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

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EML</th>
<th>Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>fludarabine (oral &amp; IV)</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>☒</td>
<td>☐</td>
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<tr>
<td>rituximab</td>
<td>☐</td>
<td>☒</td>
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<tr>
<td>bendamustine</td>
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<td>☒</td>
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<tr>
<td>vincristine</td>
<td>☒</td>
<td>☐</td>
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<tr>
<td>prednisone</td>
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</table>

(1) Does the application adequately address the issue of the public health need for the treatment of the disease?

Yes ☒ No ☐

Comments:

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

Yes ☒ No ☐

Comments:

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

Yes ☒ No ☐

Comments: RCT shows combination of fludarabine PLUS cyclophosphamide increases PFS by 20-23 months. Addition of rituximab increase PFS from 20 to 52 months. Fludarabine tested both IV and oral. Addition of bendamustine to rituximab found EFS was 33.9 months (but this is less than the 52 months above, no clear comparison). This was only a phase II study (Fischer 2012).
(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 ☐ No ☐

Comments: bone marrow suppression, infections, allergic reactions to rituximab. Continued monitoring is needed

ADDITIONAL CONSIDERATIONS:

(5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?

Yes ☐ ☑ No ☐

Comments: facilities for blood testing, flow cytometry, iv transfusion capacity for rituximab. Age and fitness of patients should be considered

(6) Are there any issues regarding the registration of the proposed medicines by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes ☐ No ☐

Comments: all approved by US regulatory authority; rituximab widely approved

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

Fludarabine – off patent; bendamustine – not off patent until 2016;
Rituximab off patent; biosimilars available

(8) Any additional comments on the application?

(9) Please summarise the action(s) you propose the Expert Committee take.
Recommend addition of rituximab and fludarabine, but not bendamustine based on poor evidence of efficacy for latter, as well as potential cost.