ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ROUTE OF ADMINISTRATION, APPLICANTS IN THE MEMBER STATES

Member State EU/EEA	**Applicant company name, address**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact 2,5 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Belgium	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Denmark	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Ribomustin	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Finland	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Ribomustin	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
France	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Germany	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Ireland	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use

Member State EU/EEA	**Applicant company name, address**	**(Invented) Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Italy	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Ribomustin	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Luxembourg	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Norway	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Poland	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
Spain	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Levact	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use
United Kingdom	Astellas Pharma GmbH Georg-Brauchle-Ring 64 - 66 80992 München Germany	Ribomustin	2.5 mg/ml	Powder for concentrate for solution for infusion	Intravenous use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR POSITIVE OPINION

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF LEVACT AND ASSOCIATED NAMES (SEE ANNEX I)

Levact contains bendamustine, an alkylating anti-tumour agent which acts by impairing DNA matrix functions and DNA synthesis and repair. Bendamustine has been used clinically as an antineoplastic agent in the German Democratic Republic since 1971 and there is therefore substantial clinical experience with bendamustine in Germany. An application for a decentralised procedure was submitted in November 2007 for the following three indications: first-line treatment of chronic lymphocytic leukaemia (CLL), first-line treatment of advanced indolent non-Hodgkin´s lymphomas (NHL) in rituximab-refractory patients and advanced multiple myeloma (MM). During this procedure, all involved member states agreed on the CLL indication, however, no agreement was reached for the MM and NHL indications. A number of concerned member states raised potential serious risks to public health with regards to the efficacy of the medicinal product in these indications, considering that non-inferiority or superior efficacy when compared to the efficacy of well established chemotherapy regimens recommended in international guideline had not been demonstrated. The procedure was subsequently referred to the CHMP.

Efficacy of bendamustine in multiple myeloma (MM)

The Applicant provided data from a prospective, multi-centre randomised controlled pivotal trial comparing the efficacy of first-line chemotherapy with bendamustine and prednisone (BP) to melphalan and prednisone therapy (MP) in patients with previously untreated multiple myeloma. The primary endpoints were time to treatment failure (TTF) and the secondary endpoints were survival time, survival rate after 2 years, rate and duration of remission, toxicity, quality of life and cross-resistance. Patients in the BP group demonstrated a longer TTF (14 vs. 9 months) and a higher percentage of complete remission (32% vs. 11%). According to the CHMP anticancer guideline (CPMP/EWP/205/95/Rev.3/Corr.), TTF as primary endpoint does not allow the assessment of efficacy. The Applicant therefore provided a retrospective calculation of progression free survival (PFS) which demonstrated an advantage for the BP arm (15 vs. 12 months) but of borderline statistical significance. Only the overall response rate (ORR) and the complete remission rates were superior in the BP arm. Even though the duration of remission was longer in the BP arm (18 vs. 12 months), overall survival was similar (35 vs. 33 months). The prospectively planned subgroup analysis in patients over 60 years showed an advantage of BP over MP in terms of TTF (14 vs. 9 months) and also in terms of PFS (18 vs. 11 months). The Applicant presented consistent similar results for patients >65 years and also provided case reports of heavily pre-treated and otherwise refractory MM patients who could be rescued with bendamustine combination therapy. Finally, the Applicant noted the characteristic neurotoxicity profiles of recently authorised drugs and emphasized the non-overlapping and well-established toxicity profile of bendamustine (no neurotoxicity) for patients not eligible for thalidomide or bortezomib.

The CHMP noted the methodological and procedural deficiencies of the submitted trials, and that the primary endpoint and retrospective calculation of PFS rightfully attract criticism, but did not consider the control group to be under-treated. The CHMP agreed that the BP regimen had documented efficacy in multiple myeloma as shown by the longer median PFS and TTF compared to the MP arm. Results in subgroups of patients older than 60 or 65 years are consistent and in clinical practice, bendamustine in combination with prednisone is currently recommended to patients over 80 years by the German Oncology Society. This confirms that the efficacy of bendamustine is not negated by safety concerns among frailer patients. Supportive evidence for the efficacy of bendamustine can also be derived from the high complete remission rate, an increasingly important endpoint in multiple myeloma. In the opinion of the CHMP, the proposed restricted indication clearly describes a fairly small patient population who cannot profit from the superior recently introduced regimens MPT (melphalan, prednisone and thalidomide) or MTV (melphalan, topotecan and VP-16 phosphate), including thalidomide or bortezomib. This will limit the risk of under-treatment of patients who would

benefit from these treatments or high intensity treatment. The CHMP agreed that the past decades of clinical use have demonstrated the very low neurotoxicity of bendamustine.

