact in terms of morbidity. However, the public health impact of LEVACT cannot be assessed in the absence of overall survival data.

LEVACT could offer an additional response to the identified public health need for patients who do not respond to treatment with rituximab.

Overall, it is impossible to assess the public health benefit of LEVACT in this indication.

It is intended for second-line or subsequent therapy;

Alternative medicinal products exist;

The actual benefit is substantial.

C. Multiple myeloma

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

It is intended for palliative treatment;

Public health benefit:

The public health burden of multiple myeloma in the population matching the indication in question is low given the small number of patients affected.

The availability of treatments enabling an improved survival of patients with multiple myeloma is a public health need.

In view of the data available, the proprietary product LEVACT in combination with prednisone has an impact in terms of reducing morbidity associated with multiple myeloma in patients aged over 65. However, in view of the lack of any significant difference compared to the benchmark product in terms of overall survival, no impact in terms of mortality is to be expected. Furthermore, there is inadequate data allowing evaluation of the impact of LEVACT on the quality of life of patients undergoing treatment.

The combination of LEVACT and prednisone could offer an additional response to the identified public health need for patients who cannot be treated with thalidomide or bortezomib.

Consequently, LEVACT in combination with prednisone is not expected to benefit public health in this indication.

The efficacy/adverse effects ratio of bendamustine in combination with prednisone is high;

This is a first-line treatment for patients aged over 65 who are not eligible for autologous stem cell transplant or for treatment including thalidomide or bortezomib.

There are treatment alternatives.

The actual benefit is substantial.

4.2. Improvement in actual benefit (IAB)

A. Chronic lymphocytic leukaemia

LEVACT provides a moderate improvement in actual benefit (IAB III) compared to chlorambucil in terms of efficacy in the treatment of patients suffering from chronic lymphocytic leukaemia where combination chemotherapy including fludarabine is not suitable.

B. Non-Hodgkin's lymphoma

Despite the methodological limits of the non-comparative studies, but taking account of the efficacy and tolerance observed in comparison to current management, the transparency Committee considers that LEVACT provides a moderate improvement in actual benefit (IAB III) in the treatment strategy of indolent and progressive non-Hodgkin's lymphoma following treatment with rituximab.

C. Multiple myeloma

In view of the low evidential quality of the research (study stopped prematurely, choice of irrelevant primary efficacy endpoint and lack of direct comparison with benchmark treatments), the Committee is of the opinion that LEVACT combined with prednisone provides any improvement in actual benefit (IAB V) compared to the usual first-line therapeutic management of multiple myeloma.
However, as this product is not neurotoxic, the Committee considers that it does offer a useful additional treatment option for patients aged over 65 who are not eligible for autologous transplant or for treatment with thalidomide or bortezomib.

4.3. Therapeutic use

A. Chronic lymphocytic leukaemia

The decision as to whether to treat the patient (or wait) depends on the patient's general condition (age and comorbidities) and on the stage of the disease and presence of factors pointing to a poor prognosis (time for doubling of peripheral lymphocytes less than 12 months, elevated β2-μglobulin, p53 mutation, etc.). The most common cases of the disease, i.e. Binet stage A or Rai stages 0, I and II, are asymptomatic and do not justify any specific treatment.
Where treatment for CLL is introduced, the first-line treatments are:

- an alkylating agent: chlorambucil either alone or in combination with corticosteroids, cyclophosphamide;
- a purine analogue, particularly fludarabine phosphate (alone or in combination), which can be used as a first-line or second-line treatment;
- COP or CVP (cyclophosphamide, vincristine, prednisone) and CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) combination regimens;
- a monoclonal antibody (rituximab).

Autologous stem cell transplant can be offered in particular to young patients in complete remission.
The standard first-line treatment for patients with few comorbidities is rituximab + fludarabine + cyclophosphamide (R-FC)[6,7]. Alemtuzumab is used for cases which are refractory or which progress at an early stage, especially in the case of 17p deletion. Other treatments such as bendamustine will be administered for subsequent relapses. Early data, not validated by the MA of bendamustine, indicate that bendamustine in combination with rituximab may be effective[8].

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[6] Eichhorst B, Hallek M, Dreyling M : Chronic lymphocytic leukaemia : ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 21 (5) : v162-v164, 2010
7 Société Française d'Hématologie [French Society of Haematology], 2009 guidelines
8 Fisher, ASH 2009, summary 205; Fisher, ASH 2008, summary 330

The normal first-line treatment for patients with comorbidities is chlorambucil. A recent study showed that treatment with fludarabine alone did not offer any additional advantage in terms of overall survival compared with chlorambucil monotherapy in patients over 65[9]. The available alternatives are combinations based on low-dose purine (fludarabine + cyclophosphamide or R-FC or pentostatin + cyclophosphamide + rituximab) or bendamustine.

