Updated diagnosis and treatment for LTBI and TB

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Disclosures

- None

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Objectives

At the completion of this presentation, the participant will be able to:

1) Review screening criteria concerning for TB and LTBI

2) Identify the benefits and drawbacks of available diagnostic modalities

3) Review treatment updates for TB

Review screening criteria concerning for TB and LTBI

Background

- Active TB infection is caused by *Mycobacterium tuberculosis,* an acid-fast bacterium due to high levels of mycolic acid in it's cell wall.
- People with latent TB infection (LTBI) are infected with *M. tuberculosis* but do not have any signs or symptoms of active disease.
- They are infected with TB but not contagious

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

Background

- Up to 13 million people in the US are estimated to have LTBI
- 5-10% of people with LTBI will develop active TB disease in their lifetimes if not treated for LTBI
- Progression from untreated LTBI to TB disease accounts for approximately 80% of U.S. TB cases.

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

Signs and symptoms concerning for active TB infection

- Cough lasting 3 weeks or longer
- Hemoptysis
- Night sweats
- Weight loss
- Chest pain
- Abnormal chest X ray
- Extrapulmonary symptoms

Targeted Screening for LTBI

Aimed at identifying:

1) People who are at a high risk of TB exposure or infection

2) People who are at a high risk of developing active TB disease after infection with *M. tuberculosis*

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

People who at a high risk of TB exposure or infection

- Contacts of people known or presumed to have active pulmonary TB
- People born in or who frequently travel to countries where TB is common, anywhere outside the US, Canada, Australia, New Zealand, and Northern and Western Europe.
- People who currently or previously lived in a large group setting such as homeless shelters, prisons, jails, or nursing homes.
- Employees of high-risk congregate settings

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

People who at a high risk of TB exposure or infection

- Health care workers who serve patients with TB
- Populations defined as having an increased incidence of LTBI or TB, medically underserved, low-income, people who use illicit drugs and alcohol
- Infants, children, and adolescents exposed to adults who are at a high risk of LTBI or TB.

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

People who are at a high risk of developing active TB disease after infection with *M. tuberculosis*

- People living with HIV
- Children <5 years of age
- People recently infected with *M. tuberculosis* (<2 years)
- History of untreated or inadequately treated active TB disease.
- People who are receiving immunosuppressive therapy: TNF-alpha antagonists, systemic corticosteroids =/> 15mg prednisone/day, immunosuppressive therapy following organ transplant

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

People who are at a high risk of developing active TB disease after infection with *M. tuberculosis*

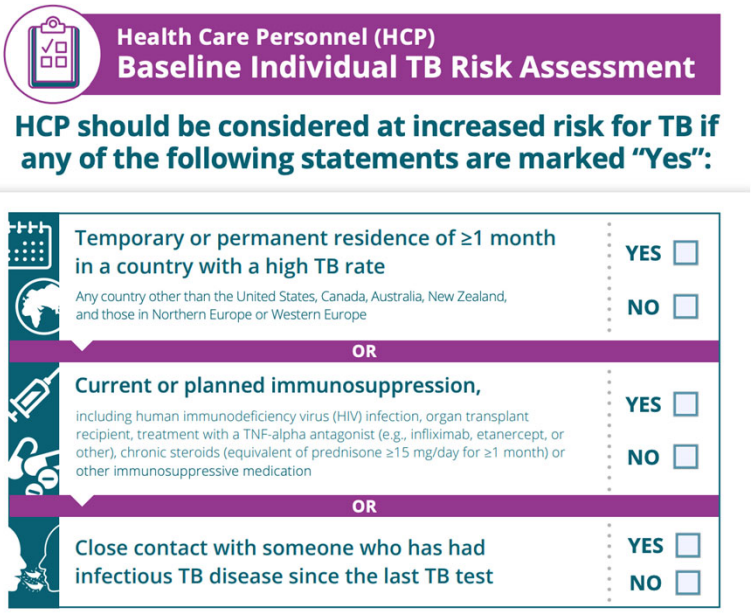
- Diagnosed with silicosis, chronic renal failure, diabetes, leukemia, cancer of head, neck, or lung
- s/p gastrectomy or jejunoileal bypass
- Low body weight
- Populations defined as having an increased incidence of LTBI or TB, medically underserved, low-income, people who use illicit drugs and alcohol

