Expert peer review on application for Review of MDR TB therapy for children

4. Assessment of public health need (same for all medicines in review)
   a. Please provide the public health need for this product (1-2 sentences)

   MDR in children a growing problem

   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

   Current MDR-TB guidelines recommend including a second-line injectable agent from Group 2, a fluoroquinolone from Group 3, and then adding additional drugs from Groups 4 and 5 to create a treatment regimen with at least 4-5 active drugs.

   Currently in list: amikacin, capreomycin, cycloserine, ethionamide, kanamycin, ofloxacin and p-aminosalicylic acid

   This review also includes: will also include levofloxacin, moxifloxacin, and terizidone, clofazamine and linezolid

   Main issue is whether more medicines should be added to list to provide more options from each group (1 – 5).

   Each group of medicines is reviewed separately:
2 – Fluoroquinolones – Ofloxacin, Levofloxacin, and Moxifloxacin

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes – search is documented, thorough

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Data in humans from observational studies of adults: Cochrane Review did not identify any randomised trials of FLQs specifically for MDR-TB treatment (100). Multiple systematic reviews also did not identify any randomized trials in MDR-TB, but did synthesize the many observational studies (106-108). Two recent individual patient data (IPD) meta-analyses used reports identified in these systematic reviews to provide a more detailed analysis. The first included data from 9,153 patients from 32 observational cohorts, and reported improved treatment success with the use of a later-generation FLQ versus no FLQ (adjusted Odds Ratio [aOR] 2.8, 95% CI 1.3-6.1) and versus ofloxacin (aOR 2.1, 95% CI 1.2-3.9), and with the use of ofloxacin versus no FLQ (aOR 2.0, 95% CI 1.2-3.3) (106). A second IPD meta-analysis found that the adjusted odds ratios of treatment success versus treatment failure, relapse or death, for those with MDR-TB and second-line-injectable-resistance, MDR-TB and FLQ resistance, and XDR-TB, compared to MDR-TB alone were 0.6, 0.4, and 0.2 respectively (109).


In a systematic review of children treated for MDR-TB, FLQs were a component of the treatment regimen in all included studies, which had a pooled treatment success of 81.67% (6). More recently, in a cohort of children with MDR-TB in which a FLQ was a key component of the treatment regimen, 137/149 (92%) had cure or probable cure, further supporting its use. No comparators.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      Limited data, similar profile to adults, CNS effects, prolongation of QT interval.
      Cartilage damage main concern in children - reversible

3. Assessment of cost and availability
   a. Have all relevant data provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences) low cost
   d. Is the product available in several low and middle income countries?
      Yes, multiple manufacturers

4. Assessment of public health need (same for all medicines in review)
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
      yes, WHO and multiple guidelines for adults

5. Are there special requirements for use or training needed for safe/ effective use?
   If yes, please provide details in 1-2 sentences

6. Is the proposed product registered by a stringent regulatory authority?
   Yes, US FDA but not for this indication

7. Any other comments
   Pediatric formulations needed

8. What is your recommendation to the committee (please provide the rationale)

   Agree with review recommendation: recommend that levofloxacin or moxifloxacin due to their greater potency, be the preferred FLQ for treatment of DR-TB in children. Recommend that ofloxacin remain on the Essential Medicine List for DR-TB in children. Little clinical differentiation among the drugs.
3 Aminoglycosides and Cyclic-polypeptides – Amikacin, Kanamycin, and Capreomycin

Group 2 drugs

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes, to my knowledge
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Limited data from human studies, particularly in children – meta-analyses of IPD observational data: The second IPD meta-analysis showed that of patients with XDR-TB, those who had resistance to both an aminoglycoside (kanamycin or amikacin) and to capreomycin had a significantly lower odds of success compared to those with XDR alone (aOR 0.4, 95% Confidence Interval 0.2-0.8. The third IPD meta-analysis found that the adjusted odds ratios of treatment success versus treatment failure, relapse or death, for those with MDR-TB and SLI-resistance, MDR-TB and fluoroquinolone resistance, and XDR-TB, compared to MDR-TB alone were 0.6, 0.4, and 0.2 respectively (109).

2. Assessment of safety
   a. Have all relevant studies on safety been included
      yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   ototoxicity main risk – 24% in one cohort

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   more expensive than fluoroquinolones

   d. Is the product available in several low and middle income countries?

   Several manufacturers

4. Assessment of public health need
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

   From report: “The most up-to-date guidance from the World Health Organization recommends an 8-month long intensive phase, increased from 6 months in previous guidelines, which would generally include a SLI drug (232), though children will rarely require treatment with a SLI drug beyond 6 months, and often do equally well with shorter courses (114) (Unpublished data – James Seddon, H Simon Schaaf, et al).”

4
5. Are there special requirements for use or training needed for safe/effective use?
   Iv or im administration

6. Is the proposed product registered by a stringent regulatory authority?
   Yes, US FDA

7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

   Agree with report: Retain on eml as second line, limit max dose
**4 – Ethionamide and Prothionamide**

1. **Assessment of efficacy**
   a. Have all relevant studies on efficacy been included
      Yes

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Observational data, an individual-patient meta-analysis of over 9,153 patients with MDR-TB, in which use of ETH or PTH was associated with an increased odds of treatment success versus failure or relapse (aOR 1.7, 95% CI 1.3–2.3) and versus failure, relapse or death (aOR 1.7, 95% CI 1.4–2.1) (106).

