Proposed medicines(s) for treatment of mCRC (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>leucovorin (= calcium folinate, folic acid (INN))</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>☒</td>
<td>☐</td>
</tr>
<tr>
<td>oxaliplatin</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>irinotecan</td>
<td>☐</td>
<td>☒</td>
</tr>
<tr>
<td>capecitabine</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: Exec summary – less costly is 5FU/leucovorin and capecitabine. Delete deadly in the first sentence of public health relevance. See comments on adjuvant CRC for inclusion in this section eg regarding screening. The introduction should include that surgical resection is the treatment of choice for isolated liver or lung metastases. Although the 5 year survival in surgical case series is about 40%, only 20% of patients with metastatic disease are surgical candidates. A small number (5-10%) of patients with metastatic disease may become surgical candidates following induction chemotherapy to downsize metastatic lesions.

Diagnostics section should focus on stage IV disease rather than staging per se of CRC. For patients with metastatic disease the aim of staging is to determine and volume of disease and potential for resection.

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

Yes ☐ No ☒

Comments: I wouldn’t include the early studies with cisplatin (ie delete reference 4 from 1993). The first drug to work was 5FU. Then need to include the studies which show 5FU = capecitabine (Van Cutsem, E., P. M. Hoff, P. Harper, et al. 2004. "Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials." Br J Cancer 90(6):1190-
From there the combos of oxaliplatin or irinotecan with fluopyrimidine (ie FOLFOX, FOLFIRI, CAPOX etc).

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

Yes ☐ No ☒

Comments: See above comments

(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:

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: Need to include capecitabine 1250mg/m2 twice daily po days 1-14 given 3 weekly until disease progression.
Standard regimens are until disease progression for metastatic. So need to delete adjuvant with 12 cycles from page 12 – just leave.
Need to include fixed dose leucovorin 50mg as no difference between high and low dose.

(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.
Cost effective in most countries

(8) Any additional comments on the application?
Nil

(9) Please summarise the action(s) you propose the Expert Committee take.
Support oxaliplatin, Irinotecan and capecitabine.