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

TB Screening and Testing of Health Care Personnel

- The CDC and the National Tuberculosis Controllers Association (NTCA) updated recommendations for TB screening, testing, and treatment of health care personnel in 2019
- All U.S. health care personnel should be screened for TB upon hire (i.e., pre-placement) with two-step TST (repeat TST in 1-3 weeks) or blood test.
- Annual TB testing of health care personnel is **not** recommended unless there is a known exposure or ongoing transmission.
- The screening process includes a baseline individual TB risk assessment, TB symptom evaluation, TB test (TB blood test or TST), and additional evaluation for TB disease as needed.

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021



Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

Identify the benefits and drawbacks of available diagnostic modalities

Screening Tests

- Tuberculin Skin Test (TST)
- Mantoux tuberculin skin test involved injecting 0.1 ml of 5 tuberculin units of purified protein derivative (PPD) solution subcutaneously. Interpretation of TST reactions within 48–72 hours after administration. Area of induration only is measured.

- Blood tests called Interferon Gamma Release Assays (IGRA)

1) QuantiFERON-TB Gold In-Tube test (QFT-GIT)
2) T-SPOT TB test (T-SPOT)

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

Interpretation of Tuberculin Skin Test (TST) Reactions

5 or more millimeters

A TST reaction of **≥5 mm** of induration is considered positive for:

- People living with HIV
- Recent contacts of people with infectious TB
- People with chest x-ray findings suggestive of previous TB disease
- People with organ transplants
- Other immunosuppressed patients (e.g., patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone or those taking TNF-alpha antagonists)

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

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Interpretation of Tuberculin Skin Test (TST) Reactions

10 or more millimeters

A TST reaction of **≥10 mm** of induration is considered positive for:

- People born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala
- People who abuse drugs
- Mycobacteriology laboratory workers
- People who live or work in high-risk congregate settings (e.g., nursing homes, homeless shelters, or correctional facilities)
- People with certain medical conditions that place them at risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, or certain intestinal conditions)
- People with a low body weight (<90% of ideal body weight)
- Children younger than 5 years of age
- Infants, children, and adolescents exposed to adults in high-risk categories

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

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Interpretation of Tuberculin Skin Test (TST) Reactions

15 or more millimeters
A TST reaction of **≥15 mm** of induration is considered positive for: • People with no known risk factors for TB

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

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Benefits and drawbacks of screening tests

- Neither TST or IGRA differentiate between active and latent TB.
- Once positive, expect it to stay positive
- Both can be falsely negative in immunosuppressed patients
- IGRA is preferred in patients with history of BCG vaccination and those who are unlikely to return to have PPD read.

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

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Benefits and drawbacks of screening tests

- TST more likely to be falsely positive in setting of several NTB infections such as *M. avium and M. hemophilum*.
- IGRA less likely to be falsely positive in setting of NTB, rare cases of false positive with primarily *M. kansasii*
- T-SPOT may be more helpful in use with immunocompromised patients than QFT-GIT

Du, F., Xie, L., Zhang, Y. *et al.* Prospective Comparison of QFT-GIT and T-SPOT.TB Assays for Diagnosis of Active Tuberculosis. *Sci Rep* **8,** 5882 (2018). https://doi.org/10.1038/s41598-018-24285-3

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Testing for active pulmonary TB disease

- Induced sputum x 3 with AFB smear and both liquid and solid mycobacterial culture if available, liquid if only one is available.
- NAAT testing on all samples as positive AFB can be either TB or NTB.
- Bronchoscopic sampling when induced sputum is not feasible.
- Molecular drug sensitivity testing for rifampin +/- isoniazid.

Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children, *Clinical Infectious Diseases*, Volume 64, Issue 2, 15 January 2017, Pages 111–115, https://doi.org/10.1093/cid/ciw778

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Review treatment updates for TB

Previous LTBI Treatment

ISONIAZID† (6H/9H)	6 months	Daily	180	**Adults** Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
		Twice weekly	52	
	9 months	Daily	270	**Children** Daily: 10–20 mg/kg#; 300 mg maximum Twice weekly: 20–40 mg/kg#; 900 mg maximum
		Twice weekly	76	

- with pyridoxine 50 mg daily to decrease risk of neuropathy

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

Considerations

- The most recent comprehensive LTBI treatment guidelines for the US prior to 2020 which were published in 2000.
- 9 months of daily isoniazid was considered the standard
- Concern that 6 or 9 months of daily isoniazid has a higher toxicity risk, and lower treatment completion rates.
- Decreased effectiveness

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020.AUSterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, Menzies D, Horsburgh CR Jr, Crane CM, Burgos M, LoBue P, Winston CA, Belknap R SOMMWR Recomm Rep. 2020;69(1):1. Epub 2020 Feb 14

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Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

Recommendations and Reports / February 14, 2020 / 69(1);1–11

Timothy R. Sterling, MD[1]; Gibril Njie, MPH[2]; Dominik Zenner, MD[3]; David L. Cohn, MD[4]; Randall Reves, MD[4]; Amina Ahmed, MD[5]; Dick Menzies, MD[6]; C. Robert Horsburgh Jr., MD[7]; Charles M. Crane, MD[8]; Marcos Burgos, MD[8,9]; Philip LoBue, MD[2]; Carla A. Winston, PhD[2]; Robert Belknap, MD[4,8] (View author affiliations)

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Updated treatment recommendations

	DRUG	DURATION	FREQUENCY	TOTAL DOSES
Preferred	ISONIAZID† AND RIFAPENTINE†† (3HP)	3 months	Once weekly	12
	RIFAMPIN§ (4R)	4 months	Daily	120
	ISONIAZID† AND RIFAMPIN§ (3HR)	3 months	Daily	90

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

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3HP

- Weekly dosing strongly recommended for adults and children >2yrs.
- Recommended for HIV positive individuals (taking into consideration possible drug interactions.
- All 12 doses administered through DOT
- Equivalent to 9 months of daily isoniazid but with less hepatotoxicity

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3HP

- In a noninferiority study of HIV negative individuals with 3HP and 9H, treatment completion was higher in 3HP with less hepatotoxicity.
- In HIV positive individuals 3HP was noninferior to 9H.
- A noninferiority study of 3HP did find inferior completion rate of self-administered therapy to DOT.

3HP

- Disadvantages include:
- Cost of medications higher than alternatives
- Additional costs associated with DOT
- Pill burden with weekly dosing

3HP is NOT recommended for:

- Children < 2 yrs old
- Individuals with HIV/AIDS who are taking antiretroviral medications with clinically significant drug interactions with rifapentine
- People presumed to be infected with INH- or RIF-resistant *M. tuberculosis*
- Pregnant women or women expecting to become pregnant during the 3-month regimen

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

4R

- A 4-month regimen of daily rifampin
- Recommended for HIV-negative adults and children of all ages.
- Especially recommended for people who cannot tolerate INH or who have been exposed to INH-resistant TB.
- Caution should be used in HIV positive people due to interactions with several anti viral medication.
- In situations where RIF cannot be used, sometimes rifabutin (RBT) may be substituted.

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

3HR

- 3-month regimen of daily INH and RIF
- One of the recommended short-course rifamycin-based regimens for adults and children of all ages, including HIV-negative and HIV-positive patients as drug interactions allow.
- One of the 3 regimens approved for treatment of LTBI in pregnancy which includes: 3HR, 4R, and 6H-9H.

Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. http://www.cdc.gov/tb/publications/LTBI/default.htm. 2020. Accessed July 21, 2021

Active TB treatment

- Should be guided by DST of sputum or tissue sample
- If high likelihood of active infection, should start empiric treatment for drug-susceptible TB.
- Treatment involves intensive phase for 8 weeks and continuation phase for 18 weeks.
- Intensive phase treatment: isoniazid, rifampin, pyrazinamide, and ethambutol (with pyridoxine) either 5 days/week (40 doses) or 7 days/week (56 doses).
- Continuation phase treatment: isoniazid and rifampin 7 days/week (126 doses) or 5 days/week (90 doses)

Executive Summary: Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, *Clinical Infectious Diseases*, Volume 63, Issue 7, 1 October 2016, Pages 853–867, https://doi.org/10.1093/cid/ciw566

Nitrosamine Contamination

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February 2021

TAG
Treatment Action Group

TAG Information Note:

N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine

Written by: Sandrine Cloëz and Mike Frick

Reviewed by: Jeremy Hill, Lindsay McKenna, Payam Nahid, Regina Osih, Christophe Perrin, Tina Shah, Karin Turner, and staff of the Global Drug Facility

Treatment Action Group. Information Note: N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine. New York, Treatment Action Group. http://www.treatmentactiongroup.org/wp-content/uploads/2021/02/nitrosamine_technical_brief_2021.pdf. Accessed on July 21, 2021.

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Nitrosamine Contamination

- In 2018, health regulatory authorities in the EU, USA, Canada, and other countries began investigating the presence of impurities in medication form a possible human carcinogen, N-nitrosamine.
- Initially, N-nitrosamine called N-nitrosodimethylamine (NDMA) was identified in ARBs.
- N-nitrosamines have since been identified in other categories of drugs including: heartburn products (ranitidine), antidiabetic drugs (metformin), and in anti-TB medication (rifampicin, rifapentine).

Treatment Action Group. Information Note: N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine. New York, Treatment Action Group. http://www.treatmentactiongroup.org/wp-content/uploads/2021/02/nitrosamine_technical_brief_2021.pdf. Accessed on July 21, 2021.

Nitrosamine Contamination

- Everyone is exposed to some level of N-nitrosamines in daily life. They are present in drinking water, foods (processed foods, cured or grilled meats, dairy products, and vegetables), direct and indirect tobacco exposure.
- Identification of N-nitrosamines in medicines is not a new problem, only newly recognized. Likely present for years to decades.
- The known risks of not treating or preventing TB outweigh the theoretical risk of cancer associated with N-nitrosamine exposures from rifampicin and rifapentine
- All people receiving TB and LTBI treatment should receive information on N-nitrosamines and TB medicines

Treatment Action Group. Information Note: N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine. New York, Treatment Action Group. http://www.treatmentactiongroup.org/wp-content/uploads/2021/02/nitrosamine_technical_brief_2021.pdf. Accessed on July 21, 2021.

Nitrosamine Contamination

Table 4: Estimated Food and Total Background Exposure to NDMA

Source of NDMA exposure	Estimated exposure in ng/day	Estimated annual exposure in µg[α]
Processed meats in adults in EU[β] (lifetime daily)	25 to 85 X365 days	*9 to 31*
Total mean background exposure[χ] (lifetime daily)	100 to 1000 X365 days	*36.5 to 365*

α. 1000 ng (nanograms) = 1 µg (microgram).
β. Source: EFSA Panel on Food Additives and Nutrient Sources added to Food. Re-evaluation of potassium nitrite (E 249) and sodium nitrite (E 250) as food additives. EFSA Journal. 2017;15(6):e04786. doi: 10.2903/j.efsa.2017.4786.