LEVACT is a new validated option for the management of patients suffering from chronic lymphocytic leukaemia who are not eligible for combination chemotherapy including fludarabine.

B. Non-Hodgkin's lymphoma[9,10,11,12]

Indolent NHL is typically a follicular lymphoma diagnosed at a median age of approximately 60, at disseminated stage III or IV in 80% of cases, with a "low" tumour mass in 50% of cases.
Asymptomatic patients with a small tumour mass (20 to 30% of cases) require regular treatment. Patients with a large tumour mass undergo immunochemotherapy, i.e. combination chemotherapy (CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone or CVP: cyclophosphamide, vincristine and prednisone) and an anti-CD20 monoclonal antibody (rituximab).
If the patient fails to respond or suffers a rapid relapse (within 6 months), a second-line protocol is offered: treatment options are available (rituximab monotherapy, radioimmunotherapy or various combinations). No consensus exists, except for allogenic transplant for young patients only.

LEVACT monotherapy is a new validated option for the management of patients with indolent non-Hodgkin's lymphoma that is progressing following treatment with rituximab.

C. Multiple myeloma

The current classification of myeloma drawn up according to the criteria established by the International Myeloma Workshop Group[11] places patients into one of two groups: asymptomatic patients, for whom monitoring alone is usually sufficient, and symptomatic patients (bone damage, renal insufficiency, hypercalcaemia, anaemia, intercurrent infections, amylosis) requiring management suitable for the patient's age and comorbidities.
First-line treatment depends on whether or not the patient is eligible for intensive treatment once induction chemotherapy has led to complete or partial remission. It has been shown that intensification following autologous transplantation has significantly increased 5-year survival in patients aged less than 70 years[12]. After this intensification, a consolidation treatment can increase the rate of remission (namely it can decrease the tumour mass), prolong the duration of the response and improve survival[13].

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9 Eichhorst BF, Busch R, et al. German CLL Study Group (GCLLSG). First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009 ;114(16):3382-91.
10. ALD 30 Guide médecin – Affection longue durée – Lymphomes non hodgkiniens ganglionnaires de l'adulte (Guide for doctors ALD 30- Long-term condition, gangliomic non-Hodgkin's lymphomas in adults), September 2009, HAS, INCA
11. Dreyling M. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up M. Dreyling Annals of Oncology, 5, v181-v183, 2010
12 International Myeloma Working Group. Criteria for the classification of monoclonal gammapathies, multiple myeloma and related disorders: a report of the International Myeloma Workshop group. Br J Haematol 2003, 120:749-757.
[12] 13*Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Björkholm M.* Patterns of Survival in Multiple Myeloma: A Population-Based Study of Patients Diagnosed in Sweden From 1973 to 2003. *J Clin Oncol 25:1993-1999, 2007*
1514Attal M, Harousseau JL, Leyvraz S et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood 2006;108:3289-3294.

Patients aged ≥ 65 or who are not eligible for intensification are given first-line treatment involving melphalan-prednisone-thalidomide (MPT) or melphalan-prednisone-bortezomib (MPV) combinations[14]. Patients with severe comorbidities precluding treatment with MPT or MPV are still treated with the conventional MP combination[15].

LEVACT in combination with prednisone is a useful additional alternative for management of multiple myeloma in patients aged over 65 who are not eligible for autologous stem cell transplants or treatment with bortezomib or thalidomide.

4.4. Target population

A. Chronic lymphocytic leukaemia

The target population for LEVACT in this indication comprises patients suffering from Binet stage B or C CLL who require first-line treatment and are not eligible for combination chemotherapy including fludarabine.

The incidence of CLL in 2005[16] in France was estimated at 3,224 cases.
Stages B and C account for almost 45% of cases (1,450 patients)[17].
Combination chemotherapy including fludarabine is not appropriate mainly in cases where a chromosome 17 abnormality is present and for patients suffering from an immunodependent cancer or significant comorbidities. The expert view is that this group probably comprises a population of 400 to 650 patients a year.

Consequently, the target population for LEVACT in this indication is estimated at 400 to 650 patients a year.

B. Non-Hodgkin's lymphoma

The target population for LEVACT in this indication comprises patients suffering from indolent non-Hodgkin's lymphoma which is progressing during or within six months after treatment with rituximab alone or in combination.

