DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020591/S-012

SUPPLEMENT APPROVAL

Abbot Laboratories
Attention: Janette Meyer
Associate Director
Regulatory Affairs, Pharmaceutical Products Group
DEPT. PA77 / Bldg. AP30-1E
200 Abbott Park Road
Abbott Park, Il 60064-6157

Dear Ms. Meyer:

Please refer to your supplemental new drug application dated March 26, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tarka (trandolapril/verapamil hydrochloride) 2/180, 1/240, 2/240 and 4/240 mg Tablets.

We acknowledge receipt of your submission dated August 24, 2007 and March 3, 2011.

The March 3, 2011, submission constituted a complete response to our July 14, 2008, action letter.

This supplemental new drug application provides for the following labeling changes:

1. Under the **DESCRIPTION** section, the trandolapril component information has been revised

   FROM:

   Trandolapril is the ethyl ester prodrug of a nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. It is chemically described as (2S,3aR,7aS)-1-[(S)-N-[(S)-Carboxy-3-phenylpropyl]alanyl] hexahydro-2-indolinecarboxylic acid, 1-ethyl ester. Its empirical formula is C_{24} H_{34} N_2O_5 and its structural formula is:

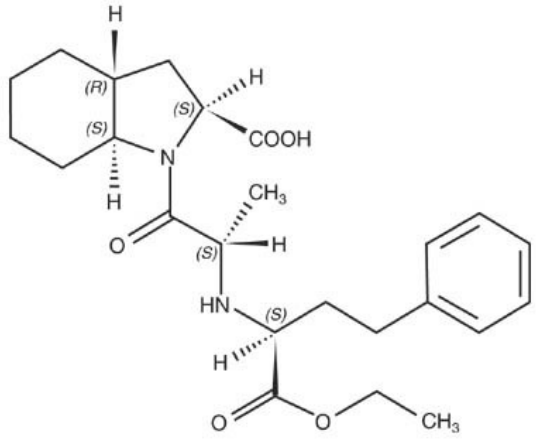
(b) (4)

Trandolapril is a with a molecular weight of 430.54. It is soluble (>100 mg/mL) in chloroform, dichloromethane, and methanol.

TARKA tablets are formulated for oral administration, containing verapamil hydrochloride as a controlled release formulation and trandolapril as an immediate release formulation. The tablet strengths are trandolapril 2 mg/verapamil hydrochloride ER 180 mg, trandolapril 1 mg/verapamil hydrochloride ER 240 mg, trandolapril 2 mg/verapamil hydrochloride ER 240 mg, and trandolapril 4 mg/verapamil hydrochloride ER 240 mg. The tablets also contain the following ingredients: corn starch, dioctyl sodium sulfosuccinate, ethanol, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, synthetic iron oxides, talc, and titanium dioxide.

TO:

Trandolapril is the ethyl ester prodrug of a nonsulfhydryl angiotensin converting enzyme (ACE) inhibitor, trandolaprilat. It is chemically described as (2S,3aR,7aS)-1-[(S)-N-[(S)-1-Carboxy-3-phenylpropyl]alanyl] hexahydro-2-indolinecarboxylic acid, 1-ethyl ester. Its empirical formula is C_{24} H_{34} N_2O_5 and its structural formula is:



Trandolapril is a white or almost white powder with a molecular weight of 430.54. It is soluble (>100 mg/mL) in chloroform, dichloromethane, and methanol.

TARKA tablets are formulated for oral administration, containing verapamil hydrochloride as a controlled release formulation and trandolapril as an immediate release formulation. The tablet strengths are trandolapril 2 mg/verapamil hydrochloride ER 180 mg, trandolapril 1 mg/verapamil hydrochloride ER 240 mg, trandolapril 2 mg/verapamil hydrochloride ER 240 mg, and trandolapril 4 mg/verapamil hydrochloride ER 240 mg. The tablets also contain the following ingredients: corn starch, dioctyl sodium sulfosuccinate, ethanol, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, synthetic iron oxides, talc, and titanium dioxide.

2. Under the **CLINICAL PHARMACOLOGY**, *Pharmacokinetics and Metabolism* section, the following was revised:

FROM:

(b) (4)

TO:

The elimination half life of trandolapril is about 6 hours. At steady state, the effective half-life of trandolaprilat is 22.5 hours. Like all ACE inhibitors, trandolaprilat also has a prolonged terminal elimination phase, involving a small fraction of administered drug, probably representing binding to plasma and tissue ACE.

