

<b>F.7</b>	<b>Ethambutol IV infusion - tuberculosis</b>
Does the application adequately address the issue of the public health need for the medicine?	<input type="checkbox"/> <input type="checkbox"/> No <input type="checkbox"/> <p>Comments: The need for IV therapy in general, is not in doubt. IV therapy is recommended in WHO guidelines in specific circumstances (e.g. TB meningitis) . However, it should be noted that the issues for IV ethambutol are not the same as IV rifampicin and IV isoniazid as its role in the treatment of CNS disease is less important and other agents (e.g. quinolones, aminoglycosides) are often used in its place.</p> <p>The application does not provide an estimate of the numbers of patients who might need IV therapy globally. There is reference to the high early mortality on treatment, but the case that this is due to route of administration is not made.</p>
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	<p>Ethambutol plays an important role in the oral treatment of TB and is listed on the EML in its oral preparation only. The proposal is to add IV therapy as an alternative option for treatment.</p> <p>The indication for IV therapy as proposed in the application (P1) include (i) Severe disease (ii) acute or chronic GI disease (iii) severe co-morbidities (iv) patient unwilling or unable to take treatment</p>
Have all important studies and all relevant evidence been included in the application?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <p>If no, please provide brief comments on any relevant studies or evidence that have not been included:</p>
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not applicable <p>Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).</p> <p>Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?</p> <p>The report does not provide evidence of head-to-head comparison in the use of IV therapy against more traditional oral therapy or its use in key populations. Its use would be considered standard of care in those unable to swallow (particularly is reduced level of consciousness) and/or absorb medication</p>

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<p>Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?</p>	<p><input type="checkbox"/> Yes  <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The report does not provide evidence of head-to-head comparison in the use of IV therapy against more traditional oral therapy or its use in key populations. Its use would be considered , though not usually as a preferred options, in those unable to swallow (particularly is reduced level of consciousness) and/or absorb medication</p>
<p>Are there any adverse effects of concern, or that may require special monitoring?</p>	<p><input checked="" type="checkbox"/> No  <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>As noted in the application, there is very limited safety data. Aside from the complications of IV therapy, there are not likely to be specific toxicities associated with IV therapy. I might be expected that toxicities are higher if drug levels are higher. However, safety considerations are not a major concern in this application.</p>
<p>Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)</p>	<p>There are some circumstances (where oral therapy is impossible) that IV therapy will be of clear benefit to the patient. However, for the overwhelming number of patients who are able to take medicine, there is no case for benefit of ethambutol</p>
<p>Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)</p>	<p>There are very few studies that have addressed this question and those presented are of low quality.</p>
<p>Are there any special requirements for the safe, effective and appropriate use of the medicine(s)? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)</p>	<p><input checked="" type="checkbox"/> Yes  <input type="checkbox"/> No  <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>The additional use of IV cannulation as outlined in the application.</p>
<p>Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)</p>	<p><input type="checkbox"/> Yes  <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>No</p>

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<p>Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: <a href="https://www.who.int/publications/who-guidelines">https://www.who.int/publications/who-guidelines</a>)</p>	<p><input type="checkbox"/> Yes X <input checked="" type="checkbox"/> No <input type="checkbox"/> Not applicable</p> <p>Comments:</p> <p>Updated WHO guidelines for TB treatment in 2017 make reference to IV steroid treatment, but not antiTB therapy. There is no reference to IV therapy in 2010 guidelines</p>
<p>Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.</p>	<p>There are list prices presented for IV medication in the application. Data is presented showing a lower price for oral medication in France medication. This is not surprising given the size of market for the two formulations. .</p>
<p>Any additional comments</p>	
<p>Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.</p>	<p>In section 11 of the application, it is stated that IV ethambutol is a rare presence on most of the world markets. This would benefit from a reference to assess the scale and nature of the problem. The assertion that any lack of access is due to the fact that it is not listed on the EML/EMLc is not supported by evidence.</p> <p>Similarly, a concern expressed previously in relation to listing has been the potential to create financial incentives for practitioners to prescribe TB therapy when it is not required. However, more data would be helpful in understanding the extent to which this is a problem and whether IV therapy when provided, is covered by national programmes.</p> <p>The consideration of ethambutol differs from that for rifampicin and isoniazid as it would be generally considered that other agents may be preferable when IV therapy required</p>
<p>References (if required)</p>	