DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020387/S-059

SUPPLEMENT APPROVAL

Merck Sharp& Dohme Corp.
Attention: Jeffrey L. Seeburger, Ph.D.
Associate Director
Worldwide Regulatory Affairs
P.O. Box 1000, UG-50
North Wales, PA 19454

Dear Dr. Seeburger:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 11, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Hyzaar (losartan/hydrochlorothiazide) 50/12.5 mg, 100/12.5 mg, and 100/25 mg Tablets.

We also refer to our approval letter dated January 17, 2014 which contained the following error: the Patient Package Insert (PPI) was not appended to the letter.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain January 17, 2014, the date of the original approval letter.

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

1. In the Boxed Warning, the following text was added/deleted:

> ~~**USE IN PREGNANCY**~~**warning: fetal toxicity**
>
> ~~**When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.**~~
>
> - **When pregnancy is detected, discontinue HYZAAR® ~~should be discontinued~~ as soon as possible. ~~See WARNINGS, *Fetal/Neonatal Morbidity and Mortality*.~~**
> - **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 following text was added/deleted:

Fetal Toxicity~~/Neonatal Morbidity and Mortality~~
Pregnancy Category D

~~Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin converting enzyme inhibitors. When pregnancy is detected, HYZAAR should be discontinued as soon as possible.~~

~~The u~~Use of drugs that act ~~directly~~ on the renin-angiotensin system 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~~ reduces renal function ~~failure,~~ and increases fetal and neonatal morbidity and death. Resulting ~~O~~oligohydramnios ~~has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been~~ can be associated with fetal ~~limb contractures, craniofacial deformation, and hypoplastic~~ lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue HYZAAR as soon as possible. ~~Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.~~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 ~~These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to~~ 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.

~~Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of HYZAAR as soon as possible.~~

In the unusual case that there is ~~Rarely (probably less often than once in every thousand pregnancies),~~ no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the ~~an angiotensin II receptor antagonist will be found. In these rare cases, the~~ mother~~s should be apprised~~ of the potential ~~hazards~~ risk to ~~their~~ the fetus.~~es, and~~ Perform serial ultrasound examinations ~~should be performed~~ to assess the intra-amniotic environment.

If oligohydramnios is observed, discontinue HYZAAR ~~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)~~ Fetal testing may be appropriate, ~~depending upon~~ 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 HYZAAR ~~an angiotensin II receptor antagonist 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.~~

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

Pregnancy: Female patients of childbearing age should be told about the consequences of ~~second and third trimester~~ exposure to HYZAAR during pregnancy. Discuss treatment options with women planning to become pregnant. ~~drugs that act on the renin angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These p~~Patients should be asked to report pregnancies to their physicians as soon as possible.

~~*Pregnancy*~~

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

Neonates with a history of *in utero* exposure to HYZAAR:

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.

The following change was made to the PPI:

4. Under **What is the most important information I should know about HYZAAR?**, the following text was added/deleted:

- ~~**Do not take HYZAAR if you are pregnant or plan to become pregnant**~~**HYZAAR can cause harm or death to an ~~your~~ unborn baby ~~causing injury or even death. Stop taking HYZAAR if you become pregnant and call your doctor right away~~.**
- ~~If you plan to become pregnant t~~Talk to your doctor about other ~~treatment options before taking HYZAAR~~ways to lower your blood pressure if you plan to become pregnant.

- If you get pregnant while taking HYZAAR, tell your doctor right away.

5. There are multiple editorial changes throughout the label and the PPI (i.e. footnote symbols in Table 1 were revised; the "<" symbol was replaced with the words "less than"; the trademark statement was updated and relocated; the patent website was information was added; the copyright statement was updated.)
6. 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 this supplemental application, and it is 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, PharmD.
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
01/17/2014