DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019558/S-055; 019778/S-048

SUPPLEMENT APPROVAL

Merck, Sharp, & Dohme
Attention: David R. Hobart
Manager, Worldwide Regulatory Affairs
P.O. Box 2000, RY 33-208
Rahway, NJ 07065

Dear Mr. Hobart:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received May 18, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) Prinivil (lisinopril), 5 mg, 10 mg, and 20 mg Tablets (NDA 019558), and Prinzide (lisinopril/hydrochlorothiazide) 10/12.5 mg and 20/12.5 mg Tablets (NDA 019778).

This "Prior Approval" supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

For NDA 019558:

1. The boxed warning was revised:

> ~~**USE IN PREGNANCY**~~**WARNING: FETAL TOXICITY**
> ~~**When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus.**~~
> • **When pregnancy is detected, discontinue PRINIVIL ~~should be discontinued 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* ~~*Fetal/Neonatal Morbidity and Mortality*~~.**

2. Under **WARNINGS**, **Fetal Toxicity**, the following text was added/~~deleted~~:

> **Fetal~~/Neonatal Morbidity and Mortality~~ Toxicity**
> **Pregnancy Category D**
>
> ~~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.~~
>
> ~~In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers 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.~~

~~The u~~Use of ~~ACE inhibitors~~ drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces ~~has been associated with~~ fetal renal function and increases fetal and neonatal morbidity ~~injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure,~~ and death. Resulting o~~O~~ligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. ~~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.~~ Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death.~~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.~~ When pregnancy is detected, discontinue PRINIVIL as soon as possible. These adverse outcomes are usually associated with the 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 reninangiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

~~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 PRINIVIL as soon as possible.~~

In the unusual case that there is no appropriate alternative therapy ~~with~~ to drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. ~~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~~ Perform serial ultrasound examinations ~~should be performed~~ to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue PRINIVIL, ~~should be discontinued~~ unless it is considered lifesaving for the mother. Fetal testing ~~Contraction stress testing (CST), a non stress test (NST), or biophysical profiling (BPP)~~ may be appropriate based ~~depending up~~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 i~~I~~nfants with histories of *in utero* exposure to PRINIVIL ~~ACE inhibitors should be closely observed~~ for hypotension, oliguria, and hyperkalemia (see Precautions, *Pediatric Use)*. ~~If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.~~

3. Under **PRECAUTIONS**, *Pregnancy* the following text was added/~~deleted~~:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ~~ACE inhibitors~~ PRINIVIL during pregnancy. Discuss treatment options with women planning to become pregnant. ~~These p~~Patients should be asked to report pregnancies to their physicians as soon as possible.

~~NOTE: As with many other drugs, certain advice to patients being treated with PRINIVIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.~~

4. Under **PRECAUTIONS**, *Pediatric Use*, the following section was added:

   Neonates with a history of *in utero* exposure to PRINIVIL:
   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. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

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

6. The revision date and version number were updated.

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

For NDA 19778:

1. The boxed warning was revised:

   ~~USE IN PREGNANCY~~WARNING: FETAL TOXICITY
   ~~When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus.~~
   • **When pregnancy is detected, discontinue PRINZIDE ~~should be discontinued 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* ~~*Fetal/Neonatal Morbidity and Mortality*~~.**

2. Under **WARNINGS**, **Fetal Toxicity**, the following text was added/~~deleted~~:

   Fetal~~/Neonatal Morbidity and Mortality~~ 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 PRINZIDE as soon as possible. These adverse outcomes are usually associated with the 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 to 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 PRINZIDE, 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 PRINZIDE for hypotension, oliguria, and hyperkalemia (see PRECAUTIONS, *Pediatric Use*).

3. Under **WARNINGS**, *Lisinopril-Hydrochlorothiazide,* the following text was ~~deleted~~:

~~When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, PRINZIDE should be discontinued as soon as possible. (See *Lisinopril, Fetal/Neonatal Morbidity and Mortality*, below.)~~

~~*Lisinopril*~~
~~*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.~~

~~In a published retrospective epidemiological study, infants whose mothers had taken an ACE inhibitor drug during the first trimester of pregnancy appeared to have an increased risk of major congenital malformations compared with infants whose mothers 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.~~

~~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 PRINZIDE 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, PRINZIDE should be discontinued unless it is considered lifesaving 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 appear 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 dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.~~

4. Under **PRECAUTIONS**, *Pregnancy* the following text was added/~~deleted~~:

Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to ~~ACE inhibitors~~ PRINZIDE during pregnancy. Discuss treatment options with women planning to become pregnant. ~~These p~~Patients should be asked to report pregnancies to their physicians as soon as possible.

~~NOTE: As with many other drugs, certain advice to patients being treated with PRINZIDE is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.~~

5. Under **PRECAUTIONS**, *Pediatric Use*, the following section was added:

Neonates with a history of *in utero* exposure to PRINZIDE:
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. Lisinopril, which crosses the placenta, has been removed from neonatal circulation by peritoneal dialysis with some clinical

benefit, and theoretically may be removed by exchange transfusion, although there is no experience with the latter procedure.

~~Safety and effectiveness in pediatric patients have not been established.~~

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

7. The revision date and version number were updated.

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
06/07/2012