LAHAN
Los Angeles County Health Alert Network

# LAC DPH Health Advisory: Rifapentine Shortage and Detection of Nitrosamine Impurity

July 13, 2020

County of Los Angeles Public Health

*This message is intended for all healthcare providers in Los Angeles County. Please distribute as appropriate.*

## Key Messages

- There are rifapentine shortages because global demand has increased and because the sole manufacturer has voluntarily paused release of the drug due to the detection of nitrosamine impurities.
- Rifapentine is indicated for treatment of latent tuberculosis infection (LTBI) and should NOT be confused with the other rifamycins (rifampin, rifabutin).
- Treatment of latent tuberculosis infection (LTBI) is considered an essential health service during the ongoing COVID-19 pandemic.
- Healthcare providers should consider temporarily refraining from initiating the once-weekly 3-month isoniazid-rifapentine (3HP) regimens until rifapentine shipments have resumed and local supplies of rifapentine have been reestablished. Providers should continue to offer LTBI treatment using one of the preferred rifamycin-based regimens: 4 months of daily rifampin (4R) or 3 months of daily isoniazid and rifampin (3HR).

## Situation

A shortage of rifapentine was announced by the FDA in March 2020 and attributed to increased global demand since late 2019. Subsequently, on June 18, 2020, state and local health jurisdictions were notified by the CDC that Sanofi, the sole manufacturer of rifapentine in the United States, had detected low levels of a nitrosamine impurity and potential carcinogen, 1-cyclopentyl-4-nitrosopiperazine, in some market-ready batches of the drug at production facilities in Italy. It is not yet known whether supplies of the drug in the United States were similarly affected.

Neither the FDA nor Sanofi have requested a drug recall for rifapentine and no new FDA advisories have been issued regarding nitrosamine impurities in rifapentine. No clinical safety signal related to this impurity has been observed in pharmacovigilance databases and further investigation is being conducted by the manufacturer in concert with FDA.

Nonetheless, out of an abundance of caution, the manufacturer has paused any additional release of rifapentine and this is expected to exacerbate pre-existing shortages of the drug. Rifapentine does remain available for purchase in the United States, albeit on allocation with intermittent supply, but CDC has recommended that patients with LTBI should not start rifapentine until local supplies are reestablished. See the CDC Dear Colleague Letter Reported Rifapentine Impurity for more information.

*The importance of access to LTBI treatment*

The effectiveness of LTBI treatment in preventing TB disease is ≥90%, and continued access to this essential health service should be prioritized during the ongoing COVID-19 pandemic. This is particularly important in the setting of widespread community transmission of COVID-19 in Los Angeles County, where cases of co-infection with COVID-19 and tuberculosis continue to be observed, and individuals who sustain lung damage due to severe COVID-19 disease may be at increased risk of progression from LTBI to active pulmonary TB disease. A summary of the LAC DPH recommended LTBI treatment regimens is included below.

**Actions Requested of Providers**

*Diagnosis of LTBI*

- Continue to prioritize TB risk assessment and testing (if indicated) for TB infection, using either interferon-gamma release assays (preferred) or tuberculin skin test, in high risk individuals including the following groups:
    - persons identified as close contacts to persons with infectious TB disease;
    - persons born in or frequently travelling to countries where TB disease is common AND have not been tested since their last period of travel;
    - persons who are immunocompromised or immunosuppressed;
    - persons who have history of incarceration or homelessness AND have not been tested since their last incarceration or period of homelessness.

  See Diagnosis of Tuberculosis Infection: A Practical Guide for LA County for risk assessment and testing resources.
- If the TB test is positive or the patient is symptomatic, obtain a chest radiograph to exclude active pulmonary TB disease, as described in the LAC DPH TB toolkit for providers.

*Treatment of LTBI*

- Consider temporarily refraining from starting treatment with 3HP until local supplies of rifapentine have been reestablished.
- Continue to offer treatment for newly diagnosed LTBI, especially among high risk individuals, using one of the preferred rifamycin-based regimens: 4R or 3HR.

- For patients who are unable to take either of the preferred rifamycin-based regimens, 6 or 9 months of daily isoniazid monotherapy are reasonable alternatives.
- For patients who are already taking 3HP, and for whom the local supply is adequate to complete the full treatment course, use a patient-centered decision-making approach to determine whether to continue 3HP or switch to another LTBI treatment regimen.
- If the rifapentine-based regimen is discontinued early for any reason, the LTBI treatment can be completed with a proportionate duration of an alternative regimen such as 4R or 3HR. Call the TB Control Program for consultation if needed (see *Reporting and Consultation* below).
- For patients initiating any of the shorter rifamycin-based regimens during the ongoing COVID-19 pandemic, work with pharmacy partners to implement strategies to reduce potential COVID-19 exposures, for example dispensing the entire 3-4 month supply of LTBI medications with the first fill, or arranging home delivery of medications to patients' residences.

**Recommended LTBI Treatment Regimens**

Los Angeles County Department of Public Health's Tuberculosis Control Program recommends the following first-line LTBI treatment regimens for non-pregnant adults and children ≥2-years-old:

- 3 months of once-weekly, high-dose isoniazid and rifapentine (also known as, "3HP")
- 4 months of daily, standard-dose rifampin ("4R")
- 9 months of daily, standard-dose isoniazid ("9H")

Among pregnant individuals and children <2-years-old, 4R and 9H can be used for LTBI treatment. Due to improved completion rates, as well as equivalent toxicity profiles in recent randomized controlled trials, the shorter rifamycin-based regimens (3HP and 4R) have clear advantages over conventional isoniazid monotherapy. Since June 2018, CDC also issued permissive guidance that 3HP may be administered via self-administered therapy, making this regimen an increasingly attractive option. More recently, in May 2020, CDC has also endorsed two additional regimens as acceptable alternatives for carefully selected patients:

- 3 months of daily, standard-dose isoniazid and rifampin ("3HR")
- 6 months of daily, standard-dose isoniazid ("6H")

## Reporting and Consultation

All suspected or proven cases of tuberculosis should be reported in writing within 1 working day.

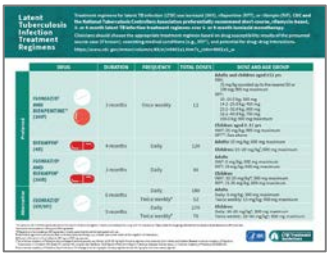
**Los Angeles County DPH TB Control Program:**
Download forms at http://ph.lacounty.gov/tb/reporting.htm and fax to 213-749-0926
For enquiries, call 213-745-0800 during business hours. For urgent consults after hours call 213-974-1234 and ask for the emergency physician on call.

**Long Beach Health and Human Services:**
Download forms at http://www.longbeach.gov/health/diseases-and-condition/reporting-requirement/tb-laws-and-regulations/ and fax to 562-570-4391
For enquiries, call 562-570-4283 or 562-570-4235.

**Pasadena Public Health Department:**
Download forms at https://www.cityofpasadena.net/public-health/wp-content/uploads/sites/32/Pasadena-Confidential-Morbidity-Report-CMR-Form-09-2011.pdf?v=1590182630275 and fax to 626-744-6115 or send by encrypted/secure email to nursing@cityofpasadena.net.
For enquiries, call 626-744-6089.

## Resources

- **LAC DPH Health Advisory**: Tuberculosis During the COVID-19 Pandemic (June 1, 2020) LAHAN
- **LAC DPH TB provider webpage** http://ph.lacounty.gov/tb/healthpro.htm
- **CDC LTBI regimens** cdc.gov/tb/topic/treatment/pdf/LTBITreatmentRegimens.pdf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