Proposed medicines(s) for treatment of follicular lymphoma (refer to application for specific protocols):

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EML</th>
<th>Addition</th>
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<tbody>
<tr>
<td>rituximab</td>
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<tr>
<td>bendamustine</td>
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<td>cyclophosphamide</td>
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<tr>
<td>vincristine</td>
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<td>prednisone</td>
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<td>doxorubicin</td>
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(1) **Does the application adequately address the issue of the public health need for the treatment of the disease?**

Yes, the application reports that follicular lymphoma (FL) accounts for 10-20% of all lymphomas in Western countries and accounts for one third of non-Hodgkin lymphomas. It also states the incidence of FL is on the rise in accordance with the GLOBOCAN 2012 data, especially in the North America, the United Kingdom, and South Africa.

(2) **Have all important studies that you are aware of been included in the application?**

Yes, most of the relevant trials on rituximab for FL have been included in this application.

**Other trials not included in this application:**
1. Superior efficacy of rituximab with bendamustine combination was also proved in a recent phase I/II trial*, which also showed better tolerance profile with this regimen. [*Maddocks K, Christian B, Jaglowski S, Flynn J, Jones JA, Porcu P, et al. A phase 1/II study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. Blood. 2015 Jan 8;125(2):242-8]. Since this is a Phase I trial it is not very relevant to the application.

2. Flinn IW et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014 May 8;123(19):2944-52. doi: 10.1182/blood-2013-11-531327. In this study only patients with Grade 1 & 2 follicular lymphoma was included. The endpoint reported here is only
after 6-8 cycles of treatment. Five-year follow-up is not reported in this paper as the study ends in 2017.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

Yes, the application provides evidence for efficacy/effectiveness of rituximab as a part of combination regimen such as R-CHOP or R-CVP in patients with symptomatic advanced Follicular Lymphoma.

In patients with Limited stage FL the standard of care is involved field radiotherapy. Hence chemotherapy becomes necessary only for those with symptomatic Advanced Stage FL. Addition of Rituximab to CHOP or CVP has shown to improve overall survival (OS), time to progression and a 65% reduction in risk of death due to lymphoma. The evidence for maintenance therapy with rituximab is not strong as it does not improve OS.

Though there is some evidence that Bendamustine and Rituximab may offer advantages in terms of low toxicity, there is not enough evidence with Bendamustine as the trials are still ongoing and long term data are not available.

(4) Does the application provide adequate evidence of safety for the proposed treatment regimen(s)? Are there any adverse effects of concern, or that may require special monitoring?

Yes, safety and adverse effects of rituximab are adequately discussed.

Rituximab can cause significant systemic allergic reactions during administration. It is important that rituximab is administered slowly and that medicines are available both as premedications and to treat allergic reactions as required. Rituximab may also cause neutropenia and, infrequently, viral infection or reactivation of latent viral infection, including viral hepatitis and JC virus resulting in progressive multifocal leukoencephalopathy.

Bendamustine can cause severe lymphocytopenia. Neutropenia and thrombocytopenia are also common. Patients may experience dermatologic effects including rash and pruritus, though the reaction is typically mild.

ADDITIONAL CONSIDERATIONS:

(5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?
Yes, rituximab can cause allergic reactions and anaphylaxis and must be given slowly, with close monitoring and supportive medicines, including adrenaline, steroids and antihistamines, readily available. Premedication with paracetamol, hydrocortisone and diphenhydramine 30-60 minutes prior to rituximab administration (at least prior to the first rituximab) is recommended.

Medicines for the treatment of allergic reactions and monitoring facilities (clinical & laboratory) should be accessible to the treating physician.

(6) Are there any issues regarding the registration of the proposed medicines by regulatory authorities?

Both medicines have been approved for use. The US-FDA has given black box warnings for the usage of rituximab. They are fatal infusion reactions, severe mucocutaneous reactions, progressive multifocal leukoencephalopathy and reactivation of hepatitis B. In January 2011, the FDA approved rituximab for maintenance therapy for patients with previously untreated follicular CD-20 positive B-cell non-Hodgkin lymphoma who achieve a response to rituximab in combination with chemotherapy.

Bendamustine has been approved by US-FDA in the year 2007 and currently the on-label indications are as follows,
1. Chronic lymphocytic leukemia (CLL) and
2. Indolent B-cell non-Hodgkin’s lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen.

(7) Comment briefly on issues regarding cost and affordability of treatment.

Rituximab, is much more costlier than the conventional CHOP or CVP regimen. Addition of Rituximab significantly elevates the cost of therapy multifold. However considering that there is a 65% reduction in risk of death due to lymphoma in those with symptomatic advanced FL, rituximab should be included.

The procurement cost of generic versions of rituximab in a tertiary care hospital of South India is Rs. 19215 and Rs. 3819, for a 500 mg (Dr. Reddy’s) and 100 mg (Intas) vial, respectively.

Bendamustine costs Rs. 1795 (about 29 USD) for 100 mg/ 10 mL vial from Naprod in India.

(8) Any additional comments on the application?

No

(9) Please summarise the action(s) you propose the Expert Committee take.

I would support the inclusion of rituximab in the EML for the treatment of symptomatic advanced FL.

However, I do not support the inclusion of bendamustine in the EML at this point of time as evidence is quite sparse regarding its efficacy and safety.