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## Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor) Drugs and Pregnancy

[ACE inhibitor drugs include Benazepril (Lotensin), Captopril (Capoten), Enalapril/Enalaprilat (Vasotec oral and injectable), Fosinopril (Monopril), Lisinopril (Zestril and Prinivil), Moexipril (Univase), Perindopril (Aceon), Quinapril (Accupril), Ramipril (Altace), and Trandolapril (Mavik)]

**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 inhibitors) 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 inhibitor drugs are labeled as pregnancy category C for the first trimester of pregnancy, though they are labeled pregnancy category D during the second and third trimesters and the existing prescribing information recommends discontinuing the ACEI as soon as possible if a patient becomes pregnant. Because of the preliminary nature of the newly published data, the FDA does not plan to change the pregnancy categories at this time, but healthcare professionals should take these findings into consideration with other information about a patient's medical situation during early pregnancy.

*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.*

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### Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor) Drugs

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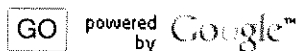
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**FDA Public Health Advisory****Angiotensin-Converting Enzyme Inhibitor (ACE inhibitor) Drugs and Pregnancy**

[ACE inhibitor drugs 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)]

A new study in the *New England Journal of Medicine* suggests that angiotensin-converting enzyme inhibitor drugs (ACE inhibitors or ACEIs) may be associated with increased risk of birth defects when used in the first three months of pregnancy. While the results of this single study do not establish a causal relationship between exposure to the drugs early in pregnancy and birth defects, they are concerning. ACE inhibitors are already known to have risks to the developing infant when used in the last six months of pregnancy. The prescribing information for all ACE inhibitor drugs has long emphasized that women who become pregnant should be taken off ACE inhibitors as soon as possible to avoid exposure of the fetus in the second and third trimesters, which is known to cause fetal abnormalities, especially related to the kidneys and related structures. The findings from this new study, which was supported by funding from the Agency for Healthcare Policy & Research and FDA, confirm the importance of this recommendation.

ACE inhibitor drugs are used to treat high blood pressure by slowing the body's production of a hormone that constricts blood vessels. The labels for all the ACE inhibitors begin with a boxed warning that the drugs may harm unborn babies in the second and third trimester of pregnancy. FDA recommends the following:

- Healthcare providers who care for women of reproductive age should counsel those who are treated with an ACE inhibitor about the potential risks of these drugs throughout pregnancy, especially during the second and third trimesters.
- Pregnant women should only be prescribed ACE inhibitors if the expected benefit clearly exceeds the potential risk.
- Women who become pregnant should have their ACE inhibitor changed to a different medication as soon as possible.
- Women who are taking ACE inhibitors to treat high blood pressure should tell their healthcare professionals if they are planning a pregnancy or think they might be pregnant.


The observational study published on June 8, 2006 (one that reports on patients who are being treated with usual medical care, not in a clinical trial) reports that babies whose mothers had taken an ACE inhibitor during the first three months of pregnancy had an increased risk of birth defects, compared with babies whose mothers had not taken any drugs for high blood pressure.

ACE inhibitors are labeled with a pregnancy category D for the last six months (the second and third trimesters) and C for the first three months. Pregnancy category D means that there have been studies in pregnant women showing that the drug was associated with some risk for the unborn baby (fetus), but the benefit of the drug may still outweigh that risk for some patients. Pregnancy category C means that the risk in pregnancy is possible but unknown, because no good studies of pregnant women have been done, and animal studies either have shown risk in pregnancy or have not been done. For more information about the pregnancy categories and also about the risk of leaving diseases untreated in pregnant women, see the story posted at [http://www.fda.gov/fdac/features/2001/301\\_preg.html#danger](http://www.fda.gov/fdac/features/2001/301_preg.html#danger)

At this time, based on this one observational study, the FDA does not plan to change the pregnancy categories for ACE inhibitors. FDA will work with the Agency for Healthcare Quality and Research to identify other potential sources of data that will help determine the degree of risk associated with first trimester exposures to these drugs.

For the recent study, 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.

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## Patient Information Sheet

### Angiotensin-Converting Enzyme Inhibitor Drugs (ACE Inhibitors)

This is a summary of the most important information about prescription ACE inhibitors. For more information, talk to your healthcare professional.

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**FDA ALERT [06/2006]:** Blood pressure medicines called angiotensin-converting enzyme inhibitors (ACE inhibitors) may be associated with increased risk of birth defects if taken during early pregnancy (first three months, or first trimester).

On June 8, 2006, the *New England Journal of Medicine* published an article reporting a study that showed babies whose mothers had taken an ACE inhibitor during the first three months of pregnancy had an increased risk of birth defects. The number of birth defects was small, and the study has not been repeated.

Before this study, it was known that ACE inhibitors can harm an unborn baby when taken during the last six months of pregnancy (second and third trimester).

If you are pregnant or planning to become pregnant and take a blood pressure medicine, talk with your healthcare professional. High blood pressure is a condition that needs treatment. Your healthcare professional can advise you on the blood pressure medicine that is best for you and your baby during pregnancy.

*This information reflects FDA's preliminary analysis of data concerning these drugs. 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.*

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#### What Are ACE Inhibitors?

- ACE inhibitors are used alone or with other medicines to treat high blood pressure in adults.

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).

There is a list of prescription ACE inhibitors available at: [http://www.fda.gov/cder/drug/infopage/ace\\_inhibitors/default.htm](http://www.fda.gov/cder/drug/infopage/ace_inhibitors/default.htm)

#### Who Should Not Take ACE Inhibitors?

If you are pregnant or planning to become pregnant and take a blood pressure medicine, talk with your healthcare professional. ACE inhibitors can harm or even cause death to

an unborn baby (fetus) if taken during the last six months of pregnancy.

#### What Are The Risks?

*The following are the major potential risks and side effects of ACE inhibitor therapy. However, this list is not complete.*

- **Birth defects or death of an unborn baby.**
- **Kidney problems** that include worsening of kidney problems that you already have. Symptoms include a sudden weight gain and swelling of your arms, hands, legs, and feet.

*The most common side effects with ACE inhibitors are:*

- Dizziness
- Dry cough
- Sore throat

#### What Should I Tell My Healthcare Professional?

Before you start taking an ACE inhibitor, tell your healthcare professional if you:

- have had hives or allergic-type reactions after taking another ACE inhibitor
- have kidney problems
- are trying to become pregnant, are already pregnant, or are breast-feeding

If you are already taking an ACE inhibitor, tell your healthcare professional if you

- become pregnant.
- notice swelling of your face, mouth or throat, or have difficulty swallowing or breathing – this could be serious and you should get medical help right away.

#### Can Other Medicines or Food Affect ACE Inhibitors?

ACE inhibitors and certain other medicines can interact with each other. Tell your healthcare professional about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them with you to show your healthcare professional.





## Information for Healthcare Professionals

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

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**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.

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#### 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



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(5600 Fishers Lane, Rockville, MD 20852-9787),  
or by telephone (1-800-FDA-1088).



## Information for Healthcare Professionals

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

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).



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