19th Expert Committee on The Selection and Use of Essential Medicines

April 8-12 2013

Expert peer review on application for second-line antituberculosis drugs in children

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)

      There are no randomized controlled trials that have evaluated the incremental efficacy of any of the drugs in Groups 2 to 4 for treating MDR-TB. Notwithstanding, treatment regimens containing 4 to 5 drugs from these groups have become the standard of care for MDR-TB. Thus, evidence to inform the choice is essentially limited to outcome data from treatment cohorts. Such data indeed confirm the efficacy of the drugs in groups 2 to 4 for treating MDR-TB. Moreover, these data indicate that later generation fluoroquinolones such as levofloxacin and moxifloxacin might be more efficacious than ofloxacin in MDR-TB.

   c. Please provide any additional relevant information with reference

      None.

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)

      Safety data from children with MDR-TB are very limited. Available data, however, do not suggest that the frequency and profile of adverse effects in children is any different from adults. This seems to be true for fluoroquinolones as well.

   c. Please provide any additional relevant information with reference

      None.

3. Assessment of cost and availability
   a. Have all relevant data on cost been 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)

      Levofloxacin costs the same as ofloxacin; but, moxifloxacin is more costly than ofloxacin.

      Linezolid and terizidone are costly.
c. Please provide any additional relevant information with reference

None.

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

Terizidone availability may be limited. Others are available.

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

The 62nd World Health Assembly had adopted a resolution (WHA62.15) urging Member States to take action towards achieving universal access to diagnosis and treatment of M/XDR-TB by 2015. Recent data indicate that MDR-TB is as common among children as in adults with TB. In fact, children might be at a higher risk of MDR-TB in certain southern African countries.

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

Yes.


5. Are there special requirements for use or training needed for safe/effective use?

If yes, please provide details in 1-2 sentences

Yes. Availability and use of these drugs should be restricted to DOTS-Plus programmes and centres experienced in treating MDR-TB patients. Otherwise, unregulated use of these drugs might lead to amplification of drug-resistance in TB.

6. Is the proposed product registered by a stringent regulatory authority?

*No – fluoroquinolones (ofloxacin, levofloxacin and moxifloxacin), linezolid, are not approved for the treatment of TB.

Ethionamide is approved in the USA but prothionamide is approved for tuberculosis only in Germany. Terizidone is approved in Germany for tuberculosis in adolescents aged 14 years or older and in adults.

7. Any other comments

The review is extremely well written with all the essential elements included. Child friendly formulations may need to be made available widely to permit appropriate dosing in small children.

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

All three second-line injectables in group 2 (amikacin, kanamycin, and capreomycin) should be retained in the EML. Cross-resistance to these agents is not invariable and resistance to any one of injectable second-line drugs is associated with a modest decrease in treatment success. (Data, however, indicate that use of any of these second-line injectables is not independently associated with treatment success.)

Levofloxacin should replace ofloxacin on the EMLc for the treatment of MDR-TB, the reasons being that the former is more efficacious and costs the same as ofloxacin. However, it may be stated that in the event that levofloxacin is unavailable, ofloxacin may be used as an alternative.

Ethionamide should remain on the EML. Addition of prothionamide is not required, since it does not offer any advantage over ethionamide and exhibits complete cross-resistance.

Cycloserine should remain on the EML.

Addition of terizidone is not required, since it does not offer any great advantage over cycloserine and available information on terizidone in children is sparse.

Para-aminosalicylic acid (PAS) should remain on the EML in view of the robust data on its efficacy in the pre-rifampicin era.

Linezolid and clofazimine cannot be considered “essential” as only a subset of MDR-TB patients would need them as a part of an effective regimen. Further, present data do not suggest that clofazimine is effective for MDR-TB. On the other hand, empirical evidence suggests good efficacy for linezolid, but its use for MDR-TB is associated with a very high risk of adverse events and high cost. Hence linezolid and clofazimine should not be included in the EMLc at present until more evidence is available.