



SUMMARY POINTS ON PEDIATRIC FORMULATIONS OF SECOND-LINE DRUGS FOR TUBERCULOSIS

This is an exciting time in the treatment of children with drug-resistant tuberculosis (DR-TB), and for the first time ever, dispersible, child-friendly formulations of many of the second-line drugs are now available through The StopTB Partnership's Global Drug Facility (GDF). While the biggest challenge in the field of pediatric DR-TB is diagnosis and treatment of the estimated 24-33,000 children whom become sick with DR-TB each year, those who are started on treatment receive adult medications that must be cut, crushed and mixed to deliver to children. The novel pediatric formulations will revolutionize the treatment of DR-TB in children and facilitate therapy for children, caregivers, health care providers and treatment programs. Here are some key summary points on the novel drug formulations.

- The drugs available include scored dispersible tablets of the following medications: ethambutol, pyrazinamide, moxifloxacin, levofloxacin, and ethionamide. A 125mg capsule of cycloserine is also available. Soon scored, dispersible tablets of isoniazid and linezolid will likely be quality-assured.
- These products offer distinct advantages over the current treatment practices in pediatric DR-TB. Currently, all children treated globally are given adult tablets because there have been no other alternatives available. Many adult tablets are not scored—meaning active drug is not equally distributed throughout the tablet—and are not meant to be crushed or mixed with food, and may result in sub-optimal treatment for children. For example, pharmacokinetic data from a study of the dispersible levofloxacin tablet done in Cape Town found more consistent therapeutic levels were reached with the new pediatric formulation than compared with using adult tablets. Furthermore, dosing these adult tablets requires significant amounts of work from pharmacy and hospital staff and are usually too complicated to be managed in homes or health centers. This means children are hospitalized for prolonged periods with significant costs to the health system and to the child's development and return to health.
- The new dispersible tablets have been reviewed by the WHO pre-qualification system and are recommended products that have undergone quality testing, including bioequivalence studies. The GDF has a further quality assurance system in place so that countries can be sure they are receiving products that meet high standards.

- The drugs will be available from the GDF and should be ordered using the standard forms. Product should be ordered immediately after quantification is done and orders should not be placed on hold to wait for yearly procurement cycles. Due to the large minimum order quantities and small demand, there may be delays in deliveries while orders are consolidated.
- The drugs will NOT be registered in any countries in the near future and therefore they will need to be imported via a waiver mechanism. The mechanisms to be used will vary depending on the country, but they should be similar to those that were used import new drugs such as bedaquiline.
- A forecasting approach has been developed for initial forecasts and can be used to quickly estimate need for the next 12 months. This approach is based on past numbers of children treated for DR-TB disease and infection in the country. Because the new products are dispersible, their shelf-life is short and therefore it is recommended that countries be realistic in their forecasts and ordering. Stockouts should be avoided at all costs, but should a problem arise, then the standard practice of using adult formulations can be used as a fall back mechanism to avoid treatment interruptions.
- Assessments of the acceptability of these new formulations will be built in to their use, depending on country-specific objectives. It is anticipated these new formulations will be a marked improvement over the current practice based on data from a formal study of the levofloxacin dispersible formulation done in Cape Town, which showed the new formulation was greatly preferred over the adult formulations by children, caregivers and providers.
- Pediatric formulations are the standard of care in pediatric HIV and more recently in pediatric TB. Thus the move to these formulations for pediatric DR-TB is in keeping with best practices in the treatment of children with chronic infectious diseases. The continued use of adult formulations to treat children with DR-TB is not consistent with Good Clinical Practice and will need to be justified in the setting of the availability of these pediatric products.
- Prices for the tablets are available on the GDF website (http://www.stoptb.org/gdf/drugsupply/drugs_available.asp). It is estimated that the use of these products will result in substantial cost savings for programs due to decreased hospitalization for children with DR-TB (currently done because the preparation of second-line drugs for children is too complicated in the community) and decreased personnel time needed to prepare and administer the tablets by pharmacy, nursing, and ancillary staff.
- The Sentinel Project on Pediatric Drug-Resistant TB is able to provide training and technical support around data collection, implementation and optimal product use. GDF is able to provide technical assistance to support quantification and forecasting. A series of field tools and standard operating procedures will be available at <http://sentinel-project.org/>. For additional information, please contact Dr. Jennifer Furin at jenniferfurin@gmail.com.