Proposed medicines(s) for treatment of GIST (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>imatinib</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

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

| Yes | ❌ | No | ❌ |

Comments: Executive summary for adjuvant treatment – high risk needs to be more precisely defined as per the key study: a) primary GIST greater than 5 cm with a mitotic count of greater than 5/50 high power fields (HPF); or b) primary GIST greater than 10 cm with any mitotic rate; or c) primary GIST with a mitotic count of greater than 10/50 HPF.

Testing and imaging for follow up – worth stating that the added benefit of PET/CT in metastatic GIST is unclear.

Mutation testing is not routine.

(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: For advanced GIST the median survival increased from 18 to 57 mths in: Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with
unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008; 26:620.

This study has the longest follow up.

(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: Baseline TSH and repeat if clinically indicated. Also if pre-existing cardiac disease, do LV EF. Replace warfarin with LMWH.

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: Adjuvant therapy is for up to 3 years (not at least 3 years – see page 3). Patients with metastatic or unresectable disease who achieve a response to treatment at an imatinib dose of 400 mg per day should be continued at this dose and assessed for response at regular intervals. Patients who fail to achieve a response to 400 mg per day may have their dose increased to 600 mg per day. Doses higher than 600 mg/day do not show incremental benefit (ie do not recommend up to 800 mg/day – more toxicity tiny change in PFS but not change in OS; possibly benefit exon 9 mutations). For advanced patients – interruption of imatinib results in rapid progression and shouldn’t be tried unless significant toxicity.

(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: 

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

Imatinib and Sunitinib cost effective in most developed countries. Regorafenib is not.

(8) Any additional comments on the application?

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

Recommend Imatinib