DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021540/S-028

SUPPLEMENT APPROVAL

Pfizer Inc., US Agent for
Pfizer Ireland Pharmaceuticals
Attention: Tricia Douglas, MS, RAC
Sr. Manager, Worldwide Regulatory Strategy
235 East 42nd Street 150/7/9
New York, NY 10017

Dear Ms. Douglas:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 21, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) Caduet (amlodipine/atorvastatin) 5 / 10 mg, 10 / 10 mg, 5 / 20 mg, 10 / 20 mg, 5 / 40 mg, 10 / 40 mg, 5 / 80 mg and 10 / 80 mg Tablets.

We acknowledge your amendment submitted October 25, 2012.

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~~):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES,** the following text was added:

Dosage and Administration (2)	10/2012
Warnings and Precautions / Myopathy and rhabodmyolysis (5.1)	10/2012
Drug Interactions (7)	10/2012

2. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS**, the following text was added:

   - Myopathy and rhabdomyolysis: Advise patients to promptly report to their physician unexplained and/or persistent muscle pain, tenderness, or weakness. CADUET therapy should be discontinued if myopathy is diagnoses or suspected (5.1, 8.5).

3. In **HIGHLIGHTS/DRUG INTERACTIONS**, the following text was added to the table:

Increased Risk of Myopathy/Rhabdomyolysis (2, 5.1, 7, 12.3)	
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
Lopinavir plus ritonavir	Use lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

4. Under **DOSAGE AND ADMINISTRATION**/Atorvastatin (Hyperlipidemia), the following text was added/deleted from the fifth paragraph:

> *Use with Cyclosporine, Clarithromycin, Itraconazole, or Certain Protease Inhibitors:* In patients taking cyclosporine or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), avoid therapy with atorvastatin . In patients with HIV taking lopinavir plus ritonavir, use the lowest necessary dose of atorvastatin. In patients taking clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, limit therapy with atorvastatin to 20 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed. In patients ~~with HIV~~ taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, limit therapy with atorvastatin to 40 mg, and make appropriate clinical assessment to ensure that the lowest dose necessary of atorvastatin is employed *[see Warnings and Precautions (5.1), Drug Interactions (7.13)]*.

5. Under **WARNINGS AND PRECAUTIONS/Myopathy and Rhabdomyolysis**, the following text was added to the fourth paragraph:

> There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.
>
> Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing CADUET. CADUET therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

6. Under **WARNINGS AND PRECAUTIONS**, the following text was added to Table 2:

Table 2. Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily

7. Under **ADVERSE REACTIONS/Postmarketing Experience**, the following text was added:

Atorvastatin

Adverse reactions associated with atorvastatin therapy reported since market introduction that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, fatigue, tendon rupture, fatal and non-fatal hepatic failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare reports of immune-mediated necrotizing myopathy associated with statin use *[see Warnings and Precautions (5.1)]*.

There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally nonserious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

8. Under **DRUG INTERACTIONS/Atorvastatin,** the following text was added:

7.13 Strong Inhibitors of CYP3A4: Atorvastatin is metabolized by CYP3A4. Concomitant administration of atorvastatin with strong inhibitors of CYP3A4 can lead to

increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 80 mg with clarithromycin (500 mg twice daily) compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking clarithromycin, avoid atorvastatin doses >20 mg *[see Warnings and Precautions, Skeletal Muscle (5.1) and Dosage and Administration (2)]*.

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing atorvastatin and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of atorvastatin should not exceed 20 mg *[see Warnings and Precautions (5.1) and Dosage and Administration (2)]*. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of LIPITOR should not exceed 40 mg and close clinical monitoring is recommended.

Itraconazole: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin 40 mg and itraconazole 200 mg *[see Clinical Pharmacology (12.3)]*. Therefore, in patients taking itraconazole, avoid atorvastatin doses >20 mg *[see Warnings and Precautions (5.1) and Dosage and Administration (2)]*.

9. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added to Table 5:

Co-administered drug and dosing regimen	**Atorvastatin**		
	Dose (mg)	**Change in AUC**	**Change in Cmax**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 870%	↑1070%
[#]Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days	10 mg, SD	↑ 940%	↑ 860%
[#]Telaprevir 750 mg q8h, 10 days	20 mg, SD	↑ 790%	↑ 1060%
[#, ‡]Saquinavir 400 mg BID/ritonavir 400mg BID, 15 days	40 mg QD for 4 days	↑ 390%	↑ 430%
[#]Clarithromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 440%	↑ 540%
[#]Darunavir 300 mg BID/ritonavir 100 mg BID, 9 days	10 mg QD for 4 days	↑ 340%	↑ 230%
[#]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 330%	↑ 20%
[#]Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	10 mg QD for 4 days	↑ 250%	↑ 280%

#Fosamprenavir 1400 mg BID, 14 days	10 mg QD for 4 days	↑ 230%	↑ 400%
#Nelfinavir 1250 mg BID, 14 days	10 mg QD for 28 days	↑ 74%	↑ 220%
#Grapefruit Juice, 240 mL QD*	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less than 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
#Rifampin 600 mg QD, 7 days (co-administered) †	40 mg SD	↑ 30%	↑ 2.7-fold
#Rifampin 600 mg QD, 5 days (doses separated) †	40 mg SD	↓ 80%	↓ 40%
#Gemfibrozil 600 mg BID, 7 days	40mg SD	↑ 35%	↓ Less than 1%
#Fenofibrate 160 mg QD, 7 days	40mg SD	↑ 3%	↑ 2%
Boceprevir 800 mg TID, 7 days	40 mg SD	↑2.30 fold	↑2.66 fold

10. Under **PATIENT COUNSELING INFORMATION**, the following text was added:

> **Muscle Pain:** Advise patients starting therapy with CADUET of the risk of myopathy and to report promptly any unexplained muscle pain, tenderness, or weakness particularly if accompanied by malaise or fever or if these muscle signs or symptoms persist after discontinuing CADUET. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (>1 liter) of grapefruit juice. They should discuss all medication, both prescription and over the counter, with their healthcare professional.

11. In the Patient Package Insert, under **What are the possible side effects of CADUET?**, the following text was added:

> **Call your doctor right away if:**
> - you have muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual. This may be an early sign of a rare muscle problem.
> - muscle problems that do not go away even after your doctor has advised you to stop taking CADUET. Your doctor may do further tests to diagnose the cause of your muscle problems.
> - allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away
> - you have nausea and vomiting, stomach pain
> - you are passing brown or dark-colored urine

- you feel more tired than usual
- your skin and white of your eyes get yellow
- you have allergic skin reactions

- **Chest pain that does not go away or gets worse.** Sometimes when you start CADUET or increase your dose, chest pain can get worse or a heart attack can happen. If this happens, call your doctor or go to the emergency room right away.

12. 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, 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
10/31/2012