DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019851/S-42

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Yifeng Jia
Global Brand Regulatory Manager
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Jia:

Please refer to your Supplemental New Drug Application (sNDA) dated November 18, 2011, received November 18, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lotensin (benazepril) 5 mg, 10 mg, 20 mg and 40 mg tablets.

We also acknowledge receipt of your submission dated April 6, 2012.

We also refer to our approval letter dated May 17, 2012 which contained the following error: The sentence, "In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate" was mistakenly marked for deletion in the approval letter, it should be retained.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain May 17, 2012, the date of the original approval letter.

This "Prior Approval" supplemental new drug application provides for the following revisions:

In the **BOXED WARNING** the following has been added or ~~deleted~~:

~~**USE IN PREGNANCY**~~

~~**When used in pregnancy, ACE inhibitors can cause injury and even death to the developing fetus**. When pregnancy is detected, Lotensin should be discontinued as soon as possible. See **WARNINGS, Fetal/Neonatal Morbidity and Mortality.**~~

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue Lotensin 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

Under **DESCRIPTION** the structural formula was replaced with a clearer image.

Under **CLINICAL PHARMACOLOGY** the following was added or ~~deleted~~:

A Clinical Studies subheading was added.

Under Hypertension, Adult

~~Administration of Lotensin to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt- and/or volume-depleted (see WARNINGS).~~

In single-dose studies, Lotensin lowered blood pressure within 1 hour, with peak reductions achieved 2-4 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. In multiple-dose studies, once-daily doses of 20-80 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 6-12/4-7 mmHg. The trough values represent reductions of about 50% of that seen at peak.

Four dose-response studies using once-daily dosing were conducted in 470 mild-to-moderate hypertensive patients not using diuretics. The minimal effective once-daily dose of Lotensin was 10 mg; but further falls in blood pressure, especially at morning trough, were seen with higher doses in the studied dosing range (10-80 mg). In studies comparing the same daily dose of Lotensin given as a single morning dose or as a twice-daily dose, blood pressure reductions at the time of morning trough blood levels were greater with the divided regimen.

~~During chronic therapy, the maximum reduction in blood pressure with any dose is generally achieved after 1-2 weeks. The antihypertensive effects of Lotensin have continued during therapy for at least two years. Abrupt withdrawal of Lotensin has not been associated with a rapid increase in blood pressure.~~

~~In patients with mild-to-moderate hypertension, Lotensin 10-20 mg was similar in effectiveness to captopril, hydrochlorothiazide, nifedipine SR, and propranolol.~~

The antihypertensive effects of Lotensin were not appreciably different in patients receiving high- or low-sodium diets.

~~In hemodynamic studies in dogs, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance, with an increase in cardiac output and renal blood flow and little or no change in heart rate.~~ In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate.

Use of Lotensin in combination with thiazide diuretics gives a blood-pressure-lowering effect greater than that seen with either agent alone. By blocking the renin-angiotensin-aldosterone axis, administration of Lotensin tends to reduce the potassium loss associated with the diuretic.

Under **INDICATIONS AND USAGE** the following was added or ~~deleted~~

Lotensin is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

~~In using Lotensin, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that Lotensin does not have a similar risk (see WARNINGS).~~

~~Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks. It should also be noted that in controlled clinical trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks.~~

Under **CONTRAINDICATIONS** the following was added or ~~deleted~~

Lotensin is contraindicated in patients who are hypersensitive to benazapril ~~this product~~ or to any other ACE inhibitor.

Lotensin is also contraindicated in patients with a history of angioedema with or without previous ACE inhibitor treatment.

Under **WARNINGS** the following was added or ~~deleted~~

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received Lotensin. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to nonblacks.

~~**Neutropenia/Agranulocytosis**~~

~~Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be~~

~~considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.~~

Fetal 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 Lotensin as soon as possible. These adverse outcomes are usually associated with 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 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 Lotensin, 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 Lotensin for hypotension, oliguria, and hyperkalemia *[see Precautions, Pediatric Use]*.

- No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.

