# Moxifloxacin

Essential medicine status ✓



ATC codes: J01MA14

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| Indication | Tuberculosis ICD11 code: 1B4Z |
| INN | Moxifloxacin |
| Medicine type | Chemical agent |
| Antibiotic groups | W WATCH |
| List type | Core |
| Formulations | Oral > Solid > tablet: 400 mg |
| EML status history | First added in 2021 (TRS 1035) |
| Sex | All |
| Age | Adolescents and adults |
| Therapeutic alternatives | The recommendation is for this specific medicine |
| Patent information | Patents have expired in most jurisdictions<br>Read more about patents. |
| Wikipedia | Moxifloxacin |
| DrugBank | Moxifloxacin |

## Expert Committee recommendation

The Expert Committee noted that tuberculosis is a major cause of ill health and one of the top 10 causes of death worldwide. About a quarter of the world's population is infected with Mycobacterium tuberculosis, with the life-time risk of developing tuberculosis disease of about 5–10% among those infected. The Committee noted the results from Study 31 that a shorter 4-month regimen containing isoniazid, moxifloxacin, rifapentine and pyrazinamide was shown to be non-inferior to the standard 6-month regimen containing ethambutol, isoniazid, pyrazinamide and rifampin for patients with drug-susceptible tuberculosis. The Committee also noted that the 4-month regimen containing moxifloxacin and rifapentine will be included in the updated WHO guidelines for treatment of drug-susceptible tuberculosis. The Committee considered that a reduction in the length of the course of treatment from 6 months to 4 months may improve patient adherence and result in cost savings. The Expert Committee therefore recommended the inclusion of moxifloxacin 400 mg tablets and rifapentine 150 mg and 300 mg tablets on the core list of the EML for the new indication of treatment of drug-susceptible tuberculosis in adults and children older than 12 years of age.

## Background

Moxifloxacin 400 mg tablets were added to the complementary list of the EML and EMLc in 2017 for use in the treatment of multidrug-resistant tuberculosis (1). In 2019, a 100 mg dispersible tablet formulation was added to the complementary list of the EMLc for this indication for use in children (2). Rifapentine (150 mg tablet) was added to the core list of the EML and EMLc in 2015 for treatment, in combination with isoniazid, of latent tuberculosis infection (now known as tuberculosis preventive treatment) (3). A separate application to the 2021 Expert Committee meeting requests listing for a 300 mg strength tablet of rifapentine for tuberculosis preventive treatment.

## Public health relevance

The public health relevance of medicines for the treatment of tuberculosis is well established. Globally in 2019, an estimated 10 million people fell ill with tuberculosis, 1.2 million deaths occurred among HIV-negative people and 208 000 deaths among HIV-positive people (4). Treatment of drug-susceptible pulmonary tuberculosis is a standard 6-month daily regimen, composed of 2 months of isoniazid (H), rifampin (R), ethambutol (E) and pyrazinamide (Z) followed by 4 months of isoniazid and rifampin (2HREZ/4HR). The standard 6-month regimen is well known and widely implemented worldwide. Rifapentine-based regimens have potent antimycobacterial activity and may allow shortening of a treatment course in patients with drug-susceptible pulmonary tuberculosis.

