DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-184/S-013 & S-014

Solvay Pharmaceuticals, Inc.
Attention: Julie Brideau, Pharm.D.
901 Sawyer Road
Marietta, GA 30062

Dear Dr. Brideau:

Please refer to your supplemental new drug applications dated February 21, 2008 (S-013) and April 11, 2008 (S-014), submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Aceon (perindopril erbumine) 2, 4, and 8 mg Tablets.

These "Changes Being Effected" supplemental new drug applications provide for draft electronic labeling with the following changes to the **USE IN PREGNANCY**, **WARNINGS**, **PRECAUTIONS**, and **ADVERSE REACTIONS** sections of the package insert.

S-013

1. Under the **USE IN PREGNANCY** section, the following sentence has been revised from:

   When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus.

   to:
   When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus.

2. Under **WARNINGS**, **Fetal/Neonatal Morbidity and Mortality** subsection, the following paragraphs have been changed from:

   The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development. Prematurity, intrauterine growth retardation and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

   These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor

exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACEON® Tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

to:
The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation and hypoplastic lung development.

Prematurity, intrauterine growth retardation, patent ductus arteriosus, and other structural cardiac malformations, as well as neurological malformations, have been reported following exposure to ACE inhibitors during the first trimester of pregnancy.

When patients become pregnant, physicians should make every effort to discontinue the use of ACEON® Tablets as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

3. Under the **PRECAUTIONS**/***Pregnancy*** subsection, the following section has been revised from:

Pregnancy: Female patients of childbearing age should be told about the consequences of second and third trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

to:
Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ACE inhibitors during pregnancy. Discuss other treatment options with women planning to become pregnant. Women who do become pregnant while on an ACE inhibitor (including ACEON) should be asked to stop the medication and contact their physician as soon as possible.

4. Under the **WARNINGS**/***Pregnancy*** subsection, the following sentence has been changed from:

Pregnancy: Pregnancy Categories C (first trimester) and D (second and third trimesters). (See **WARNINGS: Fetal/Neonatal Morbidity and Mortality**.)

to:
Pregnancy: Pregnancy Category D. (*See* **WARNINGS: Fetal/Neonatal Morbidity and Mortality**.)

5. Under the **WARNINGS/Geriatric Use** subsection, the following language has been added:

   Perindopril should be used with caution when administered to elderly patients who are at an increased risk for falls due to age, their underlying disease and/or their concurrent use of medications(s) associated with falls. Falls and fall-related events may be exacerbated by the central nervous system effects of dizziness and syncope as well as the symptomatic hypotension, including orthostatic, associated with perindopril.

6. Under the **ADVERSE REACTIONS/Potential Adverse Effects Reported with ACE Inhibitors** subsection, the following events have been added:

   pemphigus, falls, psoriasis

7. We also note deletion of all trailing zeros throughout the package insert.

S-014

8. Under the **PRECAUTIONS/Drug Interactions** subsection, the following interaction has been added:

   Gold: Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE Inhibitor therapy including ACEON®.

We have completed our review of these supplemental new drug applications, and they are approved, effective on the date of this letter, for use as recommended in the draft electronic SPL labeling dated February 21, 2008 (S-013) and April 11, 2008 (S-014).

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Alisea Crowley, Pharm.D., Regulatory Project Manager, at (301) 796-1144.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge

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