20th Expert Committee on Selection and Use of Essential Medicines

Peer Review Report #1

Early Stage Colon Cancer

Proposed medicines(s) for treatment of Early Stage Colon Cancer (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>calcium folinate (= leucovorin, folinic acid (INN))</td>
<td>❌</td>
<td>☐</td>
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<tr>
<td>fluorouracil</td>
<td>❌</td>
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<tr>
<td>oxaliplatin</td>
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<td>❌</td>
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<tr>
<td>capecitabine</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 ☒ No ☐

Comments: The executive summary: a) should also include the option of monotherapy with capecitabine. This is non-inferior to 5FU/calcium folinate b) bolus fashion should be qualified as weekly bolus. Days 1-5 bolus of 5FU is more toxic than weekly bolus yet the two regimens are equivalent in terms of disease free and overall survival.

Recommendations for screening for CRC in developed countries is high-sensitivity faecal occult blood testing, sigmoidoscopy or colonoscopy from age 50 yrs. Most countries don’t have population based colonoscopy programs for average risk people.

Diagnostics – delete “on the site of metastasis” this is repeated twice. Bone pain is vanishingly rare as a presentation for metastatic CRC – suggest delete.

Delete “she” from the sentence beginning A critical aspect.

The diagnostics include the diagnosis of the disease and also the management of chemotherapy side effects (last paragraph). It would be worthwhile to insert a heading to make the intent of each section clear.

Administration – delete reference to Mayo or make a recommendation that this should not be used because there are safer equally efficacious alternatives.

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

Yes ☒ No ☐
Comments: Delete Mayo as above – it is too toxic and there are safer alternatives. Capecitabine – dose 1250mg/m2 – based on the evidence
Re dose of calcium folinate – this statement could be stronger IE could recommend low dose as the default. Also many centres use fixed dose 50mg – this should be included as an option.

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

Yes ☒ No ☐

Comments: well summarised

(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: Strongly state Mayo is not recommended. Neuropathy
It would be useful to include a comparative table on side effects which vary by method of administration of 5FU (infusional vs bolus).
DPD deficiency – partial or complete have increased risk of severe and can be fatal toxicity – diarrhea, mucositis, pancytopenia. The incidence of deficiency is higher in women and black people.

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: As per all chemotherapy plus monitor for peripheral neuropathy for oxaliplatin – toxicity greater than grade 2 requires dose reduction or delay. Oxaliplatin is an irritant with vesicant properties; can cause laryngo-pharyngeal dysesthesia esp. in response to cold; 5FU is an irritant.

(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: Nil
(7) Comment briefly on issues regarding cost and affordability of treatment. Relatively cheap

(8) Any additional comments on the application? Chemotherapy should start within 8 weeks of surgery, delay beyond this time may compromise outcomes (see x2 metaanalyses).

(9) Please summarise the action(s) you propose the Expert Committee take. Agree that oxaliplatin and capecitabine should be added however it should be made clear that both are only for stage III.