## Benefits

The Tuberculosis Trials Consortium Study 31/AIDS Clinical Trials Group A5349 (Study 31/A5349) was an international, multicentre, randomized, open-label, phase III, non-inferiority trial that aimed to determine whether treatment regimens that included rifapentine, at a once-daily dose of 1200 mg (with or without a once-daily dose of 400 mg of moxifloxacin) can provide a durable cure in participants with drug-susceptible pulmonary tuberculosis in 4 months, as compared with the standard 6-month regimen (5). Two shorter regimens were assessed: (i) 2 months of isoniazid (H), rifapentine (P), ethambutol (E) and pyrazinamide (Z), followed by 2 months of isoniazid and rifapentine (2PHZE/2PH), with rifapentine replacing rifampin; and (ii) 2 months of isoniazid, rifapentine, moxifloxacin (M) and pyrazinamide, followed by 2 months of isoniazid, rifapentine and moxifloxacin (2PHZM/2PHM), with rifapentine replacing rifampin and moxifloxacin replacing ethambutol. These two 4-month regimens were compared with a standard 2RHZE/4RH regimen using a non-inferiority margin of 6.6 percentage points. The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug. The rifapentine with moxifloxacin regimen was non-inferior to the control regimen in the microbiologically eligible population (15.5% versus 14.6% had an unfavorable outcome; difference 1.0 percentage point, 95% confidence interval (CI) −2.6 to 4.5) and in the assessable population (11.6% versus 9.6%; difference 2.0 percentage points; 95% CI −1.1 to 5.1). Non-inferiority was shown in the secondary and sensitivity analyses. Non-inferiority of the rifapentine without moxifloxacin regimen to the control regimen was not shown in either the microbiologically eligible population (17.7% versus 14.6% with an unfavorable outcome; difference 3.0 percentage points, 95% CI −0.6 to 6.6) or the assessable population (14.2% versus 9.6%; difference 4.4 percentage points, 95% CI 1.2 to 7.7).

## Harms

No evidence of a difference between the rifapentine with moxifloxacin and control regimens in the primary safety outcome was found: on-treatment grade 3 or higher adverse events were reported in 159 (18.8%) participants in the rifapentine–moxifloxacin regimen and 159 (19.3%) in the control regimen (adjusted difference –0.6, 95% CI –4.3 to 3.2). The percentage of participants with on-treatment grade 3 or higher adverse events was lower in the rifapentine without moxifloxacin regimen than the control regimen (adjusted difference –5.1, 95% CI –8.7 to –1.5). In addition, all-cause mortality during treatment was low and similar across treatment regimens (0.8%, 0.4% and 0.5% in the control, rifapentine–moxifloxacin and rifapentine regimens, respectively) (5). There was no evidence of a difference in tolerability between the rifapentine–moxifloxacin regimen and the control regimen (risk difference –1.0, 95% CI –3.6 to 1.6). The rifapentine regimen was better tolerated than the control regimen (–3.3, 95% CI –5.7 to –0.9) (5).

## Cost / cost effectiveness

Cost–effectiveness data were not presented in the application. The guideline development group noted that implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and its availability improved.

## WHO guidelines

The WHO Global Tuberculosis Programme received data from the Study 31 investigators and convened a guideline development group in April 2021 to review study results. The available evidence reviewed by the guideline development group on the 4-month regimen for treatment of drug-susceptible pulmonary tuberculosis supports the use of this regimen as a possible alternative to the current standard 6-month regimen. The shorter regimen has showed similar performance to the current standard regimen, both in terms of efficacy and safety. The 4-month regimen, which is shorter, effective and all oral, would be preferred by many patients and

also national tuberculosis programmes, allowing faster cure and easing the burden on both patients and the health care system. However, implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and its availability improved. Rigorous antibacterial stewardship will also be required to ensure the appropriate use of the first-line regimen given that it contains moxifloxacin, an antibiotic usually used for the treatment of drug-resistant tuberculosis. Updated WHO policy guidelines will be released later in 2021, as part of the 2021 update of the WHO consolidated guidelines on tuberculosis. The guidelines will incorporate all current recommendations on the treatment of drug-susceptible tuberculosis (6).

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 ( WHO Technical Report Series, No. 1006); https://apps.who.int/iris/handle/10665/259481, accessed 13 August 2021).
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 ( WHO Technical Report Series, No. 1021; https://apps.who.int/iris/handle/10665/330668, accessed 13 August 2021).
3. 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 13 August 2021).
4. Global tuberculosis report 2020. Geneva, World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336069, accessed 13 August 2021).
5. Dorman SE, Nahid P, Kurbatova EV, Phillips PPJ, Bryant K, Dooley KE, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384(18):1705–18.
6. Treatment of drug-susceptible tuberculosis: rapid communication. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/341729, accessed 13 August 2021).