The incidence of non-Hodgkin's lymphoma[18] in France was estimated at 10,224 cases in 2005.
Indolent lymphomas account for almost 40-50% of non-Hodgkin's lymphomas,[18] i.e. between 4,090 and 5,110 cases.
The number of patients suffering from indolent non-Hodgkin's lymphoma in progression and who have been treated with rituximab is estimated on the basis of the following data and hypotheses:

- the management of follicular lymphoma (the most common form of indolent non-Hodgkin's lymphoma) is regarded as representative of that of other indolent forms;
- the condition is diagnosed at stage I-II in 15 to 20% of cases[11,19], which means that between 3,270 and 4,345 patients are diagnosed at stage III-IV;
- asymptomatic patients without a large tumour mass are managed by regular monitoring (20 to 30% of cases according to the expert opinion), which means that treatment is introduced in 70 to 80% of cases (i.e. between 2,290 and 3,475 patients);
- after treatment with rituximab as part of combination chemotherapy, the failure percentage was observed to be 13% in patients with an indolent lymphoma or mantle

16. 15 Harousseau JL, Dreyling M : Multiple myeloma : ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, 21 (5) : v155-v157, 2010
17 16 Société Française d'Hématologie [French Society of Haematology] 2009 guidelines, http://sfh.hematologie.net/hematolo/UserFiles/File/REFERENTIEL_SFH_2008_2009.pdf
[16] 17 Presentation of the most recent data on cancer incidence and mortality in France and the trends over the past 25 years (1980-2005) - Press conference held on 21 February 2008. INVS/Hôpitaux de Lyon/FRANCIM/INCA
[17] 18 Binet J.L et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981; 48:198-206.
19 ALD 30 Guide médecin – Affection longue durée – Lymphomes non hodgkiniens ganglionnaires de l'adulte (Guide for doctors ALD 30- Long-term condition, gangliomic non-Hodgkin's lymphomas in adults), September 2009, HAS, INCA
[19] 20 Hiddemann W, Buske C, Dreyling M et al. Treatment Strategies in Follicular Lymphomas: Current Status and Future Perspectives. J Clin Oncol. 2005; 23: 6394-6399

cell lymphoma which had not undergone previous treatment or had relapsed or failed to respond[20], (i.e. between 297 and 451 patients); no data is available on the percentage of patients experiencing a relapse during treatment or within six months.

Consequently, the target population for LEVACT in this indication is estimated at 300 to 450 patients a year.

C. Multiple myeloma

The target population for LEVACT is made up of patients with multiple myeloma (Durie-Salmon stage II with progression or stage III) aged over 65 who are not eligible for autologous stem cell transplant and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

According to data from the French Institute for Public Health Surveillance (Institut national de veille sanitaire, INVS)[21], the incidence of multiple myeloma in France increased from 3,565 new cases per year in 2000 to 4,516 in 2005. 3,327 of these patients (74%) were 65 or older.
The percentage of patients who are asymptomatic and thus for whom simple monitoring is sufficient is estimated to be between 15[22, 23] and 20%[24], i.e. the number of patients requiring treatment would be between 2,660 and 2,830.
No epidemiological data is available, and so it is not possible to calculate the proportion of patients not eligible for autologous stem cell graft and who have neuropathy at the time of diagnosis. The expert view is that this sub-group might represent 5 to 10% of symptomatic patients aged over 65 (i.e. 160 to 340 patients).

Consequently, the target population for LEVACT in this indication is estimated at 135 to 285 patients a year.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicine approved for hospital use and various public services in the marketing authorisation's indication and dosage.

21 Schulz H, Bohlius j et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma : a systematic review and meta-analysis J Natl Cancer Inst 2007;99:706-14

[21]22 Evolution de l'incidence et de la mortalité par cancer en France de 1980 à 2005; Fiche Myélome Multiple et Maladies Immunoprolifératives (Changes in the incidence and mortality of cancer in France from 1980 to 2005; Multiple Myeoloma and Immunoproliferative Diseases file) INVS 30/01/2008:
http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/donnees_localisation/myelome/myelome.pdf

[22] 23 TNS Health Care. Prise en charge des myélomes multiples. (Management of multiple myeloma) May 2007 and April 2008

[23]. 24 Rajkumar SV. MGUS and Smoldering Multiple Myeloma: Update on Pathogenesis, Natural History, and Management. Amer Soc Hematol; Hematogy 2005:340-345

[24]. 25 He Y, Wheatley K, Clark O, Glasmacher A, Ross H, Djulbegovic B. Early versus deferred treatment for early stage multiple myeloma. Cochrane Database of Systematic Reviews 2003, Issue 1

APPENDIX 1: Response criteria according to the NCIWG 1996 (Cheson et al, 1996)
(chronic lymphocytic leukaemia)