Efficacy of bendamustine in rituximab-refractory non-Hodgkin´s lymphoma (NHL)

The Applicant presented a pivotal and a supportive uncontrolled trial to support this indication, together with a protocol and preliminary data for another uncontrolled trial with similar design. Furthermore, the Applicant proposed to perform a comparative post-approval trial in the rituximab-refractory setting (bendamustine compared to investigator's best choice). Co-primary endpoints in both trials were overall response rate and duration of response. Efficacy in rituximab-refractory NHL is supported by 75% overall response rates (ORR), 58% partial response and 14% complete response (CR) with a median duration of response of 40.14 weeks. Subgroup analyses of ORR, disease rate and PFS results demonstrate overall homogeneous results. In addition, a reduction of tumour burden of over 50% was observed in 78% of the supportive study patients, suggesting a likely clinical benefit for this population. The Applicant presented an abstract of the final analysis of a trial in first line setting, comparing bendamustine in combination with rituximab (B-R) to R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin (Adriamycin), Oncovin (vincristine), and prednisone) treatment, allowing the contribution of bendamustine vs CHOP to be deduced. The trial included 549 patients and the ORR was similar between the two groups (93.8% vs. 93.5%). The CR rate was significantly higher for the B-R group (40.1 vs. 30.8%), PFS was higher (54.8 vs. 34.8 months) and the Hazard Ratio (HR) was 0.5765. According to the Applicant, the superior efficacy was achieved with lower toxicity. The Applicant also noted that there is currently only one approved radio-immunotherapy for patients refractory to rituximab therapy, comparing the specific eligibility requirements and the complex administration conditions for this therapy to the ease of bendamustine administration and its well-known safety profile. Finally, the Applicant discussed the hurdles associated with performing a randomised study suitable to support the current application as well as the selection of an appropriate primary endpoint, raising the issues of the impact of the limitations of the only currently available treatment option for patients refractory to rituximab therapy (britumomab tiuxetan) on the recruitment of patients and the ethical concerns of a comparison against the investigators best. While PFS would be the best primary endpoint in a randomised study, with ORR as secondary endpoint, this would require a prohibitively large number of patients for a confirmative approach. In conclusion, the Applicant acknowledged that a randomised study may be needed in case of insufficient overall evidence of efficacy or unclear safety profile but that for bendamustine, the safety profile is clear and the efficacy is supported by long clinical experience.

The CHMP considered that the long clinical experience, the well established safety profile with manageable toxicities and the promising results presented in the submitted trials support the use of bendamustine in a population in need of further treatment options. The Applicant also provided a study report from an additional uncontrolled study performed in Japan, in which the overall results were consistent with earlier experience. Durable responses may be linked to patient benefit by clinically relevant reduction of disease burden (greater than 50% decrease of measurable disease in 78% of patients). The CHMP also agreed with the hurdles as presented by the Applicant, although it considered that the superiority of bendamustine can only be assumed, in the absence of controlled data. Regarding the StiL study, the CHMP was of the opinion that although a single trial should not be the basis for changing the standard of care for the first line setting, the data shows the superiority of bendamustine over an established combination chemotherapeutic regimen (each in combination with rituximab) which clearly provides a rationale to use bendamustine also in the refractory setting. The CHMP noted the Applicant proposal to perform a randomised trial comparing bendamustine with the investigator's best choice and was of the opinion that such a study will provide valuable information on relative efficacy and safety compared to the currently used treatment options. Noting the commitment by the Applicant to perform this post-approval study, the CHMP therefore considered the submitted data sufficient for this restricted indication, even though the data submitted does not comply with the criteria of the 'Guideline on the evaluation of anticancer medicinal products in man'.

Conclusion

The CHMP noted the submitted trials assessing the role of bendamustine in CLL, MM and rituximab-refractory NHL. The quality of the presented trials is variable, in particular in indications for which the product is already known to the effective, such as multiple myeloma, where the design of the studies is weak in comparison to the current standards. However, this lack of ICH-compliant efficacy data is compensated by a well established safety profile with expected and manageable toxicities. In addition, the safety profile of bendamustine presented in the SPC is in line with previous experience. Therefore, the CHMP considered that the benefit-risk ratio is positive for all applied indications, albeit with different degrees of certainty. For multiple myeloma, the longstanding use of bendamustine outweighs the lack of clear efficacy data in the specific patient population subgroup. Regarding the rituximab-refractory NHL indication, the lack of controlled data is acceptable as long as the wording of the indication clearly reflects the refractory nature of the disease. Nonetheless, it was the opinion of the CHMP that a confirmatory study comparing bendamustine to investigator's best choice using time-to-event-data should be performed as a post-approval commitment. Based on the submitted data and in view of the adequate commitments, the CHMP considered the referred indications to be approvable.

In conclusion, the CHMP adopted the following 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 lymphomas as monotherapy 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 clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment."

GROUNDS FOR POSITIVE OPINION

Whereas

- the submitted data is sufficient to conclude on a positive benefit-risk ratio for the referred indications, albeit with different degrees of certainty,

- the lack of ICH-compliant efficacy data is compensated by a well established safety profile with expected and manageable toxicities which are correctly reflected in the proposed Product Information,

- the commitment of the Applicant to carry out a post-authorisation comparative trial in patients refractory to prior rituximab treatment is considered satisfactory,

the CHMP has recommended the granting of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Levact and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination group procedure.

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

The National Competent Authorities, coordinated by the Reference Member State, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

The MAH will perform, as a post-authorisation commitment, a comparative randomised multicentre Phase 3 trial to investigate the efficacy of bendamustine in the treatment of patients with indolent non-Hodgkin’s lymphoma refractory to rituximab.