ASTHMA MEDICATION RECEIVES NEW WARNING

- The labeling of omalizumab (Xolair), a drug used to treat allergic asthma, now carries a warning that its use may slightly increase the risk of cardiovascular complications. The drug may also pose an increased risk of inducing cancer.

The Food and Drug Administration (FDA) has revised the warnings in the labeling of omalizumab (Xolair), a drug used in the treatment of allergic asthma. Omalizumab's labeling now warns that the drug may carry a slightly elevated risk of cardiovascular complications (specifically transient ischemic attack, myocardial infarction, unstable angina, pulmonary hypertension, pulmonary embolism, and venous thrombosis).

Omalizumab is administered every two to four weeks as a subcutaneous injection to patients with moderate-to-severe persistent, allergic asthma and an elevated IgE level and whose allergic asthma symptoms aren't well controlled with corticosteroids. Omalizumab is a monoclonal antibody that inhibits the binding of IgE to high-affinity IgE receptors on the surface of mast cells and basophils. Treatment with omalizumab reduces the allergic response that produces asthma symptoms.

This labeling revision constitutes an update to a July 16, 2009, FDA announcement, "Early Communication About an Ongoing Safety Review of Omalizumab (Marketed as Xolair)." That announcement came in response to interim safety data from the then ongoing five-year observational study intended to assess the long-term safety of omalizumab. Five thousand patients treated with omalizumab and 2,500 controls were enrolled in the study, known as the Evaluating the Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS) trial. Although the primary purpose of that study was to assess the risk of cancer with omalizumab, the 2009 interim report showed a higher number of cardiovascular and cerebrovascular adverse events in patients receiving omalizumab, compared with those who didn't receive the drug. In the FDA's 2014 review of the final data from that trial, which prompted the labeling revision, a "higher incidence rate per 1,000 patient years of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non–Xolair-treated patients." Specifically, they found higher rates of myocardial infarction, unstable angina, transient ischemic attack, pulmonary embolism or venous thrombosis, and pulmonary hypertension.

Although the findings suggest increased risk of serious adverse events, the FDA thought several limitations of the study made it difficult to determine what actual risk omalizumab might pose: the observational design of the study, the inclusion of patients previously exposed to the drug (88% of those in the treatment arm had previously been prescribed omalizumab for a mean of eight months prior to starting the study), a higher baseline cardiovascular risk among omalizumab users (there was a higher percentage of patients with severe asthma in the treatment group [50%] than in the placebo group [23%]), an inability to adjust for unmeasured risk factors, and a high study dropout rate (46% in the treatment arm and 40% in the placebo arm).

In an effort to better understand the data from the EXCELS trial, the FDA also examined data pertaining to omalizumab's cardiovascular and cerebrovascular risk in a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials involving a total of 6,237 patients (3,342 of whom received omalizumab and 2,895 of whom received a placebo). The studies were eight to 52 weeks in duration. There were eight events in total among the patients receiving omalizumab and 15 among those who received placebo; no differences in the rates of specific cardiovascular events were seen. Also, the mean age of patients in the studies (38 years) was lower than that in the EXCELS trial (45 years), and the mean follow-up was only 6.8 months. In light of these limitations, the FDA felt that findings from the pooled analysis could neither confirm nor controvert the EXCELS findings.

The FDA also analyzed the EXCELS study data related to the risk of malignancy. This was because in the initial clinical trials there had been a greater number of various cancers in those who received omalizumab than in those who didn't. Final data from the EXCELS study didn't reveal an increased risk of malignancy with omalizumab use, however, although the FDA offers a disclaimer stating that study limitations prevent completely ruling it out. The FDA has also modified the warning of omalizumab's labeling to reflect the uncertain findings related to possible cancer risks.

NPs who prescribe or administer omalizumab should consider the uncertainty regarding the increased risk of cardiovascular events, particularly in light of the limitations in the EXCELS trial, and weigh it against the risks related to uncontrolled asthma in each patient. Patients receiving omalizumab should be monitored for cardiovascular problems. Nurses should not only provide patients with the drug's medication guide and encourage them to read it carefully, they should also discuss the possibilities of elevated cardiovascular and malignancy risks, especially

in patients already at increased risk.

