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CDC HEALTH ADVISORY

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Recommendations for Drug Allocation, Tuberculosis Prevention, and Patient Care During Isoniazid Shortages

Summary: *Shortages of isoniazid (INH), a cornerstone drug for treating tuberculosis disease (TB) and latent* Mycobacterium tuberculosis *infection (LTBI), are continuing. This notice gives an update on the shortages and expands general guidance to public health officials and clinicians about how to adjust practices in response to the shortages from that outlined in CDC's December 21, 2012, Morbidity and Mortality Weekly Report (MMWR) (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6150a4.htm). It also outlines national plans for restoring INH supplies and lists published guidance that could assist in making treatment decisions when INH is unavailable.*

Background

U.S. INH production has been interrupted, and stocks are dwindling. Consequent to the critical shortage of 300 mg tablets that was recently reported (*1*), the stocks of 100 mg tablets in some localities are reportedly being depleted. An initial forecast date for restoring INH production has been extended from late January 2013 to as late as March 2013 (*1,2*); however, the forecasts are unstable and vary by company. One of three pharmaceutical companies supplying INH, VersaPharm Incorporated, Marietta, Georgia, has notified public health officials that it is cancelling all INH backorders and not accepting new orders.

Clinical and Public Health Recommendations

While INH is in shortage, clinicians should coordinate TB and LTBI treatment plans with their jurisdictional public health officials, who should set priorities for allocating INH stock locally. These priorities should be set according to the immediate medical needs of individual patients and a general TB control strategy:

1) treating patients who have TB disease,
2) treating LTBI patients who are diagnosed during contact tracing of contagious TB (i.e., contact investigations), and
3) treating LTBI patients who face the greatest likelihood of TB disease (e.g., HIV-infected patients) or the hazard of severe illness (e.g., children <5 years old).

Treatment for LTBI can be postponed when the likelihood or hazard of TB disease is low, but systems should be developed for recalling patients when INH becomes available.

The World Health Organization (WHO) recommends that "drugs for the full course of treatment are reserved for the patient at the outset of treatment" (*3*). However, the abrupt onset of the INH shortage means that treatment for some TB patients could be disrupted in mid-course. Decisions for continuing treatment in these situations should be made on a case-by-case basis in consultation with a TB expert, as arranged by jurisdictional public health officials.

Fixed dose combination formulations of INH and rifampin or INH, rifampin, and pyrazinamide can be used for treating TB disease if the dosages of all the drugs are correct for the patient (4). However, at least one fixed dose combination is already on backorder, and stocks are believed to be depleted. A full treatment course of drugs should be secured before starting treatment with one of these combinations.

Regimens without INH for treating TB disease are less well studied than those with INH. CDC, the American Thoracic Society, and the Infectious Diseases Society of America have recommended a regimen of rifampin, pyrazinamide, and ethambutol for 6 months, with consideration of a fluoroquinolone, such as moxifloxacin or levofloxacin, for more extensive disease, when the infecting *M. tuberculosis* isolate is INH-resistant or the patient is intolerant of INH (*4*). Directly observed therapy should be used for reducing the potential for acquired rifampin resistance.

An alternative treatment regimen for LTBI, when the infecting *M. tuberculosis* is believed to be INH resistant, or when the patient cannot tolerate INH, is rifampin administered for 4 months, either self-administered or directly observed (5). This regimen has been adopted for routine use by some U.S. TB program directors. A combination regimen of INH and rifampin for 3 or 4 months is used overseas and in some U.S. jurisdictions, although it is not currently recommended in U.S. national guidelines (5,6). This regimen could be prescribed via a fixed dose combination of INH and rifampin if supplies for complete treatment courses are in stock. The combination regimen of rifampin and pyrazinamide for 2 months is *not recommended because of excess toxicity*. Any of the alternative regimens for TB disease or LTBI could be more expensive than the standard regimens.

CDC is working with the Food and Drug Administration (FDA), the National Tuberculosis Controllers Association, and the two pharmaceutical companies currently planning to supply INH (Teva Pharmaceuticals USA, Sellersville, Pennsylvania; and Sandoz Inc., Princeton, New Jersey) to determine current INH stocks, jurisdictions with urgent needs, and options for restoring supplies as soon as can be safely done. CDC will monitor notifications from public health officials of INH shortages and stocks, and will provide updates as they are available on the website for the Division of Tuberculosis Elimination at http://www.cdc.gov/tb/.

References for More Information:

1. CDC. Notes from the field: national shortage of isoniazid 300 mg tablets. *MMWR*. 2012;61:1029. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6150a4.htm?s_cid=mm6150a4_w
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3. World Health Organization. Treatment of tuberculosis: guidelines, fourth edition. WHO Press, 2010. Available at http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.
4. CDC. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America. *MMWR* 2003;52(No. RR-11). Available at http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.
5. CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(No. RR-6), available at http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf.
6. National Institute for Health and Clinical Excellence. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. NICE clinical guideline 117. Royal College of Physicians of London, 2006 and 2011. Available at http://www.nice.org.uk/nicemedia/live/13422/53638/53638.pdf.

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