

Management of second-line antituberculosis drugs

17.1 Chapter objectives

This chapter provides information on the procedures for procurement and management of the second-line drugs used in the treatment of drug-resistant TB. Information is included on procurement of drugs through the GLC mechanism.

17.2 WHO Model List of Essential Medicines: second-line antituberculosis drugs

Essential medicines are those that satisfy the health-care needs of the majority of the population. The drug selection is based on the development of treatment guidelines and on the evidence underlying the development of those treatment guidelines. The current version of the WHO Model List of Essential Medicines, the 14th list, dates from March 2005 and includes nine second-line drugs (see Box 17.1). This Model List does not imply that no other drugs could be useful for management of MDR-TB, but simply that these basic drugs, when used in accordance with appropriate therapeutic guidelines, cost-effectively meet the needs of an important proportion of the population.

BOX 17.1

Second-line antituberculosis drugs included in the WHO Model List of Essential Medicines

Ciprofloxacin	Levofloxacin	Ofloxacin
Kanamycin	Amikacin	Capreomycin
Cycloserine	Ethionamide	<i>P</i> -aminosalicylic acid

17.3 Drug management cycle of second-line antituberculosis drugs

The management cycle of drugs comprises six elements: drug selection, quantitative assessment of drug requirements, management of procurement, distribution, assurance of drug quality and ensuring rational drug use.

A number of factors must be considered when selecting second-line drugs, including the efficacy of the drugs, the treatment strategy, possible adverse effects and the cost of the treatment (see Chapter 7).

Accurate demand forecasting for second-line drugs, i.e. correct quantification of the drug needs for a specific period of time, is one of the elements that guarantees an uninterrupted drug supply. There are two main approaches for demand forecasting:

- The most precise method is usually the consumption-based approach, with projections of future needs based on records of past consumption of individual drugs. This method assumes that the data are complete, accurate, and properly adjusted for stock-outs and expected changes in demand and use. However, this method is recommended only for an established programme managing drug-resistant TB.
- The morbidity-based approach method is recommended for new projects. In this method, the treatment regimen (standardized, individualized or empirical) and the number of patients to be treated with each regimen are taken into account. Several other key factors must also be considered, including the existing stock, pace of patient enrolment, lead time for delivery, safety stock needed and the shelf-lives of the drugs. Shelf-lives of second-line drugs are longer than those of first-line drugs, ranging from 18 to 36 months. It is recommended that stock should be sufficient to cover for the delivery delay.

An inventory management system needs to be set up to ensure a safety stock and optimal stock movement, and to provide an accurate source of information for drug demand forecasting.

Effective management of procurement ensures the availability of the drugs selected, in the right quantities, at the right time, at affordable prices and of acceptable standards of quality. For more information see the manual *Operational principles for good pharmaceutical procurement (I)*.

Management of drug importation and distribution requires that all port and customs clearance forms are duly completed. The formalities involved depend on whether the drugs have been registered in the importing country. In many countries it is possible to obtain an exemption on the basis of the public health interest, allowing the national TB control programme to import drugs that are not locally registered.

To preserve quality, the drugs should be stored and transported by the supplier and the national TB control programme following “Good Storage Practices” and the recommendations of the manufacturer regarding temperature and humidity.¹

The quality assurance component of a drug supply system makes certain that each drug used by a patient is safe, efficacious and of appropriate quality. All drugs used in a regimen for drug-resistant TB should meet the WHO recommended standards for safety, efficacy and quality. The WHO prequali-

¹ For a more detailed discussion see “Guide to good storage practices for pharmaceuticals” of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Annex 9 (2).

fication project¹ aims at producing a list of second-line drugs and manufacturers that meet specific approved standards. The manufacturers selected to supply second-line antituberculosis drug should be (as a minimum) compliant with the WHO standards of “Good Manufacturing Practices”.²

Access to second-line drugs must be accompanied by measures to ensure rational drug use. Misuse of the drugs will result in loss of susceptibility to the second-line agents, producing circulating strains that will be extremely difficult to cure with currently available medicines. Box 17.2 lists the most important elements to consider when preparing a plan to procure second-line drugs for the management of MDR-TB.

BOX 17.2

Main elements to consider when planning procurement of second-line antituberculosis drugs

- Drug forecast based on treatment regimen, cohort size and pace of patient enrolment
- Drug registration status of products selected
- Drug labelling
- Customs regulations for importing drugs
- Shelf-life of the products
- Lead-time for delivery of the drug request
- Estimated size of buffer stock

17.4 The WHO Green Light Committee mechanism

National TB control programmes have had to face several obstacles in the area of drug procurement, including the high cost of second-line drugs, the lack of local capacity to apply a stringent quality assessment of drug manufacturers and their products, inconsistent availability, and the lack of guidelines on the proper use of second-line drugs. In order to tackle these obstacles, the GLC mechanism was set up in 2000 by WHO and its partners in the Stop TB Working Group on DOTS-Plus. GLC-approved projects purchase directly from agent(s) contracted by WHO to procure the drugs. By utilizing the GLC mechanism, a DR-TB control programme benefits from access to quality-assured drugs at concessionary prices and a continuous drug supply to the approved cohorts of patients. For further information, including details of technical assistance offered by the GLC, see Chapter 1 and Annex 1. The most up-to-date information is available on the WHO web page.³ For approved projects, additional information is provided on drug procurement through the *Procurement manual for DOTS-Plus projects approved by the Green Light Committee* (3).

¹ <http://mednet3.who.int/prequal/>

² As defined in “Good Manufacturing Practices for pharmaceutical products: main principles” of the *WHO Expert Committee on Specifications for Pharmaceutical Preparations*, Annex 4 (2).

³ <http://www.who.int/tb/dots/dotsplus/en/>

References

1. *Operational principles for good pharmaceutical procurement*. Geneva, World Health Organization, 1999 (WHO/EDM/PAR/99.5).
2. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003 (Technical Report Series No. 908).
3. *Procurement manual for DOTS-Plus projects approved by the Green Light Committee*. Geneva, World Health Organization, 2003 (WHO/HTM/TB/2003.328 Rev.1).