Parameter	Complete Remission	Partial Remission	Progressive Disease
Lymphocytes	$<4.0 \times 10^9$/L	≥50% reduction from baseline	≥50% increase to at least 5.0×10^9/L
Lymphadenopathy	Absence by physical exam	≥50% reduction (physical examination)	≥50% increase for at least 2 weeks or new palpable node ≥1cm
Organomegaly	Normal size spleen and liver by physical exam	≥50% reduction if abnormal at baseline	≥50% increase
Constitutional Symptoms	None	Not defined	Not defined
Neutrophils	$\geq 1.5 \times 10^9$/L	$\geq 1.5 \times 10^9$/L or 50% improvement from baseline	Not defined
Platelets	$>100 \times 10^9$/L	$>100 \times 10^9$/L or 50% improvement from baseline	Not defined
Hemoglobin	>11.0 g/dL (untransfused)	>11.0 g/dL or 50% improvement from baseline (untransfused)	Not defined
Bone Marrow	Normocellular for age, <30% lymphocytes, no B-lymphoid nodules.	If done, ≥30% lymphocytes and/or B-lymphoid nodules	Not defined
Response Definition	**All above to be met for at least 2 months. If persistent nodules in bone marrow = nPR**	**Meets criteria for first 3 for at least 2 months, and at least 1 other of above to be met**	**At least 1 of above to be met, or transformation to more aggressive histology**

APPENDIX 2: Response criteria according to the International Workshop Response Criteria for NH)
(non-Hodgkin's lymphoma)

Response Category	Response Criteria
Complete response (CR)	1. Complete disappearance of all detectable clinical, radiographic, or diagnostic evidence of disease (eg, abnormal LDH) definitely assignable to NHL). No disease-related symptoms. 2. All lymph nodes and nodal masses must have regressed to normal size: • If >1.5 cm before treatment, regressed to ≤1.5 cm in GTD. • If 1.1 to 1.5 cm in GTD before treatment, regressed to ≤1 cm in GTD (or at least 75% SPD). 3. Spleen and all previously enlarged organs decreased in size. 4. If bone marrow (BM) had been involved by lymphoma before treatment, the BM had to be clear on repeat aspirate and biopsy of the same site. Note: If a BM was not done at week 12 after therapy, and the BM was negative at week 4 after therapy, the result from the week 4 posttherapy BM could be used to make the response determination.
Complete response unconfirmed (CRu)	Met criteria 1 and 3 for CR, but with 1 or more of the following features: • A residual lymph node mass >1.5 cm in GTD that had regressed by >75% in SPD compared with the size of the original mass. • Individual nodes previously confluent had regressed by >75% in SPD. • Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).
Partial response (PR)	1. ≥50% decrease in SPD of the index lesions from baseline. 2. No increase in the size of the other nodes, liver, or spleen. 3. Splenic and hepatic nodules must regress by at least 50% in the SPD. 4. No new sites of disease. If a subject met radiographic CR criteria and if BM was involved by lymphoma before treatment, and the BM did not clear on repeat aspirate and biopsy of the same site, the subject was scored as a PR. If a marrow was refused or not performed, the subject was also scored as a PR.
Stable disease (SD)	SD was defined as less than PR but not PD.
Progressive disease or relapsed disease (PD/RD)	1. In subjects with PR, a ≥50% increase from nadir in the SPD of any previously identified abnormal node. In subjects with CR, a ≥50% increase in the size of previously involved sites. ≥50% GTD of any previously identified node ≥1 cm in its short axis or in the SPD of more than 1 node. 2. Previously involved site, that had not disappeared, increased by ≥50% GTD, provided the site measures ≥2 cm in GTD (at the time PD/RD was assessed), or a previously involved group of lesions increased in SPD by ≥50%. 3. Appearance of new lesion during or at the end of therapy, or any new non-nodal lesion; reappearance of a lesion that had disappeared on CT scan; or new nodal lesion ≥2 cm. 4. A BM that was previously negative became positive. 5. Rising peripheral blasts. (These were to be recorded as nonindex, or new lesions).

Abbreviations: BM = bone marrow; CR = complete response; CT = computed tomography; GTD = greatest transverse diameter; LDH = lactate dehydrogenase; PD = progressive disease; PR = partial response; RD = relapsed disease; SD = stable disease; SPD = sum of product dimensions.

APPENDIX 3: Response criteria according to the NCIWG 1996 (Cheson et al, 1996)
(multiple myeloma)

Complete remission:

- Reduction of at least 75% in plasma paraproteins (≤25g/L)
- Reduction of ≥ 90% in 24-hour urine proteins (≤200 mg/24h)
- No increase in bone damage, serum calcium within normal limits
- No blood transfusion within the past three months

Partial remission:

- Reduction of at least 25% but less than 75% in plasma paraproteins
- Reduction of at least 25% but less than 90% in 24-hour urine proteins
- No increase in bone damage, serum calcium within normal limits

No change:

- Increase or decrease of less than 25% in serum paraproteins and/or 24-hour urine proteins.

Disease progression:

- Increase of at least 25% in serum paraproteins and/or 24-hour urine proteins.
- Appearance of new bone lesions or hypercalcaemia
- Progressive increase in anaemia, with increased infiltration of plasma cells into bone marrow.