DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020312/S-034
NDA 020729/S-025

SUPPLEMENT APPROVAL

UCB, Inc.
Attention: Kristen Piatak, RAC
Associate Director, Regulatory Affairs
1950 Lake Park Drive
Smyrna, GA 30080

Dear Ms. Piatak:

Please refer to your Supplemental New Drug Applications (sNDAs) dated December 15, 2011, and received December 16, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Univasc (moexipril hydrochloride) 7.5 mg and 15 mg Tablets (NDA 020312) and Uniretic (moexipril hydrochloride/hydrochlorothiazide) 7.5/12.5 mg, 15/12.5 mg and 15/25 mg Tablets (NDA 020729).

These "Changes Being Effected" supplemental new drug applications provide for labeling revised as follows:

For NDA 020312:

1. The Boxed Warning was changed to:

> **WARNING: FETAL TOXICITY**
>
> *See full prescribing information for complete boxed warning.*
>
> - **When pregnancy is detected, discontinue Univasc as soon as possible.**
> - **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS: Fetal Toxicity**

2. Under **WARNINGS,** the section was changed from:

> ***Fetal/Neonatal Morbidity and Mortality***
>
> ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

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 were caused by the ACE inhibitor exposure.

Fetal and neonatal morbidity do not appear to have resulted from intrauterine ACE inhibitor exposure limited to the first trimester. Mothers who have used ACE inhibitors only during the first trimester should be informed of this. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of moexipril 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 intraamniotic environment.

If oligohydramnios is observed, moexipril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware; however, that oligohydramnios may not be detected until after the fetus has sustained irreversible injury.

Infants with histories of *in utero exposure* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Theoretically, the ACE inhibitor could be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

No embryotoxic, fetotoxic, or teratogenic effects were seen in rats or in rabbits treated with up to 90.9 and 0.7 times, respectively, the Maximum Recommended Human Dose (MRHD) on a mg/m2 basis.

To:

Fetal Toxicity
Pregnancy category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Univasc as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin

system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Univasc, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to Univasc for hypotension, oliguria, and hyperkalemia (see PRECAUTIONS, Pediatric Use).

No embryotoxic, fetotoxic, or teratogenic effects were seen in rats or in rabbits treated with up to 90.9 and 0.7 times, respectively, the Maximum Recommended Human Dose (MRHD) on a mg/m^2 basis.

3. Under **PRECAUTIONS, Information for Patients, Pregnancy,** the section was changed from:

   Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors and 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. Patients should be asked to report pregnancies to their physicians as soon as possible.

To:

   Female patients of childbearing age should be told about the consequences of exposure to Univasc during pregnancy. Discuss treatment options with women planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

4. Under **PRECAUTIONS/Pediatric Use**, a new section was added:

   Neonates with a history of *in utero* exposure to Univasc**:**
   If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. The revision date and version number were updated.

6. All references to Pregnancy Category C and cross references to Fetal/Neonatal Morbidity and Mortality were deleted.

There are no other changes from the last approved package insert.

For NDA 020729:

1. The Boxed Warning was changed:

> **WARNING: FETAL TOXICITY**
>
> *See full prescribing information for complete boxed warning.*
>
> - **When pregnancy is detected, discontinue Uniretic as soon as possible.**
> - **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. See WARNINGS: Fetal Toxicity**

2. Under **WARNINGS,** the section was changed from:

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

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 were caused by the ACE inhibitor exposure.

Fetal and neonatal morbidity do not appear to have resulted from intrauterine ACE inhibitor exposure limited to the first trimester. Mothers who have used ACE inhibitors only during the first trimester should be informed of this. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of moexipril 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 intraamniotic environment.

If oligohydramnios is observed, Uniretic should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be detected until after the fetus has sustained irreversible injury.

Infants with histories of *in utero exposure* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be

directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Theoretically, the ACE inhibitor could be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

(b) (4)

To:

Fetal Toxicity
Pregnancy category D
Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse events include skull hypoplasia, anuria, hypotension, renal failure and death. When pregnancy is detected, discontinue Uniretic® as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue Uniretic, unless it is considered lifesaving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of *in utero* exposure to Uniretic for hypotension, oliguria, and hyperkalemia (see PRECAUTIONS, Pediatric Use).

3. Under **PRECAUTIONS, Information for Patients, Pregnancy,** the section was changed from:

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors and 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. Patients should be asked to report pregnancies to their physicians as soon as possible.

To:

Female patients of childbearing age should be told about the consequences of exposure to Uniretic during pregnancy. Discuss treatment options with women planning to become

pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible.

4. Under **PRECAUTIONS/Pediatric Use**, a new section was added:

   Neonates with a history of *in utero* exposure to Uniretic**:**
   If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

5. The revision date and version number were updated.

6. All references to Pregnancy Category C and cross references to Fetal/Neonatal Morbidity and Mortality were deleted.

There are no other changes from the last approved package insert.

We have completed our review of these supplemental applications, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
01/19/2012