Drug Safety Revisions: FDA Update

Marvin M. Goldenberg, PhD, RPh, MS

Leflunomide (Arava®)

Manufacturer: Aventis Pharmaceuticals, Inc., Briegewater, NJ

Indications: Treatment of active rheumatoid arthritis (RA) in adults to reduce signs and symptoms; to inhibit structural damage, as evidenced by x-ray erosions and joint space narrowing; and to improve physical function.

Rationale for Labeling Change: The manufacturer has issued a letter detailing post-marketing reports of hepatotoxicity, summarized for the European Agency for the Evaluation of Medicinal Products (EMEA). This report details the experiences of patients who were given leflunomide worldwide, with a total drug exposure of 104,000 patient-years. The report describes 296 cases of hepatic abnormalities, including 129 cases of serious reactions.

Included in the 296 reports are 232 patients with liver-function test abnormalities, two with cirrhosis, and 15 with liver failure (nine of these patients died, three from liver failure and six from a concomitant illness); a total of 15 patients died. Of the patients with elevated liver-function enzymes, 58% were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) with or without methotrexate.

Of the patients with serious adverse effects, 101 (78%) were taking concomitant hepatotoxic medications. Of the 64 patients with serious hepatic events who had a clinical diagnosis of liver disease, 19 were taking concomitant methotrexate.

Confounding comorbidities included previous or concurrent alcohol abuse; hepatitis A, B and C; interstitial lung disease; renal insufficiency; autoimmune liver disease; and pancreatitis. Serious hepatotoxicities included drug-induced hepatitis, reactivation of viral hepatitis (especially hepatitis B), fulminant hepatic failure, jaundice, cholestasis, hepatomegaly, and hepatic cirrhosis. Two patients with cirrhosis had used methotrexate concomitantly or previously, and one of them had pre-existing evidence of hepatitis and cirrhosis during methotrexate therapy.

Only a few liver biopsies were performed, and these showed various abnormalities, including centrilobular necrosis with portal or periportal inflammation, steatosis, focal piecemeal necrosis, and periportal fibrosis.[1]

Labeling Change, Hepatotoxicity Section

Rare cases of severe liver injury, including cases with fatal outcomes, have been reported during treatment with leflunomide. Most cases of severe liver injury occur within six months of therapy and in a setting of multiple risk factors for hepatotoxicity, such as liver disease or other hepatotoxicity.

Current Labeling, Hepatoxicity Section

At a minimum, alanine aminotransferase (ALT) levels must be determined at the baseline evaluation and monitored monthly for the first six months; after they are stable, monitoring is recommended every two to three months. Proper monitoring in patients taking concomitant methotrexate or other hepatotoxic drugs includes a determination of both ALT levels (which might be more sensitive to leflunomide hepatotoxicity) and aspartate transaminase (AST) levels before drug therapy is initiated. AST and ALT levels should be ascertained at least monthly for six months and thereafter every one to three months. More frequent monitoring is necessary in patients with elevated liver-function enzymes, in which case the dose should be reduced or the drug discontinued. If sporadic minor elevations (more than one times and less than two times the upper limits of normal [ULN]) of AST or ALT occur, testing should be repeated within two to four weeks.

A trial of dose reduction and repeated testing are warranted for patients with moderate ALT elevation of two to three times the ULN, with discontinuation if elevation of ALT above two times ULN persists.

Although liver-function test findings are not a perfect reflection of potential drug-induced hepatotoxicity, persistently abnormal liver-function enzymes or a result above three times the ULN should not be tolerated and should prompt drug withdrawal and drug elimination (e.g., with cholestyramine):

- 4–8 g three times daily for two to three days
- 4 g three times daily for one day (to reduce leflunomide levels by about 50%
- 4 g three times a day for five days (generally adequate for washout; if pregnancy is desired, a longer washout is needed)

If leflunomide therapy is discontinued because of hepatotoxicity and a change to another hepatotoxic disease-modifying antirheumatic drug is contemplated, washout and monitoring procedures should be followed.

Conclusion: Substantial attention has recently focused on the possibility of serious liver toxicity in patients taking leflunomide.[2] Fortunately, such toxicity appears to be uncommon. However, regular monitoring of liver function during leflunomide therapy remains an important guideline, and transaminase elevations or depression of serum albumin should be taken seriously. It is not clear, according to the current literature, whether serious hepatotoxicity associated with leflunomide is mediated by potentiation of hepatotoxicity induced by concurrently used agents (including methotrexate) or by direct actions of leflunomide on the liver.

Dr. Goldenberg is Executive Director of Pharmaceutical and Scientific Services for MMG Associates in Westfield, New Jersey, and coordinates the Pharmaceutical-Approval Update column. His email address is mmgpotter@comcast.net.

