# Bedaquiline

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.5. Antituberculosis medicines

EMLc | ATC codes: J04AK05

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| **Indication** | Multi-drug resistant Mycobacterium tuberculosis ICD11 code: ML32.00 |
| **INN** | Bedaquiline |
| **Medicine type** | Chemical agent |
| **List type** | Complementary |
| **Additional notes** | Medicines for the treatment of multidrug-resistant tuberculosis (MDR-TB) should be used in specialized centres adhering to WHO standards for TB contol. |
| **Formulations** | Oral > Solid: 100 mg tablet ; 20 mg tablet (EMLc) |
| **EML status history** | First added in 2015 (TRS 994)<br>Changed in 2019 (TRS 1021)<br>Changed in 2021 (TRS 1035) |
| **Sex** | All |
| **Age** | Also recommended for children |
| **Age restriction** | ≥5 years |
| **Therapeutic alternatives** | The recommendation is for this specific medicine |
| **Patent information** | Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org<br>Read more about patents. |
| **Wikipedia** | Bedaquiline |
| **DrugBank** | Bedaquiline |

## Expert Committee recommendation

The Expert Committee recognized the importance of the availability of age-appropriate, child-friendly formulations of medicines for the treatment of multidrug-resistant tuberculosis to meet the dosing and administration needs of children. The Expert Committee noted bedaquiline, as an oral 100 mg tablet formulation, was included on the complementary list of the EML as a reserve second-line medicine for treatment of multidrug-resistant tuberculosis in adults in 2015. In 2019, it was added to the complementary list of the EMLc as a reserve second-line medicine for the treatment of multidrug-resistant tuberculosis in children aged 6 years and older. The Committee noted the acceptable pharmacokinetic data indicating therapeutic bedaquiline exposure at the recommended dose in children using the proposed 20 mg tablets formulation. The Committee therefore recommended the addition of the new formulation of bedaquiline 20 mg tablets to the complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis in children aged 5 years and older, in line with the updated WHO treatment guidelines. The Committee did not recommend the addition of this formulation to the EML for the treatment of adults, noting the high pill-burden required to achieve the recommended adult dose. The Committee also noted that the bioavailability of the 100 mg tablet formulation, when crushed or suspended in water, was not altered. The Committee considered that the 100 mg tablet formulation, crushed or suspended in water, was a suitable alternative for adult patients unable to swallow intact tablets and allowed achievement of the recommended dose with a much lower pill burden.

## Background

Bedaquiline 100 mg tablets were added to the complementary list of the EML in 2015 as a reserve second-line medicine for

treatment of multidrug-resistant tuberculosis in adults (1). In 2019, bedaquiline 100 mg tablets were added to the complementary list of the EMLc for the treatment of multidrug-resistant tuberculosis in children aged 6 years and older, in line with updated WHO treatment guidelines. It was noted that the extrapolation of evidence from adult data to children suggested therapeutic bedaquiline exposure in children and no increased safety risk (2).

## Public health relevance

The public health relevance of effective treatments for multidrug-resistant tuberculosis is well established. According to WHO's 2020 global tuberculosis report, there were an estimated 465 000 new cases of multidrug-resistant tuberculosis and rifampicin-resistant tuberculosis globally in 2019, with multidrug-resistant tuberculosis accounting for 78% of these cases. An estimated 3.3% of new tuberculosis cases and 17.7% of retreated tuberculosis cases had multidrug-resistant or rifampicin-resistant tuberculosis in 2019. In total, 333 304 people (all ages) were treated for multidrug-resistant or rifampicin-resistant tuberculosis in 2018–2019, 8986 of whom were children < 17 years (3). Based on mathematical models, about 3% of children with tuberculosis are estimated to have multidrug-resistant tuberculosis. Global estimates of the burden of multidrug-resistant tuberculosis in children range from 25 000 to 32 000 incident cases annually (4,5).

## Benefits

Paediatric data for bedaquiline have come from the TMC207-C211 trial (NCT02354014), which is an ongoing, open-label, phase II trial. The trial is designed to evaluate the pharmacokinetics, safety, tolerability and antimycobacterial activity of bedaquiline in combination with a background regimen of multidrug-resistant tuberculosis medications in children and adolescents 0 months to < 18 years of age who have confirmed or probable pulmonary multidrug-resistant tuberculosis (6). The application presented data from the week 24 primary analyses of cohort 1 (≥ 12 to < 18 years, using bedaquiline 100 mg tablets) and cohort 2 (≥ 5 to < 12 years, using bedaquiline 20 mg tablets). Cohort 1 included 15 patients with multidrug-resistant tuberculosis aged 12 to < 18 years, with baseline bodyweight ranging from 38 kg to 75 kg. These patients received bedaquiline 100 mg tablets at the recommended adult dose (400 mg once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks) in combination with a background regimen. Pharmacokinetic parameters of bedaquiline in this cohort were comparable to those in adults. In a subset of patients with culture-positive pulmonary multidrug-resistant tuberculosis at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 75% (6/8) of patients at week 24. Cohort 2 included 15 patients with multidrug-resistant tuberculosis aged 5 years to < 12 years, with baseline bodyweight ranging from 14 kg to 36 kg. These patients received bedaquiline 20 mg tablets at a dose of 200 mg once daily for 2 weeks, followed by 100 mg three times a week for 22 weeks, in combination with a background regimen. Complete pharmacokinetic data were obtained for 10 patients. In nine of these 10 patients, the mean bedaquiline maximum plasma concentration (Cmax) and area under the curve at 24 hours (AUC24h) were similar to that of adult patients with multidrug-resistant tuberculosis receiving the recommended adult dosage regimen. In a subset of patients with culture-positive pulmonary multidrug-resistant tuberculosis at baseline, treatment with bedaquiline resulted in conversion to a negative culture in 100% (3/3) of patients at week 24. Model-based pharmacokinetic analysis of bedaquiline was performed on data from patients in cohorts 1 and 2 from which the recommended dosage regimens for children and adolescents were developed.

