Rifapentine access in Europe: growing concerns over key tuberculosis treatment component

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To the Editor:

Rifapentine, a synthetic derivate of rifampicin which was developed in 1965, has interesting pharmacological properties, including a long terminal half-life (13 h, compared to 2–3 h for rifampicin) and promising bactericidal activity against *Mycobacterium tuberculosis*. Despite being approved in 1998 by the US Food and Drug Administration (FDA) for the treatment of pulmonary tuberculosis, its global use has been limited by unavailability. In the past decade, new evidence has emerged to define rifapentine as a key component for treatment of active disease and latent infection with *M. tuberculosis* (LTBI).

For LTBI, rifapentine is the backbone of newer regimens that are shorter and easier to complete than the previous standard of care [1]. In particular, the 3-month combination of weekly rifapentine and isoniazid has overall similar effectiveness and safety profile, but higher treatment completion rates, compared to previously used regimens [2]. This regimen was approved in 2014 by the US FDA and is recommended in the latest World Health Organization (WHO) guidelines for the treatment of LTBI [3]. More recently, an even shorter regimen consisting of daily rifapentine and isoniazid for 30 days has shown promising results for treatment of LTBI among people living with HIV and has also been endorsed as an alternative regimen for the prevention of tuberculosis by the WHO for HIV-negative individuals [3, 4].

For tuberculosis, a phase III multicentre, randomised, controlled clinical trial has shown a 4-month regimen including daily rifapentine and moxifloxacin to be non-inferior to the standard of care treatment for rifampicin-susceptible tuberculosis [5]. These unprecedented results have been celebrated by the global scientific community, as they represent the first successful attempt at shortening tuberculosis treatment below 6 months. Indeed, the WHO has already endorsed this regimen as a possible alternative to the current 6-month standard regimen for rifampicin-susceptible tuberculosis [6].

Therefore, rifapentine-based regimens have the potential to significantly shorten and simplify current treatment regimens for LTBI and tuberculosis, reducing the burden for national tuberculosis programmes, increasing overall adherence to treatment and, ultimately, improving outcomes and patient acceptability. Trial results appear to be applicable to persons living with HIV, favoured by the absence of major pharmacological interactions between rifapentine and antiretroviral drugs such as dolutegravir. Overall, these results emphasise the importance of the global availability of rifapentine, which is currently listed among the WHO Essential Medicines. Unfortunately, access to rifapentine is a long-standing concern. Indeed, as of 24 March 2020, rifapentine had been registered in only 13 countries worldwide [7]. Rifapentine is available *via* the Global Drug Facility in a number of low- and middle-income countries, excluding the WHO Europe region apart from a few exceptions (Republic of Moldova, Uzbekistan, Ukraine and the Russian Federation).

The situation is indeed particularly concerning in Europe. Within the Tuberculosis Network European Trials group (TBnet), a tuberculosis-oriented network of clinicians and scientists [8], a survey was performed in June–December 2020 and updated in October 2021 to investigate access to anti-tuberculosis drugs in the WHO Europe region. Out of 53 countries in the region, TBnet collaborating clinicians were contacted in 46 countries, and 43 replied: overall, rifapentine was available only in two middle-income and four high-income countries (14% of the total) [9]. Regrettably, these results are not surprising. Rifapentine obtained orphan drug designation from the European Commission in 2010, which entails several benefits to drug development.

Shareable abstract (@ERSpublications)
Lack of access to rifapentine in Europe denies patients optimal care for active tuberculosis and latent tuberculosis infection, and deprives healthcare providers of adequate tools to pursue tuberculosis control and elimination https://bit.ly/3jz85eh

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Despite this, the French manufacturer, one of the largest pharmaceutical companies worldwide and the only one with presence in the small European tuberculosis market, has not yet filed rifapentine for registration with the European Medicines Agency (EMA). In 2016, a letter signed from tuberculosis organisations from 14 European countries urging the drug manufacturer to rapidly submit rifapentine for EMA registration was left unanswered [10]. Some authors of this manuscript have directly contacted the drug manufacturer in their own country (France, Italy, Latvia and UK) to obtain access to rifapentine through compassionate use and/or strictly monitored observational research conditions, but all efforts were unsuccessful.

The current situation is unacceptable: patients are being denied access to optimal care and healthcare providers to adequate tools to pursue the goal of tuberculosis control and elimination in Europe. Public pressure can achieve results in the fight to access to affordable care, as shown by the decision of the manufacturer to withdraw its patent application for a fixed dose combination of rifapentine and isoniazid with the European Patent Office.

On behalf of three major European scientific societies and the largest European tuberculosis research network, we urge the drug manufacturer and all relevant stakeholders to immediately coordinate efforts to expedite access to rifapentine to all patients who may benefit from this drug as part of treatment regimens for active tuberculosis or for the prevention of tuberculosis in individuals with LTBI in Europe and in the world: too much time has been already wasted.

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