Information for Healthcare Professionals

Angiotensin-converting enzyme inhibitor (ACE inhibitors) drug class (names of drugs in this class listed below)

FDA ALERT [06/2006]: On June 8, 2006, the *New England Journal of Medicine* published an article reporting that infants whose mothers had taken an angiotensin-converting enzyme inhibitor (ACE inhibitor) drug during the first trimester of pregnancy had an increased risk of major congenital malformations, compared with infants who had not undergone first trimester exposure to ACE inhibitor drugs. The number of cases of birth defects is small and the findings of this study have not yet been repeated (see below for more information about the study). According to the approved labels, ACE inhibitors are labeled as pregnancy category C for the first trimester of pregnancy and pregnancy category D during the second and third trimesters. The existing prescribing information recommends discontinuing the ACE inhibitors as soon as possible if a patient becomes pregnant. The FDA does not plan to change the pregnancy categories at this time. However, healthcare professionals should take these findings into consideration with other information about a patient's medical situation when prescribing ACE inhibitors.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Considerations

Physicians caring for pregnant women or women who need antihypertensive treatment and who might become pregnant should consider the following information:

- FDA approved labeling for ACE inhibitors recommends discontinuation of the ACE inhibitor as soon as possible if a patient receiving therapy with an ACE inhibitor becomes pregnant.
- According to a new, observational study, exposure of a fetus during the first trimester of development to ACE inhibitors may place the infant at increased risk for major congenital malformations.

Data Summary

Cooper et al (2006) report that they analyzed data from the Tennessee Medicaid database, identifying infants born between 1985 and 2000, with first trimester fetal exposure to ACE inhibitors, or to other antihypertensive drugs, or no exposure to antihypertensive drugs of any kind. Other data bases were then checked for major congenital malformations in these infants. The infants who had been exposed to ACE inhibitors during the first trimester of their development had an increased overall relative risk of major congenital malformations (risk ratio 2.71 with a 95 percent confidence interval range of 1.72 to 4.27), compared to infants with no

exposure to antihypertensive drugs in the first trimester. The article (reference below) provides a breakdown of types of congenital malformations and other study details.

Potential major congenital defects were identified from birth and death certificates and hospitalizations, and then analyzed by reviewers blinded to maternal prescriptions. Of the types of defects identified, half were various cardiac septal defects, and the other half included some defects of the central nervous, urologic, or other systems. The mothers on ACE inhibitors were on average older and more likely to have other chronic conditions than were the mothers not taking any antihypertensive drugs. The investigators restricted their observations to infants whose mothers met study criteria for no diabetes, though the protocol definition might not have excluded all such patients.

ACE inhibitors are already associated with increased risks to the fetus during the second and third trimesters of pregnancy, as the fetal kidneys are developing. Angiotensin II receptors are, however, already present earlier in fetal development so the authors hypothesized that there might be increased risk then as well. If ACE inhibitors are teratogenic in early pregnancy because of widespread expression of angiotensin II receptors, then angiotensin receptor antagonist drugs might also be teratogenic. The mechanism whereby the various congenital malformations reported might occur, however, remains unclear.

See William O. Cooper, Sonia Hernandez-Diaz, Patrick G. Arbogast, Judith A. Dudley, Shannon Dyer, Patricia S. Gideon, Kathi Hall, and Wayne A. Ray. "Major congenital malformations after first-trimester exposure to ACE inhibitors." ***New England Journal of Medicine***, volume 354 number 23, pages 2443-2451. June 8, 2006. This study was supported in part by the FDA (FDA 221-02-3003).

ACE inhibitors include Benazepril (Lotensin), Captopril (Capoten), Enalapril/Enalaprilat (Vasotec oral and injectable), Fosinopril (Monopril), Lisinopril (Zestril and Prinivil), Moexipril (Univasc), Perindopril (Aceon), Quinapril (Accupril), Ramipril (Altace), and Trandolapril (Mavik).