



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

Copyright ©The authors 2022.

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 20 Feb 2022
Accepted: 6 April 2022

To the Editor:

Rifapentine, a synthetic derivative 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>

Cite this article as: Guglielmetti L, Günther G, Leu C, *et al.* Rifapentine access in Europe: growing concerns over key tuberculosis treatment component. *Eur Respir J* 2022; 59: 2200388 [DOI: 10.1183/13993003.00388-2022].



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.

Lorenzo Guglielmetti ^{1,2,3}, **Gunar Günther** ^{4,5}, **Claude Leu** ⁴, **Daniela Cirillo** ⁶, **Raquel Duarte** ^{7,8,9,10}, **Alberto L. Garcia-Basteiro** ^{11,12}, **Delia Goletti** ¹³, **Mateja Jankovic** ¹⁴, **Liga Kuksa** ^{15,16}, **Florian P. Maurer** ^{17,18,19}, **Frédéric Méchai** ²⁰, **Simon Tiberi** ^{21,22}, **Frank van Leth** ^{23,24}, **Nicolas Veziris** ^{2,25,26} and **Christoph Lange** ^{19,27,28,29} on behalf of the Study Group on Mycobacteria of the European Society of Microbiology and Infectious Diseases (ESGMIC), European Society of Mycobacteriology (ESM), European Respiratory Society (ERS) and the Tuberculosis Network European Trials group (TBnet)

¹Sorbonne Université, INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses, Cimi-Paris, Paris, France. ²APHP, Groupe Hospitalier Universitaire Sorbonne Université, Hôpital Pitié-Salpêtrière, Centre National de Référence des Mycobactéries et de la Résistance des Mycobactéries aux Antituberculeux, Paris, France. ³APHP, Infectious Disease Unit, Avicenne Hospital, Bobigny, France. ⁴Department of Pulmonology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland. ⁵Department of Internal Medicine, School of Medicine, University of Namibia, Windhoek, Namibia. ⁶WHO Collaborating Centre and TB Supranational Reference Laboratory, San Raffaele Scientific Institute, Milano, Italy. ⁷Epidemiology Research Unit (EpiUnit), Institute of Public Health, University of Porto, Porto, Portugal. ⁸Departamento de Ciências de Saúde Pública, Ciências Forenses e Educação Médica, Faculty of Medicine, University of Porto, Porto, Portugal. ⁹Serviço de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal. ¹⁰National Tuberculosis Program, Directorate-General of Health, Lisbon, Portugal. ¹¹Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Moçambique. ¹²ISGlobal, Hospital Clínic – Universitat de Barcelona, Barcelona, Spain. ¹³National Institute for Infectious Diseases L. Spallanzani-IRCCS, Rome, Italy. ¹⁴Clinic for Lung Diseases, University of Zagreb School of Medicine and University Hospital Center Zagreb, Zagreb, Croatia. ¹⁵Riga East University Hospital, TB and Lung Disease Centre, Riga, Latvia. ¹⁶Riga Stradins University, Riga, Latvia. ¹⁷National and Supranational Reference Center for Mycobacteria, Research Center Borstel, Borstel, Germany. ¹⁸Institute of Medical Microbiology, Virology and Hygiene, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. ¹⁹German Center for Infection Research (DZIF), Partner Site Hamburg-Lübeck-Borstel-Riems, Borstel, Germany. ²⁰APHP, Infectious Disease Unit, Avicenne Hospital, Université Paris 13, IAME, INSERM, Bobigny, France. ²¹Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University, London, UK. ²²Royal London Hospital, Barts Health National Health Service Trust, London, UK. ²³VU University, Department of Health Sciences, Amsterdam, The Netherlands. ²⁴Amsterdam Public Health Research Institute, Amsterdam, The Netherlands. ²⁵APHP, Groupe Hospitalier Universitaire Sorbonne Université, site Saint-Antoine, Département de bactériologie, Paris, France. ²⁶Sorbonne Université, INSERM, U1135, Centre d'Immunologie et des Maladies Infectieuses, Cimi-Paris, équipe 13, Paris, France. ²⁷Division of Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany. ²⁸Respiratory Medicine and International Health, University of Lübeck, Lübeck, Germany. ²⁹Baylor College of Medicine and Texas Children's Hospital, Global TB Program, Houston, TX, USA.

Corresponding author: Lorenzo Guglielmetti (lorenzo.guglielmetti@aphp.fr)