And under the Trandolapril Component heading

FROM:

Following oral administration of trandolapril, the absolute bioavailability of trandolapril is approximately 10% as trandolapril and (b) (4) as trandolaprilat.

TO:

Following oral administration of trandolapril, the absolute bioavailability of trandolapril is approximately 10% as trandolapril and 70% as trandolaprilat.

3. Under the **CLINICAL PHARMACOLOGY**, *Pharmacodynamics*, Trandolapril component section, the following was revised:

FROM:

After a single 2 mg dose of trandolapril, inhibition of ACE activity reaches a maximum (70-85%) at 4 hours with about (b) (4) decline at 24 hours. Eight days after dosing, ACE inhibition is still 40%.

TO:

After a single 2 mg dose of trandolapril, inhibition of ACE activity reaches a maximum (70-85%) at 4 hours with about 10% decline at 24 hours. Eight days after dosing, ACE inhibition is still 40%.

4. Under the **PRECAUTIONS/Drug Interactions** subsection, the following information has been added at the beginning of this section:

   In vitro metabolic studies indicate that verapamil is metabolized by cytochrome P450 including CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp).

   Clinically significant interactions have been reported with inhibitors of CYP3A4 (e.g. erythromycin, ritonavir) causing elevation of plasma levels of verapamil while inducers of CYP3A4 (e.g. rifampin) have caused a lowering of plasma levels of verapamil. Therefore, patients receiving inhibitors or inducers of the cytochrome P450 system should be monitored for drug interactions.

5. Under **PRECAUTIONS/Drug Interactions/Digitalis** subsection, the following sentence has been deleted:

   (b) (4)

6. Under **PRECAUTIONS/Drug Interactions/Digitalis** subsection, the following sentence has been added:

   No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and digoxin.

7. Under **PRECAUTIONS/Drug Interactions** subsection, "**Verapamil component**" has been added under the "**Lithium**" description.

8. Under **PRECAUTIONS/Drug Interactions/Cimetidine** subsection, the following text has been deleted:

   (b) (4)

9. Under **PRECAUTIONS/Drug Interactions/Cimetidine** subsection, the following sentence has been added:

   No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and cimetidine.

10. Under **PRECAUTIONS/Drug Interactions** subsection, the following text has been deleted:

    (b) (4)

(b) (4)

11. Under **PRECAUTIONS/Drug Interactions/Antiarrhythmic Agents/*Verapamil Component,*** "**Phosphate**" has been added to "**Disopyramide**".

12. Under **PRECAUTIONS/Drug Interactions/Antiarrhythmic Agents/*Verapamil Component/Nitrates*** subsection the following text has been deleted:

(b) (4)

13. Under **PRECAUTIONS/Drug Interactions/Antihypertensive Agents**, the following section has been changed

FROM:

Other

Verapamil Component

Carbamazepine

Verapamil may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

(b) (4)

Therapy with rifampin may markedly reduce oral verapamil bioavailability.

(b) (4)

Phenobarbital therapy may increase verapamil clearance.

(b) (4)

(b) (4)

Theophylline

Verapamil therapy may inhibit the clearance and increase the plasma levels of theophylline.

Inhalation Anesthetics

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Concomitant Diuretic Therapy

Trandolapril Component

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with TARKA. The possibility of exacerbation of hypotensive effects with TARKA may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with TARKA. If it is not possible to discontinue the diuretic, the starting dose of TARKA should be reduced (see **DOSAGE AND ADMINISTRATION**).

Agents Increasing Serum Potassium

Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium. (See **PRECAUTIONS** .)

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including TARKA.

Other

Trandolapril Component

(b) (4)

The anticoagulant effect of warfarin was not significantly changed by trandolapril.

TO:

Antihypertensive Agents

Concomitant use of TARKA with other antihypertensive agents including diuretics, vasodilators, beta-adrenergic blockers, and alpha-antagonists may result in additive hypotensive effects. There are reports that verapamil may result in higher concentrations of the alpha-agonists prazosin and terazosin.