Omalizumab's labeling continues to carry a boxed warning that the drug can produce anaphylaxis, which can occur at any time, from the first dose to after a year or more of repeated dosing. Patients should remain in the office and be observed for an appropriate time after receiving a subcutaneous dose of omalizumab.

Complete prescribing information can be found at www.gene.com/download/pdf/xolair_prescribing.pdf.

NEW TREATMENT FOR OPIOID-INDUCED CONSTIPATION

- The opioid antagonist naloxegol (Movantik) is now approved to treat opioid-induced constipation in adults with chronic noncancer pain.
- The most common adverse effects are abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache.

An opioid antagonist, naloxegol (Movantik), has now been approved to treat opioid-induced constipation in adults with chronic noncancer pain. Naloxegol binds to mu-opiate receptors in the gastrointestinal tract, preventing opioids from attaching to them, which prevents the gastrointestinal slowing and constipation that typically occur with opioid use.

Naloxegol is a PEGylated derivative of naloxone; PEGylation is the process of modifying biologic molecules through covalent attachment of polyethylene glycol (PEG) polymer chains. PEGylation improves drug solubility; decreases immune responses to a drug; increases drug stability; and modifies the pharmacokinetics of the drug to increase the time it stays in the circulation, allowing for less-frequent dosing. PEGylation of naloxegol makes it unlikely to enter the central nervous system and alter the analgesic effect of opioids.

In clinical trials, patients who used naloxegol had significantly more bowel movements per week than patients who received a placebo. Naloxegol hasn't been studied in patients with cancer (hence the restriction on use in such patients).

The most common adverse effects are abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache. Gastrointestinal perforation has been reported in patients receiving other opioid antagonists, so caution should be used in the administration of naloxegol to patients with diminished gastrointestinal-wall integrity. Although an intact blood–brain barrier generally minimizes any systemic effects of naloxegol, opioid withdrawal and loss of pain control have been seen in some patients; patients with an impaired blood–brain barrier and those using methadone for pain control appear to be at greater risk.

Drug interactions are related to naloxegol's metabolism via the cytochrome P-450 (CYP) enzyme system. Strong inhibitors of CYP3A4 (such as ketoconazole, clarithromycin, grapefruit, and grapefruit juice) significantly increase the circulating levels of naloxegol and can induce withdrawal symptoms; their use is contraindicated with naloxegol therapy. Moderate inhibitors of CYP3A4 (such as diltiazem, erythromycin, and verapamil) will increase circulating blood levels of naloxegol as well and should be avoided; if coadministration cannot be avoided, the dosage of naloxegol should be reduced to 12.5 mg daily, and patients should be monitored for adverse effects of naloxegol. When naloxegol is coadministered with strong inducers of CYP3A4 (such as rifampin, St. John's wort, and carbamazepine), concentrations of naloxegol will decrease; coadministration of these agents isn't recommended.

If the patient receives an additional opioid antagonist, there is potential for an additive effect, increasing the risk of opioid withdrawal and a loss of pain control. Such combinations should also be avoided.

In addition to concomitant use of strong CYP3A4 inhibitors, other contraindications to naloxegol are a known or suspected gastrointestinal obstruction (or an increased risk of recurrent obstruction) and a history of serious or severe hypersensitivity reaction to the drug.

Nurses should take a thorough drug and dietary history to confirm that the patient doesn't take other drugs or ingest any foods that will alter circulating levels of naloxegol. Nurses should confirm that patients starting naloxegol understand that they should discontinue any maintenance laxatives they may be taking. If constipation continues after three days of naloxegol therapy, the patient should contact the prescriber; in such cases the drug may be given in addition to other laxatives. Nurses should teach patients to take the drug on an empty stomach at least one hour before the first meal of the day or two hours after (because a high-fat meal will increase the extent and rate of absorption and may increase the drug's effect). The tablets should be swallowed whole; crushing or chewing should be avoided. If opioid therapy is discontinued, the nurse should confirm that naloxegol is also discontinued.

For complete prescribing information, see http://1.usa.gov/1yzGfyR. ▼

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