ComfortGel™ Nasal Mask

Manufacturer: Respironics, Inc., Murrysville, PA

Indication: Obstructive sleep apnea or respiratory failure; used in conjunction with continuous positive airway pressure (CPAP) devices. CPAP delivers a fixed pressure of normal room air, and this air pressure supports the airway and prevents it from collapsing during sleep. CPAP is considered the most successful, noninvasive way of treating obstructive sleep apnea and other sleep-related breathing disorders. It is safe and effective for patients of all ages, including children.

Reason for Recall: The mask works by exhausting all of the exhaled carbon dioxide (CO_2) out of an exhalation port that is built into the mask. The instructions inform patients that the mask contains an exhalation port and that a separate exhalation device is not required. However, the product was distributed without the exhalation port. Without the port in the breathing circuit, patients may breathe in exhaled CO_2 and may experience associated oxygen deficiency. In some cases, suffocation may result.

Conclusion: Use of the mask without the separate exhalation device exposes patients to a high risk of serious health consequences.

Sevofluran (Ultane®)

Manufacturer: Abbott Laboratories, North Chicago, IL

Indication: Induction and maintenance of general anesthesia in adults and children undergoing inpatient and outpatient surgery.

Reason for FDA Intervention: The U.S. Food and Drug Administration (FDA) intervened because of isolated reports of fire or extreme heat in the respiratory circuit of anesthesia machines when sevofluran was used in conjunction with a desiccated CO_2 absorbent, resulting in possible injury to patients.

Conclusion: Abbott has warned anesthesia providers of the potential adverse effects of sevofluran when it is used in anesthesia machines in association with a desiccated CO_2 absorbent. The company has advised the anesthesia providers about how to avoid exposing patients to the risks of such an event. For instance, the CO_2 absorbent can be replaced if it has not been used for an extended period of time. A low fresh gas flow rate over a prolonged period of time of non-use may also contribute to unexpected desiccation of CO_2-absorbent materials on the anesthesia machine.

Providers are advised to shut off the anesthesia machine completely at the end of clinical use or when a subsequent, extended period of non-use is anticipated. All vaporizers should be turned off when they are not in use, and the temperature of the CO_2-absorbent canisters should be monitored periodically.

The manufacturer and the FDA are investigating the causative and preventive factors surrounding the issues of fire, extreme heat, and potential breakdown products associated with the use of sevofluran and desiccated CO_2 absorbents.

Polypropylene Mesh (Prolene*)[3]

Manufacturer: Ethicon, a division of Johnson & Johnson, Somerville, NJ

Indication: Nonabsorbable mesh used in the repair of hernias and other fascial deficiencies.

Reason for FDA Intervention: The FDA has warned health care professionals about potential sterility problems because of a counterfeit polypropylene mesh product labeled as Prolene* polypropylene mesh. The manufacturer has sent a letter to health care professionals that the product labeled "Prolene* polypropylene mesh," code PMII, bearing lot numbers RBE609 (expiration date, January 2007) and RJJ130 (expiration date, July 2007) is a counterfeit product. Both are flat-mesh products (3 × 6 inches).

With the counterfeit product, the packaging seal sometimes does not tear open smoothly; there is clear tape on the box opening; there may be an orange dot sticker on some boxes; there is an additional small seal at the top corner edges of the package; the fabric end is jagged, not clean-cut, on the 3-inch side; there is no blank space at the end of the third line in the "Other Patent Pending" section; the word "Mesh" is in regular font; the words "LOT NO." are in the same size and in regular font; the pouch label is on an adhesive backing with obvious "slices"; the weave is tighter and asymmetrical; and the Ethicon logo appears in a more pronounced (bolder) typeface.

Recommendations: Physicians, nurses and other health care professionals are advised to carefully examine all polypropylene mesh products in their inventories, to avoid using any suspected counterfeit products, and to contact the distributor in cases of uncertainty. If they suspect that any patients have received implants with a counterfeit product, health care providers should continue to monitor patients in the same way as those with an authentic polypropylene mesh implant.

There have been no reports of an excess number of infections with the counterfeit product, but concern remains. Thus far, preliminary testing has shown the presence of these organisms on the tested samples: *Bacillus cereus, Bacillus licheniformis, Bacillus amyloliquefaciens,* and *Bacillus subtilis.*

Conclusion: Because Ethicon did not manufacture this product, the company cannot confirm the mechanical properties, the biocompatibility, or the sterility of the material, but the manufacturer wants health care professionals to be aware of this situation so that they can consider any potential health risks to patients. Ethicon is working with the FDA to investigate the matter.

REFERENCES

1. American College of Rheumatology, www.rheumatology.org.
2. Weinblatt ME, Dixon JA, Falchuk KR. Serious liver disease in a patient receiving methotrexate and leflunomide. *Arthritis Rheum* 2000;43:2609–2611.
3. Centers for Devices and Radiological Health; FDA, December 19, 2003, www.fda.gov/medwatch/SAFETY/2003/prolene.htm; www.ethicon.com (for updates).