Proposed medicines(s) for treatment of DLBCL (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>Rituximab</td>
<td>☐</td>
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<tr>
<td>Cyclophosphamide</td>
<td>☒</td>
<td>☐</td>
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<tr>
<td>Doxorubicin</td>
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<td>☐</td>
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<tr>
<td>Vincristine</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 medicine?

Yes ☑ No ☐

Diffuse Large B – Cell Lymphoma constitutes 40% burden of Non- Hodgkin’s lymphoma. Based on US National Cancer Institute SEER Database, the incidence is 7/100,000 people. Elderly patients of > 60 years are affected more than young adults and children. The case load is more in the developed countries which may be attributed to the deficiency of diagnostic facilities in the LMICs. There is some information to conclude that the burden of DLBCL is not confined to high income settings alone and so treatment facilities should be made available worldwide.

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

Yes ☐ No ☑

Huang Y et al[22], found that 5 year overall survival (OS) with R-CHOP was significantly higher than CHOP (66.6% Vs 50.4%). In non- germinal centre subtype , rituximab regimen produces better survival benefit than CHOP regimen.

Sehn LH et al[23] also noticed that rituximab has increased progression free survival (PFS) and OS of all age groups of DLBCL in British Columbia.

According to Olszewski AJ et al, [24] R-CHOP regimen has produced better prognosis in certain extra nodal DLBCL of spleen, liver and lung similar to nodal DLBCL.

Lin TY et al [25] concluded that R-CHOP has significantly decreased the risk of treatment failure in DLBCL patients in comparison with CHOP regimen.

According to the meta-analysis of rituximab-based immunochemotherapy
for subtypes of diffuse large B cell lymphoma, R-CHOP regimen achieved higher overall survival in germinal centre B Cell like (GCB) subtype than the non-GCB group (RR 1.16, 95% CI 1.03 to 1.31; I²=0%; five RCTs, n=323 patients). [26]

Refractory DLBCL patients on rituximab salvage therapy showed statistically significant OS [log Hazard Ratio (HR) of death = 0.72, 95% CI (0.55-0.94), P = 0.02] and PFS [HR = 0.61, 95% CI (0.52-0.72), P < 0.05]. [27]

**ADDITIONAL REFERENCES RELATED TO THIS TOPIC:** (The reference numbers are in continuation with that seen in the review)


(3) **Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?**

Yes √ No □

**Table 1: Comparison between the overall survival of elderly DLBCL patients with R- CHOP and CHOP regimen based on GELA-LNH 98.5 study [9]**
Table 2: Comparison of clinical endpoints achieved with R-CHOP and CHOP regimen among young DLBCL patients based on MabThera International Trial (MInT) [10]

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>R-CHOP</th>
<th>CHOP</th>
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</thead>
<tbody>
<tr>
<td>6year event free survival</td>
<td>74%</td>
<td>56%</td>
</tr>
<tr>
<td>6 year overall survival</td>
<td>90%</td>
<td>80%</td>
</tr>
</tbody>
</table>

R–CHOP provided significant clinical improvement due to the addition of rituximab. These regimens resulted in remission of disease at 5 years leading to increased lifespan of many young patients.

(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 √

Like other chemotherapeutic agents, both CHOP and R-CHOP regimens cause bone marrow suppression. Rituximab causes systemic allergic reactions especially during first infusion. It also causes re-activation of latent infection especially viral hepatitis. Doxorubicin predisposes the patient to congestive heart failure and it is dose dependent. The risks are outweighed by the potential benefits. Risk of secondary malignancies with both regimens is very low. Haematological parameters like TLC, DLC, Hb and platelet counts should be monitored regularly. Treated patients should be under surveillance for secondary malignancies to promote early detection and treatment.

ADDITIONAL CONSIDERATIONS:

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

Yes ☐ No ✓
Since rituximab cause allergic reactions during initial infusion, health personnel like intern doctors and nursing staff should be educated regarding the toxicity. Measures like slow infusion and availability of medications for treating anaphylaxis during infusion should be ensured. Patients should be followed up carefully.

The diagnostic support for detection of DLBCL also needs to be kept in mind.

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

Yes [ ] No [ √ ]

Rituximab was approved by US FDA in 1997 followed by EMA, Australia in 1998 and Canada in 2000 for its use in DLBCL along with CHOP regimen. In USA, the patent on Rituximab will be valid till 7.4.2015. Since the patent period is terminating in few days, more generics will be available shortly. The patent in Europe had expired on 21 November, 2013. It is currently registered for sale in many countries. *(Source: Martindale: The Complete Drug Reference. 38th ed., 2014)*

The drug is approved in India for use with three or more companies manufacturing the drug. The tender rates for Rituximab 100 mg/10 mL vial is Rs. 3819 (from Intas) (approx. 60 USD) and for 500 mg/50 mL vial it is Rs. 19,215 (from Dr. Reddy’s – approx. 305 USD)

(7) **Comment briefly on issues regarding cost and affordability of this medicine.**

Addition of Rituximab increases the cost 32 times - cost of CHOP therapy for a patient with BSA 1.8m² for 6cycles is $195.41 and cost of R-CHOP treatment for the same patient for 6 cycles is $6,171.79.

In India, the cost increases by about 6-7 times the cost of CHOP. As there is a government policy that treatment of all cancer patients should be free of cost in certain institutions, it is hoped that inclusion of this drug into EML will further bring down costs.

Ruiz-Delgado, G. J., et al found that the addition of rituximab to CHOP regimen failed to produce positive impact in OS of DLBCL patients. Hence, while implementing R-CHOP in low income settings, the huge cost difference should be considered.

(8) **Any additional comments on the application?**
Lee et al reported a case of pregnant women on R-CHOP regimen giving birth to preterm babies. There were 3 earlier reports of similar complication with this regimen. [25]


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

I propose that Rituximab should be added to the EML for DLBCL as addition of Rituximab to CHOP has changed the prognosis significantly for this cancer.