DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 200045 / S003, S004

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Lori Kneafsey
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Kneafsey:

Please refer to your Supplemental New Drug Applications (sNDA) dated April 13 and 18, 2011, received on April 13 and 18, 2011 respectively, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amturnide (amlodipine/aliskiren/ hydrochlorothiazide) 150/5/12.5 mg, 300/5/12.5 mg, 300/5/25 mg, 300/10/12.5 mg and 300/10/25 mg Tablets.

These "Prior Approval" supplemental new drug applications provide for the following content changes; additional minor editorial changes were made, see attached labeling:

In **HIGHLIGHTS OF PRESCRIBING INFORMATION**

The trade name has been changed to all capital letters in the Highlights Limitation Statement.

The dosage form and route of administration description has been changed from, "Tablets" to "tablets, for oral use".

Under **HL, INDICATIONS AND USAGE**

Amturnide is a combination of aliskiren, a renin inhibitor, amlodipine besylate, a dihydropyridine calcium channel blocker, and hydrochlorothiazide (HCTZ), a thiazide diuretic. Amturnide is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions:

- Not indicated for initial therapy. (1)

Under **HL, DRUG INTERACTIONS**

Aliskiren:
Cyclosporine: Avoid concomitant use (7, 12.3)
Itraconazole: Avoid concomitant use (7, 12.3)

In **FULL PRESCRIBING INFORMATION: CONTENTS**

Reference to Section 6.2 Clinical laboratory findings has been deleted and Post-marketing Experience has been re-numbered to 6.2.

In **FULL PRESCRIBING INFORMATION**, the following have been added or ~~deleted~~;

Under **INDICATIONS AND USAGE**,

Amturnide is indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes, including amlodipine and hydrochlorothiazide. There are no controlled trials demonstrating risk reduction with Amturnide.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and

effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

Under **ADVERSE REACTIONS**,

Section 6.2, **Clinical Laboratory Findings** was removed as an enumerated subsection, it remains a bolded heading. Section 6.3, **Post-marketing Experience** was renumbered to Section 6.2.
In **Post-Marketing Experience**,

The following adverse reactions have been reported in aliskiren post-marketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to ~~reliably~~ estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: angioedema requiring airway management and hospitalization

Aliskiren: Peripheral edema, Blood creatinine increased

Under **WARNINGS AND PRECUATIONS,**

Cyclosporine or Itraconazole

When aliskiren was given with cyclosporine or itraconoazole, the blood concentrations of aliskiren were significantly increased. Avoid concomitant use of aliskiren with cyclosporine or intraconazole *[see Drug Interactions (7)]*.

Under **DRUG INTERACTIONS, Aliskiren**

~~**Delete:**~~

~~*Effects of Other Drugs on Aliskiren*~~

~~Based on in vitro studies, aliskiren is metabolized by CYP 3A4.~~

~~*Irbesartan:* Coadministration of irbesartan reduced aliskiren C_{max} up to 50% after multiple dosing.~~

~~*P-glycoprotein Effects:* Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.~~

~~*Atorvastatin:* Coadministration of atorvastatin resulted in about a 50% increase in aliskiren C_{max} and AUC after multiple dosing.~~

~~*Ketoconazole:* Coadministration of 200 mg twice-daily ketoconazole with aliskiren resulted in an approximate 80% increase in plasma levels of aliskiren. A 400-mg once-daily dose was not studied but would be expected to increase aliskiren blood levels further.~~

~~*Verapamil:* Coadministration of a single oral dose of 300 mg aliskiren with 240 mg verapamil increased AUC and Cmax of aliskiren by ~2-fold. However, no dosage adjustment is necessary.~~

~~*Itraconazole:* Coadministration of 100 mg itraconazole with 150 mg aliskiren resulted in approximately 5.8-fold increase in C_{max} and 6.5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with itraconazole is not recommended.~~

~~*Cyclosporine:* Coadministration of 200 mg and 600 mg cyclosporine with 75 mg aliskiren resulted in an approximately 2.5-fold increase in C_{max} and 5-fold increase in AUC of aliskiren. Concomitant use of aliskiren with cyclosporine is not recommended.~~

~~*Drugs with no clinically significant effects:* Coadministration of lovastatin, atenolol, warfarin, furosemide, digoxin, celecoxib, hydrochlorothiazide, ramipril, amlodipine besylate, metformin and amlodipine did not result in clinically significant increases in aliskiren exposure.~~

~~*Effects of Aliskiren on Other Drugs*~~

~~Aliskiren does not inhibit the CYP450 isoenzymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and CYP 3A) or induce CYP 3A4.~~

~~*Furosemide:* When aliskiren was coadministered with furosemide, the AUC and C_{max} of furosemide were reduced by about 30% and 50%, respectively. Patients receiving furosemide could find its effect diminished after starting aliskiren.~~

~~*Drugs with no clinically significant effects:* Coadministration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril or hydrochlorothiazide.~~

~~*Warfarin:* The effects of aliskiren on warfarin pharmacokinetics have not been evaluated.~~

Add:

Cyclosporine: Avoid co-administration of cyclosporine with aliskiren.
Itraconazole: Avoid co-administration of itraconazole with aliskiren.
[See Clinical Pharmacology (12.3).]