χ. Total background from contaminated beverages and food, air and water pollution. Source: Keszei A, et al. Dietary

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Table 5: CPNP Exposure from Rifapentine-containing Regimens Compared to NDMA Background Exposure

Regimen (indication)	Dose and duration of treatment	AI-LTL (in ppm)	Exposure with batch at AI-LTL[α] AI-LTL (ppm) * MDD * treatment days	Exposure with batches at FDA interim limit (20 ppm) 20 ppm * MDD * treatment days	Approximation to NDMA background exposure[β] equivalent with batches at 20 ppm
3HP (TB infection)	900 mg weekly for 12 weeks = 12 days of treatment (<1 month of exposure)	8.5 ppm	8.5*900*12= 91.8 µg	20*900*12= 216 µg	~7 months of total background exposure

Treatment Action Group. Information Note: N-nitrosamines and Tuberculosis Medicines Rifampicin and Rifapentine. New York, Treatment Action Group http://www.treatmentactiongroup.org/wpcontent/uploads/2021/02/nitrosamine_technical_brief_2021.pdf. Accessed on July 21, 2021.

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Nitrosamine Contamination

- FDA is investigating the presence of of 1-methyl-4-nitrosopiperazine (MNP) in rifampin or 1-cyclopentyl-4-nitrosopiperazine (CPNP) in rifapentine.
- The acceptable intake limits are 0.16 parts per million (ppm) for MNP in rifampin and 0.1 ppm for CPNP in rifapentine.
- As a temporary measure the FDA is not objecting to rifampin with MNP <5 ppm and rifapentine containing CPNP < 20 ppm.

Food and Drug Administration. FDA updates and press announcements on nitrosamines in rifampin and rifapentine. 2021 January 21. http://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-rifampinrifapentine-Products. Accessed on July 21, 2021

Company (Manufacturer)	Product	Lots Tested	MNP* level (micrograms-mcg/tablet or injection)	MNP* level (ppm)
Akorn	Rx Rifampin 300 mg	3185938, 3185931, 3184496, 3174136, 3191250	0.45-0.96	1.49-3.20
Akorn	Rx Rifampin 150 mg	3178340, 3174138, 3186047	0.44-0.52	2.95-3.47
Fresenius Kabi	Rx Rifampin Injection 600 mg	6123714	0.56	0.94
Lannett	Rx Rifampin 300 mg	26702.011A, 26702.001E, 18233439C	0.56-0.76	1.88-2.52
Lannett	Rx Rifampin 150 mg	26701.001D, 26701.002B	0.33-0.36	2.22-2.43
Lupin Pharmaceuticals Inc.	Rx Rifampin 300mg	A904639, A906770, A002982, A002983, A904704, A808691	0.39-0.63	1.31-2.08
Lupin Pharmaceuticals Inc.	Rx Rifampin 150mg	A000882, A808686, A904725, A002791	0.23-0.34	1.52-2.26
Mylan	Rx Rifampin Injection 600 mg	7008768, 7008694, 7008769	0.60-1.51	0.99-2.51
Sandoz/Epic	Rx Rifampin 300 mg	ME171080, ME190353, ME200197	0.56-0.80	1.86-2.66
Sandoz/Epic	Rx Rifampin 150 mg	ME190788, ME180471, ME190156, ME190470, ME190660	0.36-0.41	2.39-2.76
Sanofi Pharmaceuticals	Rx Rifampin Injection 600 mg	9J126, A9042, A8039, 9J1261	0.48-0.67	0.80-1.11

*1-Methyl-4-Nitrosopiperazine (MNP)

Food and Drug Administration. FDA updates and press announcements on nitrosamines in rifampin and rifapentine. 2021 January 21. http://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-rifampinrifapentine-Products. Accessed on July 21, 2021

Nitrosamine Contamination

Company (Manufacturer)	Product/API	Lots Tested	CPNP level (microgram-mcg/tablet)	CPNP** level (ppm)
Sanofi	Rx Rifapentine 150 mg	9J2361, 0J0191, 0J1981	1.22-2.13	8.10-14.18

** 1-Cyclopentyl-4-Nitrosopiperazine

Food and Drug Administration. FDA updates and press announcements on nitrosamines in rifampin and rifapentine. 2021 January 21. http://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-rifampinrifapentine-Products. Accessed on July 21, 2021

Thank you

Please email any questions to :

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