## Harms

The safety assessment of bedaquiline presented in the application was based on the week 24 analysis of 30 paediatric patients in cohorts 1 and 2 (6). In cohort 1, overall, safety was generally consistent with observations from previous clinical studies with bedaquiline in adults. The most common adverse reactions were arthralgia in 6/15 (40%) patients, nausea in 2/15 (13%) patients and abdominal pain in 2/15 (13%) patients. No deaths occurred among the 15 patients during treatment with bedaquiline. Observed laboratory abnormalities were comparable to those in adults. In cohort 2, the most common adverse reactions were related to increased aminotransferases, including from hepatoxicity (3/15, 33%), which led to discontinuation of bedaquiline in three patients. Elevations in liver enzymes were reversible on discontinuation of bedaquiline and some of the background regimen drugs. No deaths occurred among these 15 patients. The bedaquiline dosing regimen for 24 weeks as part of multidrug-resistant tuberculosis therapy was generally safe and anticipated toxicities were manageable with careful monitoring and modifications of the tuberculosis treatment regimen.

## Additional evidence

A 2018 study evaluated the relative bioavailability, safety, acceptability and palatability of bedaquiline 100 mg tablets suspended in water compared with intact tablets (7). Bioavailability of the 100 mg tablet was not altered when crushed and suspended in water before administration and the suspension was well tolerated. These findings suggest that the 100 mg tablet formulation may also be suitable for administration to children unable to swallow intact tablets.

## Cost / cost effectiveness

Janssen Pharmaceutica, N.V. has a long-term agreement with the International Dispensary Association for the supply of bedaquiline by order and account of the Stop TB Global Drug Facility. The Global Drug Facility is an initiative that provides a unique package of services, including technical assistance in tuberculosis drug management and monitoring of tuberculosis drug use, to patients in need in over 135 countries. To improve lead time for delivery to countries the Global Drug Facility has setup a strategic rotating stockpile, with unassigned stock always available at the International Dispensary Association. Bedaquiline 20 mg is accessible through Global Drug Facility for US$ 25.53 for a bottle of 60 tablets. This equates to a price of US$ 200.00 for a full treatment cycle (470 tablets over 24 weeks) in children weighing 15 kg to < 30 kg, i.e. administering half the adult dose. Bedaquiline 20 mg tablet is also indicated for adults and/or adolescents who have trouble swallowing, for which a complete treatment cycle would require 940 tablets and cost US$ 400. Janssen has made bedaquiline 100 mg tablets available through the Global Drug Facility at a price of US$ 340 for a 6-month treatment course (at the adult dose) for more than 135 eligible countries. The company will also provide an escalating percentage of free goods when certain volume thresholds are reached on an annual basis: 10% above 55 000 treatment courses, 20% above 125 000 and 30% above 200 000 (10).

## WHO guidelines

The 2019 WHO consolidated guidelines on drug-resistant tuberculosis treatment (8) recommend that bedaquiline may be included in longer multidrug-resistant tuberculosis regimens for patients aged 6–17 years (conditional recommendation, very low certainty in the estimates of effect). The recommended weight-based regimen for patients 15–29 kg is 200 mg daily for 2 weeks, followed by 100 mg three times a week for 22 weeks. The 2020 WHO consolidated guidelines on tuberculosis treatment note that the US Food and Drug Admiration has extended approval for the use of bedaquiline for children aged 5 years and older (9). However, these data have not yet been assessed by WHO.

## Availability

As the 20 mg tablet formulation of bedaquiline only received US Food and Drug Administration approval on 27 May 2020, the total distribution of this formulation has been limited so far.

## Other considerations

Bedaquiline 20 mg tablets are functionally scored tablets that can be administered by four different methods. • swallowed whole, or divided in half, with water for patients able to swallow intact tablets; • dispersed in water (maximum five tablets in 5 mL water) for patients unable to swallow intact tablets; • crushed and mixed with soft food; • dispersed in water (five tablets in up to 50 mL water) and administered via nasogastric tube. The pill burden for the 20 mg tablet is high for patients of body weight ≥ 30 kg, considering the adult dosage of 400 mg (20 tablets) daily for 2 weeks, followed by 200 mg (10 tablets) three times per week for 22 weeks. Thus, the adult dose would be achieved more conveniently with the 100 mg tablets.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2015 ( WHO Technical Report Series, No. 994; https://apps.who.int/iris/handle/10665/189763, accessed 19 August 2021).
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3. Global tuberculosis report 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336069, ac cessed 19 August 2021).
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5. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. Lancet Infect Dis. 2016;16(10):1193–201.
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10. Stop TB Partnership and Johnson & Johnson, with support from USAID and The Global Fund, announce price reduction for SIRTURO® (bedaquiline) for treatment of drug-resistant tuberculosis in low- and middle-income countries [internet]. Johnson & Johnson; 6 July 2020 (https://www.jnj.com/stop-tb-partnership-and-johnson-johnson-with-support-from-usaid-and-the-global-fund-announce-price-reduction-for-sirturo-bedaquiline-for-treatment-of-drug-resistant-tuberculosis-in-low-and-middle-income-countries, accessed 19 August 2021).