FDA approves once-popular morning sickness drug

By: ELIZABETH MECHCATIE, Ob.Gyn. News Digital Network

4-9-2013

For the first time in 30 years, clinicians will be able to prescribe a Food and Drug Administration-approved treatment for their pregnant patients who are experiencing nausea and vomiting and have not responded to changes in their diet or other conservative measures.

On April 9, the FDA announced the approval of a delayed-release, fixed-dose formulation of 10 mg of doxylamine, an antihistamine; and 10 mg of pyridoxine, a vitamin B_6 analog, for "the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management."

This combination was widely used as an effective treatment for nausea and vomiting of pregnancy (NVP) in the United States and Canada in the 1960s and 1970s, and was marketed as Bendectin. But it was voluntarily taken off the U.S. market by the manufacturer in 1983, amid allegations and lawsuits that the drug caused birth defects – which were never substantiated with scientific data. The combination, which has been available as separate components in the United States, was recommended as a first-line treatment for NVP in a 2004 American College of Obstetricians and Gynecologists practice statement that was reaffirmed in 2011 (Obstet. Gynecol. 2004;103:803-15).

In a clear sign that the issue has been resolved, the FDA has assigned Diclegis a category A pregnancy risk rating, with a statement in the label summarizing the epidemiologic studies indicating that the combination of the two active ingredients has not been associated with increased risks to the fetus.

"Diclegis is now the only FDA-approved treatment for nausea and vomiting due to pregnancy, providing a therapeutic option for pregnant women seeking relief from these symptoms," Dr. Hylton V. Joffe, director of the division of reproductive and urologic products in the FDA's Center for Drug Evaluation and Research, said in the FDA statement. It is expected to be widely available in the United States by the end of May, according to the Canadian manufacturer, Duchesnay Inc., which markets the same product in Canada.

The approval "is a big victory for American women and health care professionals, especially obstetricians and family physicians, because over the last 3 decades, American women have not had an FDA-approved medication for the most common condition of pregnancy, morning sickness," said Dr. Gideon Koren, the head of the Research Leadership for Better Pharmacotherapy During Pregnancy and Lactation at the Hospital for Sick Children, Toronto. After Bendectin was removed from the market, the rate of hospitalizations for hyperemesis gravidarum markedly increased in the United States, "clearly showing that when you remove a drug that a very large number of women need, a void is created and women suffer," he added.

The FDA approval was based on a study of 261 women with NVP in the United States who were at least 18 years-of-age and who were 7-14 weeks pregnant (mean gestational age was 9.3 weeks). Those randomized to receive treatment with Diclegis for 2 weeks had greater improvements in nausea and vomiting, compared with those who received a placebo, as reflected in changes in a score that incorporated the number of daily episodes of vomiting and heaves, and hours of nausea. The most common side effect associated with Diclegis was drowsiness, which can be severe, according to the FDA.

Diclegis is taken daily and is not used as an as-needed treatment for symptoms. The recommended dosage regimen is an initial dose of two tablets at bedtime on the first day. If symptoms persist through the afternoon of the second day, the woman should take two tablets at bedtime and one tablet the following morning (day 3). If symptoms are still present on the fourth day, she should take one tablet in the morning, one tablet in the middle of the afternoon and two tablets at bedtime. Four tablets are the maximum recommended daily dose. In the study, 19% of the women treated with Diclegis took two tablets a day, 21% took three tablets a day, and 60% took four tablets a day.

The prescribing information includes a statement that the combination of doxylamine and pyridoxine "has been the subject of many epidemiologic studies (cohort, case control, and meta-analyses) designed to detect possible teratogenicity," including studies published between 1963 and 1991, which did not report evidence of fetal abnormalities associated with first trimester exposure.

In an interview, Dr. Koren, professor of pediatrics, pharmacology, pharmacy, medicine, and medical genetics at the University of Toronto, said that the safety studies include data on more than 300,000 mother-child pairs. When Bendectin was taken off the U.S. market, it was already available as a generic in Canada as Diclectin and was never taken off the market. The continuous experience with the product in Canada should also make U.S. practitioners confident with its safety, he added. Dr. Koren was the primary investigator in the U.S. study (Am. J. Obstet. Gynecol. 2010;203:571.e1-7).

Since NVP usually improves after the first trimester, "health care professionals should reassess their patients for continued need for Diclegis as pregnancy progresses," the FDA statement says. In addition, women should not use Diclegis "when engaging in activities requiring mental alertness, such as driving or operating heavy machinery, until cleared to do so by their health care provider."

The label states that Diclegis has not been studied in women with hyperemesis gravidarum and that women should not breastfeed while on the drug.