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HEALTH ALERT NETWORK | **HEALTH UPDATE** | October 16, 2020

Information on Treatment for Tuberculosis—Nitrosamine Impurities in Rifampin & Rifapentine

On August 26, 2020, the FDA issued a notice related to mitigating shortages of rifampin and rifapentine and its interim guidance to continue using these drugs in the treatment of tuberculosis (TB) after nitrosamine-class impurities were detected through recently adopted regulatory standards to assay all medications for nitrosamines.

FDA sets standard limits on the concentrations of the impurities and is allowing distribution of rifampin and rifapentine if the concentrations do not exceed interim limits while the impurities are investigated.

On September 15, 2020, the CDC's Division of Tuberculosis Elimination (DTBE) sent a Dear Colleague letter which recommends that providers continue prescribing rifampin and rifapentine for all TB and latent TB infection (LTBI) treatment per existing CDC guidelines.

Background

FDA only recently began including testing for nitrosamines, which are potential carcinogens, in rifampin and rifapentine as part of its drug safety requirements. It is possible that nitrosamines were present in rifampin and rifapentine for a substantial time (years or decades) prior to introduction of these tests. DTBE is not aware of any data showing an association between cancer and use of rifamycins in humans. However, DTBE is also not aware of any rigorous studies that have looked for this association.

Information on Rifampin

Unrelated to the detection of nitrosamine impurities, Sanofi announced the discontinuation of three oral rifampin-containing products: Rifadin® (rifampin 150 mg and 300 mg capsules); Rifamate® (a fixed-drug combination of isoniazid and rifampin), and Rifater® (a fixed-drug combination of isoniazid, rifampin, and pyrazinamide) in June 2020. Information on drug shortages and discontinuations is available from FDA. FDA is working with other manufacturers to maintain availability of rifampin, and there is no national shortage of rifampin at present. Rifampin should be prescribed as an essential part of a multi-drug regimen for the treatment of active TB disease. Rifampin can also be prescribed, as 3

months of daily isoniazid and rifampin (3HR) or 4 months of daily rifampin (4R), for treating LTBI to prevent the development of active TB disease per current National TB Controllers Association (NTCA)/CDC guidelines.

Information on Rifapentine

In June 2020, shipments of rifapentine (supplied as Priftin® 150 mg film-coated tablets manufactured by Sanofi) were paused after a nitrosamine impurity was found. FDA and Sanofi have not announced when shipments will resume, and FDA still lists rifapentine as "Currently in Shortage." Where local supplies of rifapentine are enough for complete regimens, providers can continue to prescribe the 3-month regimen of weekly rifapentine with isoniazid (3HP) for treating LTBI. Where rifapentine is in shortage, providers can consider other rifamycin-based regimens such as 3HR or 4R, which have completion rates comparable to 3HP.

Information on Drug Treatment Continuation for LTBI

Patients who are already taking rifampin or rifapentine-containing regimens for LTBI can continue their treatment. If a clinician or a patient prefers to discontinue one of these regimens, a complete regimen of 6 or 9 months of isoniazid can be started. However, isoniazid regimens are associated with increased risk of drug-induced liver injury and lower completion rates. Therefore, CDC does not recommend discontinuing rifamycin-based short-course LTBI treatment in favor of isoniazid-only treatment unless necessitated by another event (e.g., adverse reaction to a rifamycin).

The North Dakota Department of Health's TB Program recognizes nitrosamine impurity issue may cause concern for persons taking rifampin.

What patients should know about nitrosamine impurities:

1. FDA has been investigating the presence of impurities, called nitrosamines, in some types of medications.
2. Nitrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables. Everyone is exposed to some level of nitrosamines.
3. FDA, in collaboration with regulatory counterparts around the world, has set internationally-recognized acceptable daily intake limits for nitrosamines. If drugs contain levels of nitrosamines above the acceptable daily intake limits, FDA recommends these drugs be recalled by the manufacturer as appropriate.
4. Nitrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that

contains nitrosamines at-or-below the acceptable daily intake limits every day for 70 years is not expected to have an increased risk of cancer.

5. Patients taking prescription medications with potential nitrosamine impurities should not stop taking their medications. Patients should talk to their health care professionals about concerns and other treatment options.

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