2019 Expert Committee on Selection and Use of Essential Medicines

Peer Review Report

[Addition – Bedaquiline EMLc]

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

Yes ☑ No ☐

Bedaquiline is in the EML (Adults) since 2015 – So the Public Health need for this medicine is already accepted

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

Yes ☐ No ☑

Not applicable as there was no published studies to include
Application has included results from 2 on-going trials which are still recruiting patients

1. Please provide brief comments on any relevant studies that have not been included:

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

Yes ☐ No ☑

Not adequate

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

(See at the end of the report)

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes ☐ No ☑

Please provide brief details:

(See at the end of the report)

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

Uncertain since all what we have for children are results from two ongoing studies (patients are still being recruited and results could change)
ADDITIONAL CONSIDERATIONS:

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

Yes ☑️ No ☐

Please provide brief details:
Since the indication is multi-drug resistant tuberculosis, diagnosis needs special expertise. As it is given for relatively long time, monitoring and follow up are required. New medicine, hence safety data may not be complete.

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

Yes ☑️ No ☐

Off-label use (See at the end of the report)

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

Yes ☑️ No ☐

(2018) The GDG also concluded that the risk-benefit considerations for the use of Bedaquiline in patients aged 6-17 years are similar to those considered for adults but stressed the need for more data before considering an upgrade of this recommendation to a strong one (1)
(2018) Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6-17 years (1)

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

(From application) Bedaquiline is available via GDF, at a price of 400 USD for a 6-month course of adult treatment – However, there had been reports from both TAG and MSF commenting about high cost of bedaquiline and demanding from the manufacturer to reduce the price. It was also noted that the Industry has received considerable public investments on developing and testing this medicine

(10) Any additional comments?

See end of the report

(11) Please frame the decisions and recommendations that the Expert Committee could make.

Not recommended

(12) References (if required)
Summary:

1. There is no doubt about the public health need of the medicine, considering the extent of the problem of multi-drug resistant tuberculosis and the fact that Bedaquiline has been added into adult EML in 2015.
2. Application is to add Bedaquiline into EMLc with age restriction of 6 years
3. Efficacy of Bedaquiline in multi drug resistant tuberculosis in adults has been reviewed by 2015 EML expert committee and considered to be beneficial than the anticipated risks.
4. Current application is for children 6-17 years
5. Application is based on two ongoing (still recruiting) trials in children
6. 2018 update of treatment guidelines for multidrug- and rifampicin-resistant tuberculosis states “Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6-17 years
7. Current application as well as decision to incorporate Bedaquiline into the 2018 revision of guidelines were based on interpretation of two ongoing (still recruiting) clinical trials in children (Annex 10- Assessment of paediatric PK & safety data from paediatric trials of Bedaquiline)- Reference 1 above
8. One key limitation stated in Annex 10 of reference 1 “it was noted that both trials are still ongoing and not all of the data provided were verifiable”
9. Participants

<table>
<thead>
<tr>
<th>TMC207-C211</th>
<th>IMPAACT P1108</th>
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<tbody>
<tr>
<td>Count</td>
<td></td>
</tr>
<tr>
<td>15 only 6 participants with 2 week PK data</td>
<td>10 (only 9 participants with safety data and 7 participants with week 24 PK data</td>
</tr>
<tr>
<td>Age</td>
<td></td>
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<tr>
<td>14-17</td>
<td>6-17</td>
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<tr>
<td>Safety</td>
<td></td>
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<tr>
<td>Only AE for which a safety signal had net been previously reported in adults was elevated PT (N=3, 2 preceded by elevated PT at baseline or screening, all resolved within 4 weeks)</td>
<td>Reported no grade 3 or 4 physical exam or laboratory based safety endpoints.</td>
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<td>Cardiac safety</td>
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<td>6 participants experienced an increase in QTcF of 30-60 msec (concurrent medication – levofloxacin)</td>
<td>1 participant experienced an increase in QTcF of 93.7 msec. (Concurrent medication- levofloxacin and Clofazimine</td>
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<tr>
<td>Exposure</td>
<td></td>
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<tr>
<td>Satisfactory</td>
<td>Satisfactory</td>
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</tbody>
</table>

To me the evidence generated and assessed from these two ongoing studies is not adequate to justify inclusion of Bedaquiline into EMLc or to call it as off label use– To me it is “off evidence use”

10. There had been considerable delay in initiating paediatric investigation after establishing efficacy and safety in adults (3)
11. I consider the use of Bedaquiline as “off evidence” (see above), whereas the application has considered it as “Off label use”
12. WHO has published best practice guidelines (4) for off label use of Bedaquiline and delamanid, but I am unable to consider it as off label use since we do not have adequate evidence.

Additional references