Under **DESCRIPTION,**

Amturnide is a single tablet for oral administration of aliskiren hemifumarate (an orally active, nonpeptide, potent direct renin inhibitor), amlodipine besylate (a dihydropyridine calcium channel blocker) and HCTZ (a diuretic).

Under **CLINICAL PHARMACOLOGY,**

Pharmacokinetics

Add:

Metabolism and Elimination

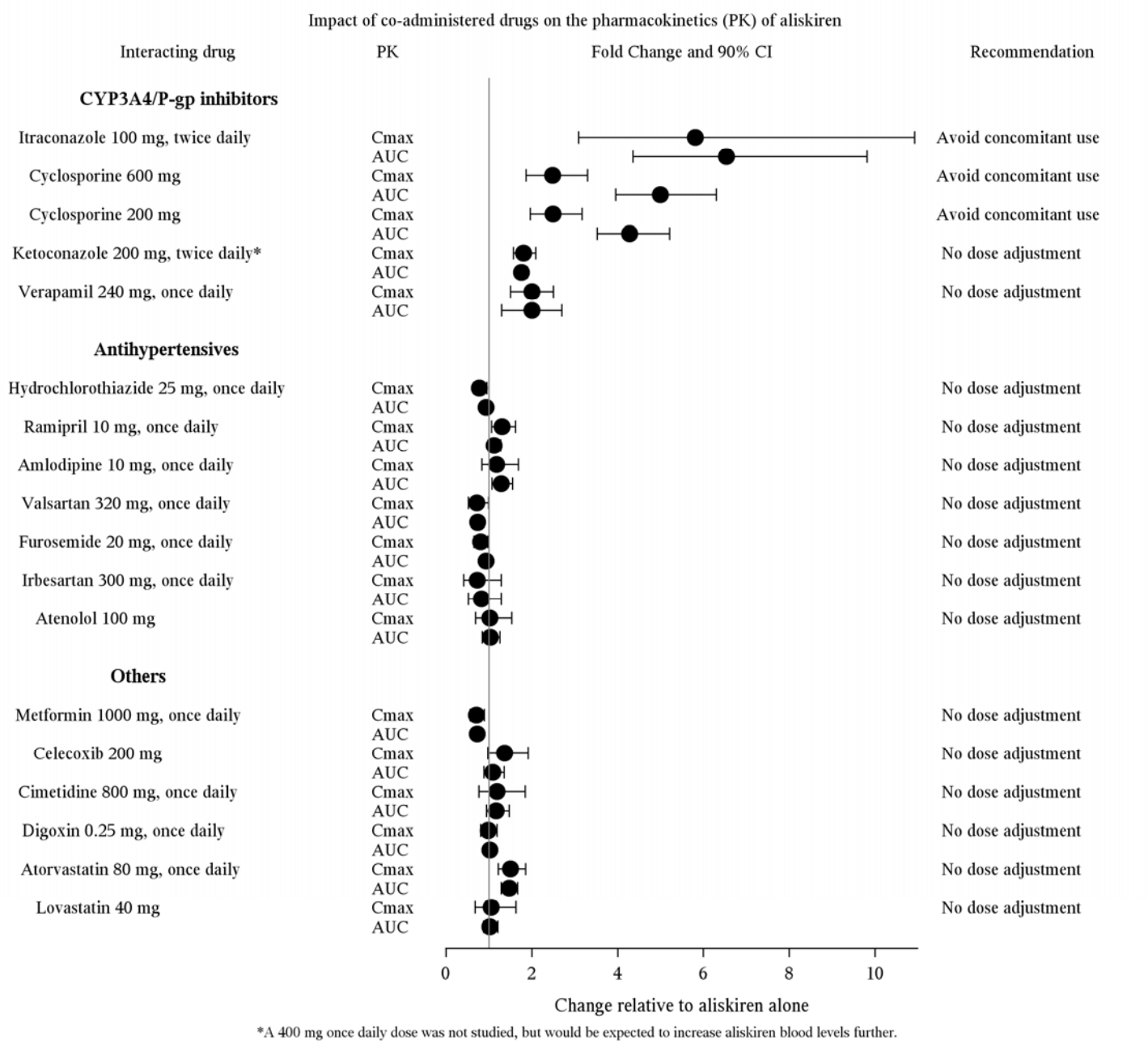
Aliskiren

About one fourth of the absorbed dose appears in the urine as parent drug. How much of the absorbed dose is metabolized is unknown. Based on the in vitro studies, the major enzyme responsible for aliskiren metabolism appears to be CYP 3A4. Aliskiren does not inhibit the CYP450 isoenzymes (CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) or induce CYP 3A4.

Transporters: Pgp (MDR1/Mdr1a/1b) was found to be the major efflux system involved in absorption and disposition of aliskiren in preclinical studies. The potential for drug interactions at the Pgp site will likely depend on the degree of inhibition of this transporter.