Acknowledgements: The authors are indebted to the TBnet country representatives and collaborators, as listed below, for the participation to the TBnet survey cited in the manuscript. Hasan Hafizi (Tirana, Albania), Naira Khachatryan, Harut Aroyan, Eduard Kabasakalyan (Yerevan, Armenia), Michael Knappik (Vienna, Austria), Alena Skrahina, Dzmitry Klimuk, Alena Nikolenka (Minsk, Belarus), Inge Muylle (Brussels, Belgium), Vladimir Milanov, Desislava Velkovska, Neli Tarinska, Elizabeta Bachiyska (Sofia, Bulgaria), Mateja Jankovic (Zagreb, Croatia), Despo Pieridou, Tonia Adamide, Nicos Nicolaou (Nicosia, Cyprus), Martina Vasakova, Mariia Sukholytka, Emilia Kopeckà, Beata Polakova (Prague, Czech Republic), Aase Bengard Anderson, Dorte Bek Folkvardsen, Erik Svensson (Copenhagen, Denmark), Manfred Danilovits, Tiina Kummik (Tartu, Estonia), Tuula Vasankari (Turku, Finland), Mathilde Fréchet-Jachym, Audrey Nahmiash (Briis-sous-Forges, France), Tamar Togonidze, Zaza Avaliani, Inga Kinkladze, Rusudan Aspindzelashvili, Teona Bichashvili, Gulnazi Losaberidze, Tsitsino Merabishvili (Tbilisi, Georgia), Barbara Kalsdorf (Borstel, Germany), Katerina Manika, Karyofyllis Tsiakitzis (Thessaloniki, Greece), Agnes Bakos (Budapest, Hungary), Tinna Rán Ægisdóttir, Guðrún Svanhvít Michelsen, Kristín Karlsdóttir (Reykjavik, Iceland), Anne-Marie McLaughlin, Margaret Fitzgibbon (Dublin, Ireland), Daniel Chemtob (Jerusalem, Israel), Luigi R. Codecasa, Maurizio Ferrarese, Stefania Torri (Milan, Italy), Majlinda Gjocaj (Pristina, Kosovo), Liga Kuksa (Riga, Latvia), Edita Davidaviciene (Vilnius, Lithuania), Gil Wirtz, Monique Perrin (Luxembourg, Luxembourg), Analita Pace Asciak (Valetta, Malta), Dumitri Chesov (Chisinau, Moldova), Wiel de Lange, Onno Akkerman (Groningen, the Netherlands), Biljana Illievska-Poposka (Skopje, North Macedonia), Ulrich Mack, Mogens Jesenius, Lajla Kvalvik, Anne Torunn Mengshoel (Oslo, Norway), Katarzyna Kruzak (Krakow, Poland), Raquel Duarte, Nadine Ribeiro (Porto, Portugal), Elmira Ibraim (Bucharest, Romania), Anna Kaluzhenina, Olga Barkanova (Volgograd, Russia), Dragica Pesut (Belgrade, Serbia), Ivan Solovic (Vysne Hagy, Slovakia), Petra Svetina (Golnik, Slovenia), Maria-Luiza de Souza-Galvão, Joan-Pau Millet, Xavi Casas, Montserrat Vives (Barcelona, Spain), Judith Bruchfeld, Paulina Dalemo, Jerker Jonsson (Stockholm, Sweden), Katrin Aeschbacher, Peter Keller (Bern, Switzerland), Seref Ozkara (Ankara, Turkey), Simon Tiberi, Christabelle Chen (London, UK), Yana Terleeva (Kiev, Ukraine) Andrii Dudnyk (Vinnytsia, Ukraine).

Conflict of interest: L. Guglielmetti is the co-principal investigator of two MSF-sponsored clinical trials testing shorter MDR-TB regimens, and has no other competing interests to disclose. All other authors have no competing interests.

Support statement: C. Lange is supported by the German Center of Infection Research (DZIF). All other authors have no funding to declare for this study. Funding information for this article has been deposited with the Crossref Funder Registry.

References

- 1 Lange C, Kay A, Mandalakas AM. The need for effective drugs for TB prevention: set your goals high, and don't stop till you get there. *Int J Tuberc Lung Dis* 2022; 26: 85–88.
- 2 Njie GJ, Morris SB, Woodruff RY, et al. Isoniazid-rifampentine for latent tuberculosis infection: a systematic review and meta-analysis. *Am J Prev Med* 2018; 55: 244–252.
- 3 World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 1: Prevention – Tuberculosis Preventive Treatment. Geneva, World Health Organization, 2020.
- 4 Swindells S, Ramchandani R, Gupta A, et al. One month of rifampentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019; 380: 1001–1011.
- 5 Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifampentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med* 2021; 384: 1705–1718.
- 6 World Health Organization. Treatment of Drug-susceptible Tuberculosis: Rapid Communication. Geneva, World Health Organization, 2021.
- 7 Treatment Action Group. An Activist's Guide to Rifampentine for the Treatment of TB Infection. Updated April 2020. Date last accessed: 12 May 2021. www.treatmentactiongroup.org/publication/an-activists-guide-to-rifampentine-for-the-treatment-of-tb-infection/
- 8 van Leth F, Brinkmann F, Cirillo DM, et al. The Tuberculosis Network European Trials group (TBnet) ERS Clinical Research Collaboration: addressing drug-resistant tuberculosis through European cooperation. *Eur Respir J* 2019; 53: 1802089.
- 9 Günther G, Guglielmetti L, Leu C, et al. Cost and availability of drugs and treatment regimens and availability of drug resistance testing for tuberculosis in Europe. *medRxiv* 2022; preprint [https://doi.org/10.1101/2022.02.15.22271006].
- 10 de Vries G. Importance of Rifampentine (Priftin®) for TB Elimination in Europe. Date last updated: 7 June 2016. Date last accessed: 17 May 2021. www.kncvtbc.org/uploaded/2017/02/Letter-to-Sanofi-re-Rifampentine-in-Europe.pdf