Beta Blockers
Verapamil Component

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction, and/or cardiac contractility. Drug interaction studies have indicated that the maximum concentrations of metoprolol and propanolol are increased after the administration of verapamil. The use of verapamil in combination with a beta-adrenergic blocker should be used only with caution, and close monitoring.
Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eyedrops and oral verapamil.

Concomitant Diuretic Therapy
Trandolapril Component

As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with TARKA. The possibility of exacerbation of hypotensive effects with TARKA may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with TARKA. If it is not possible to discontinue the diuretic, the starting dose of TARKA should be reduced (see **DOSAGE AND ADMINISTRATION**). No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and furosemide.

Agents Increasing Serum Potassium
Trandolapril Component

Trandolapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. Use of potassium-sparing diuretics (spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes concomitantly with ACE inhibitors can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be used with caution and with appropriate monitoring of serum potassium (see **PRECAUTIONS**).

HMG CoA Reductase Inhibitors (“Statins”)
Verapamil component

Interaction studies performed between simvastatin and verapamil indicate that verapamil may cause increases in the concentrations of simvastatin. Atorvastatin has increased verapamil AUC by 42% while not significantly affecting norverapamil.

There is no direct *in vivo* clinical evidence for an interaction between lovastatin and verapamil, however, there is strong potential for verapamil to significantly affect lovastatin pharmacokinetics in a similar manner to simvastatin.

Non Steroidal Anti-Inflammatory Drugs (NSAIDS)
Trandolapril component

NSAIDs may reduce the antihypertensive effects of trandolapril. Blood pressure monitoring should be increased when any NSAID is added or discontinued in a patient treated with trandolapril.

Other (Verapamil Component)
Nitrates

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and the clinical experience suggest beneficial interactions.

Carbamazepine

Verapamil may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Anti-infective Agents

Therapy with rifampin may markedly reduce oral verapamil bioavailability. There have been reports that erythromycin and telithromycin may increase concentrations of verapamil.

Barbiturates

Phenobarbital therapy may increase verapamil clearance.

Immunosuppressive Agents

Verapamil therapy may increase serum levels of cyclosporin, sirolimus and tacrolimus.

Theophylline

Verapamil therapy may inhibit the clearance and increase the plasma levels of theophylline.

Tranquilizers/ Anti-depressants

Due to metabolism via the CYP enzyme system, there have been reports that verapamil may increase the concentrations of buspirone, midazolam, almotriptan and imipramine.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-gp. Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, the potential

inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine (see **PRECAUTIONS-Drug Interactions**).

Other

Concentrations of verapamil may be increased by the concomitant administration of protease inhibitors such as ritonavir, and reduced by the concomitant administration of sulfinpyrazone, or St John's Wort.

Concentrations of doxorubicin may be increased by the administration of verapamil.
There have been reports that verapamil may elevate the concentrations of the oral anti-diabetic glyburide.

Inhalation Anesthetics

Animal experiments have shown that inhalation anesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anesthetics and calcium antagonists, such as verapamil, should be titrated carefully to avoid excessive cardiovascular depression.

Neuromuscular Blocking Agents

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Gold

Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including TARKA.

Other (Trandolapril Component)

No clinically significant pharmacokinetic interaction has been found between trandolapril (or its metabolites) and nifedipine.

The anticoagulant effect of warfarin was not significantly changed by trandolapril.

Anti-diabetic Agents

The concomitant use of ACE inhibitors such as trandolapril with antidiabetic medications (insulin or oral hypoglycemic agents) may result in increased blood glucose lowering effects.

14. Under **ADVERSE REACTIONS**, the following subsection has been added:

Post Marketing Experience

There has been a single postmarketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A4 and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended (see **PRECAUTIONS-Drug Interactions**).

15. The following revisions have been noted as minor editorial revisions:

    - Under **WARNINGS/Fetal/Neonatal Morbidity and Mortality/Trandolapril Component** subsection, "*in utero*" has been italicized in the second to the last paragraph.
    - Under the **DOSAGE AND ADMINISTRATION** section, (b) (4) was deleted and replaced with "vice" in the last sentence of the second paragraph.
    - Under the **HOW SUPPLIED** section, (b) (4) was deleted from the tablet description and replaced with "debossed" for each strength.

We have completed our review of this supplemental application, as amended. It is 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 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 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).

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
08/29/2011