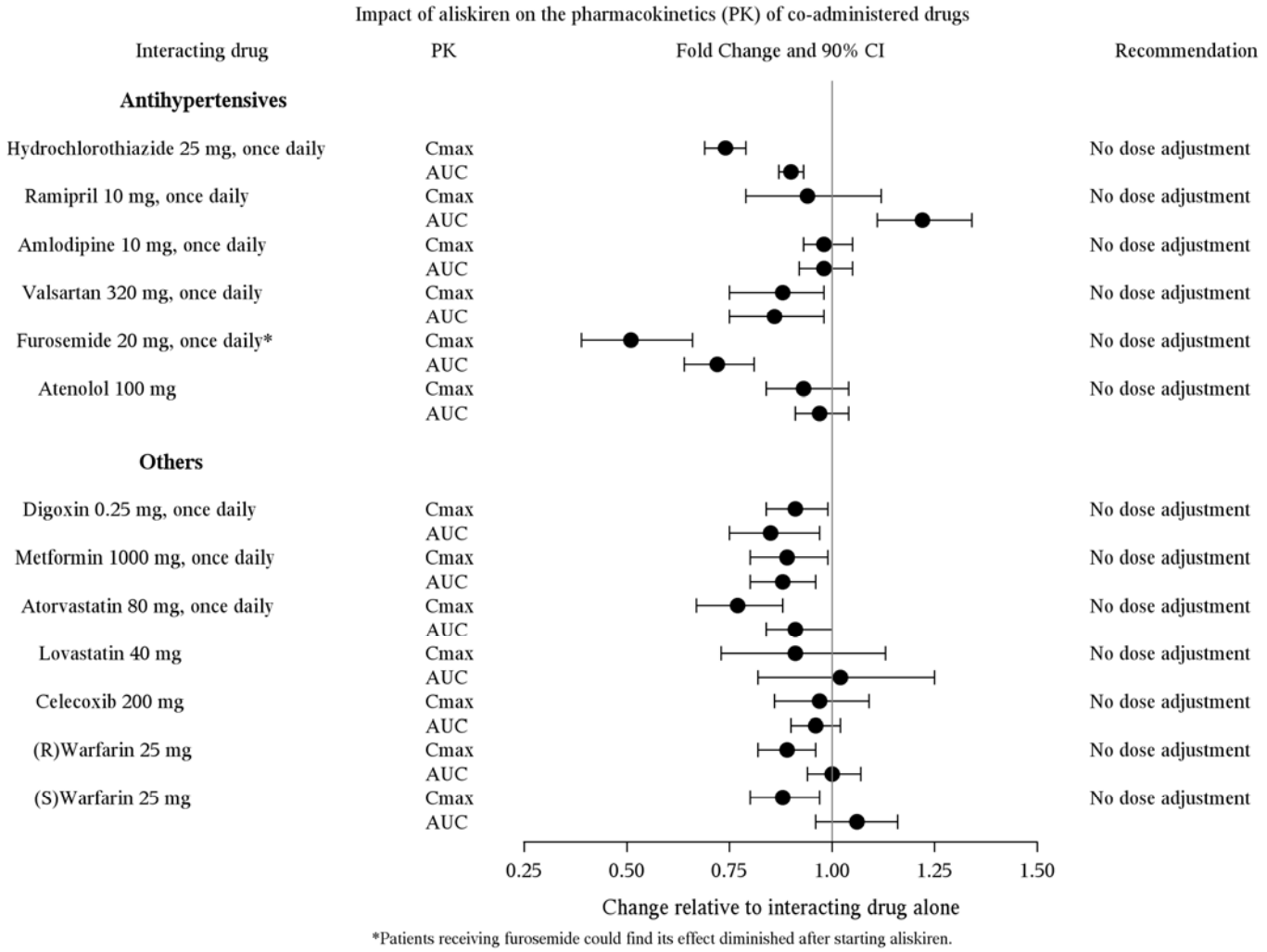
Drug interactions: The effect of co-administered drugs on the pharmacokinetics of aliskiren and vice versa, were studied in several single and multiple dose studies. Pharmacokinetic measures indicating the magnitude of these interactions are presented in Figure 1 (impact of co-administered drugs on aliskiren) and Figure 2 (impact on co-administered drugs).

Figure 1: The impact of co-administered drugs on the pharmacokinetics of aliskiren.



Warfarin: There was no clinically significant effect of a single dose of warfarin 25 mg on the pharmacokinetics of aliskiren.

Figure 2: The impact of aliskiren on the pharmacokinetics of co-administered drugs.



Under **CLINICAL STUDIES,**

There are no trials of the Amturnide triple combination tablet demonstrating reductions in cardiovascular risk in patients with hypertension, but two of the components, amlodipine and hydrochlorothiazide, have demonstrated such benefits.

Under **HOW SUPPLIED/ STORAGE AND HANDLING,**

Dispense in ~~a tight~~ original container ~~(USP)~~.

Under **PATIENT COUNSELING INFORMATION,**

See FDA-approved patient labeling (Patient Information)

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.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements and any 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.

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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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 Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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
10/12/2011