   ETH was a component of the usual treatment regimens in all the cohorts included in a recent systematic review of children with MDR-TB, which reported a pooled treatment success of 81.67% (6) – no comparators. Well tolerated

2. **Assessment of safety**
   a. Have all relevant studies on safety been included
      Yes

   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   GI intolerance, thyroid dysfunction documented in children

3. **Assessment of cost and availability**
   a. Have all relevant data on safety provided
      Yes

   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Cost similar to second line, older medicines

   d. Is the product available in several low and middle income countries?

   Multiple manufacturers

4. **Assessment of public health need**
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

   no, recommended in Lancet article

5. **Are there special requirements for use or training needed for safe/effective use?**
   If yes, please provide details in 1-2 sentences

6. **Is the proposed product registered by a stringent regulatory authority?**
   Yes USFDA Germany
7. Any other comments

Ethionamide is currently listed as an Essential Medicine for adults and children. Prothionamide is not currently listed as an Essential Medicine for adults or children.

8. What is your recommendation to the committee (please provide the rationale)

Weak recommendation to retain ethionamide. Do not list prothionamide.
5 – Cycloserine and Terizidone

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   very sparse data, case series in children, may be more on terizidone in German language

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   CNS toxicity – 20-30%

3. Assessment of cost and availability
a. Have all relevant data on safety provided
   Yes

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   cycloserine less expensive and more manufacturers

d. Is the product available in several low and middle income countries?
   Limited number of manufacturers

4. Assessment of public health need
b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable
   no

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences

6. Is the proposed product registered by a stringent regulatory authority?
   Yes, US FDA (cycloserine) and Germany (terizidone)

7. Any other comments
   Cycloserine is on EML
8. What is your recommendation to the committee (please provide the rationale)

**Review recommends:** As such, we recommend that cycloserine remain an Essential Medicine for children with MDR-TB, and we would recommend that terizidone be an alternative to cycloserine.

Evidence supporting this recommendation is very weak, not currently recommended in guidelines. Recommend deletion of cycloserine from EML
6 – Para-aminosalicylic Acid (PAS)

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Older studies from 1950s and 60s, not trials.

   Observational data, Recent individual-patient meta-analysis evaluating the impact of second-line drug resistance in patients with XDR-TB reported that, relative to those with XDR alone, patients with XDR and additional resistance to at least one Group IV drug had an adjusted Odds Ratio of treatment failure or death of 2.6 (95% CI 1.1, 6.7).

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   GI intolerance, hypothyroidism main risk, documented in children

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   more expensive than other medicines in this review

   d. Is the product available in several low and middle income countries?

   Limited number of manufacturers

4. Assessment of public health need
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

   yes, recommended as group 4 drug in WHO guideline

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences

6. Is the proposed product registered by a stringent regulatory authority?
   Yes US FDA
7. Any other comments

PAS granules and PAS-sodium remain Essential Medicines for children with drug-resistant TB.

8. What is your recommendation to the committee (please provide the rationale)

Very weak evidence supports keeping this medicine on the list, but it is recommended in WHO guidelines as a group 4 drug in WHO guideline, so retain on list. Granules need repacking
7 – Linezolid

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Two reviews of case series, small observational studies. No active comparators.

   I RCT – no difference in culture conversion at 6 months. 13/38 successfully completed treatment with no relapse.

   Four clinical trials in children for other indications and short therapy duration, less than 28 days. Case reports in children with DR-TB, culture conversion the outcome. No pharmacokinetic studies in children.

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   Adverse effects are time and dose dependent. Peripheral neuropathy with prolonged duration. Optic neuropathy with vision loss. “In a systematic review of linezolid-treated adults with MDR-TB, 47.1% reported peripheral neuropathy and 13.2% optic neuritis.” Documented in children.

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

   on patent, expensive: 60,000 U.S. dollars for one patient for a 2 year course (in South Africa)

   d. Is the product available in several low and middle income countries? no

4. Assessment of public health need
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

   this specific product not discussed in the WHO guidelines

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences

6. Is the proposed product registered by a stringent regulatory authority?
   Yes, US FDA for different indication
7. Any other comments

8. What is your recommendation to the committee (please provide the rationale)

Do not add to list due to high cost, low availability, weak evidence of efficacy and safety concerns
8 – Clofazimine

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes
   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Has been evaluated as part of multi-drug regimen in one trial. One systematic review of observational, uncontrolled studies showed wide range of treatment success

No pharmacokinetic studies in children

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

Sparse data, skin discoloration primary effect

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      Yes
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

one manufacturer, price not provided

d. Is the product available in several low and middle income countries?

no

4. Assessment of public health need
   b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

not this specific medicine

5. Are there special requirements for use or training needed for safe/effective use?
   If yes, please provide details in 1-2 sentences

6. Is the proposed product registered by a stringent regulatory authority?
   Yes, US FDA in 1986 for leprosy, not this indication

7. Any other comments

2 ongoing studies. Listed on EML for leprosy for adults and children

8. What is your recommendation to the committee (please provide the rationale)

Do not add to EML for this indication