~~**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, Lotensin should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis.~~

~~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.~~

~~In addition, use of ACE inhibitors during the first trimester of pregnancy has been associated with a potentially increased risk of birth defects. In women planning to become pregnant, ACE inhibitors (including Lotensin) should not be used. Women of childbearing age should be made aware of the potential risk and ACE inhibitors (including Lotensin) should only be given after careful counseling and consideration of individual risks and benefits.~~

~~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, benazepril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress 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. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.~~

~~No teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m^2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50-kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice), and more than 3 times (in rabbits) the maximum recommended human dose.~~

Under **PRECAUTIONS, General** the following was <u>added</u> or ~~deleted~~

~~***Impaired Liver Function:*** In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered (see WARNINGS, Hepatic Failure).~~

Under **INFORMATION FOR PATIENTS** the following was <u>added</u> or ~~deleted~~

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

Under **DRUG INTERACTIONS** the following was added or ~~deleted~~

Potassium Supplements and Potassium-Sparing Diuretics: ~~Lotensin can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others, (e.g., ciclosporin, heparin) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.~~ Concomitant use with Lotensin may effect potassium levels. Monitor potassium periodically.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors (including benazepril) during therapy with lithium. ~~These drugs should be coadministered with caution, and frequent~~ Monitor~~ing of serum~~ lithium levels when used concomitantly with Lotensin. ~~is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.~~

Non-Steroidal Anti-Inflammatory ~~Agents~~ Drugs (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including benazepril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving benazepril and NSAID therapy.

Other: ~~No clinically important pharmacokinetic interactions occurred when Lotensin was administered concomitantly with hydrochlorothiazide, chlorthalidone, furosemide, digoxin, propranolol, atenolol, or cimetidine.~~

Lotensin has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

The pharmacokinetics of benazepril are not affected by the following drugs: hydrochlorothiazide, furosemide, chlorthalidone, digoxin, propranolol, atenolol, nifedipine, amlodipine, naproxen, acetylsalicylic acid, or cimetidine. Likewise the administration of benazepril does not substantially affect the pharmacokinetics of these medications (cimetidine kinetics were not studied).

The heading **PREGNANCY CATEGORY D** has been ~~deleted~~

~~**Pregnancy Category D**~~

~~See WARNINGS, Fetal/Neonatal Morbidity and Mortality.~~

Under **PEDIATRIC USE** the following has been added or ~~deleted~~

Neonates with a history of in utero exposure to Lotensin:

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. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers with another ACE inhibitor, but experience is limited.

The antihypertensive effects of Lotensin have been evaluated in a double-blind study in pediatric patients 7 to 16 years of age (see CLINICAL PHARMACOLOGY: Pharmacodynamics, Hypertension). The pharmacokinetics of Lotensin have been evaluated in pediatric patients 6 to 16 years of age (see CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism). Lotensin was generally well tolerated and adverse effects were similar to those described in adults. (See ADVERSE REACTIONS: *Pediatric Patients*.) The long-term effects of benazepril on growth and development have not been studied. Infants below the age of 1 year should not be given Lotensin because of the risk of effects on kidney development.

Treatment with Lotensin is not recommended in pediatric patients less than 6 years of age (see ADVERSE REACTIONS), and in children with glomerular filtration rate <30 mL/min as there are insufficient data available to support a dosing recommendation in these groups. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism, *In Pediatric Patients* and DOSAGE AND ADMINISTRATION.)

Under **ADVERSE REACTIONS** the following has been added or ~~deleted~~

The side effects considered possibly or probably related to study drug that occurred in U.S. placebo-controlled trials in more than 1% of patients treated with Lotensin are shown below.

PATIENTS IN U.S. PLACEBO-CONTROLLED STUDIES

	LOTENSIN (N=964)		PLACEBO (N=496)	
	N	%	N	%
Headache	60	6.2	21	4.2
Dizziness	35	3.6	12	2.4
~~Fatigue~~	~~23~~	~~2.4~~	~~11~~	~~2.2~~
Somnolence	15	1.6	2	0.4
Postural Dizziness	14	1.5	1	0.2
~~Nausea~~	~~13~~	~~1.3~~	~~5~~	~~1.0~~
~~Cough~~	~~12~~	~~1.2~~	~~5~~	~~1.0~~

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients or with less than 1% difference in incidence between benazepril or placebo treatment), and rarer events seen in post-marketing experience, include the following (in some, a causal relationship to drug use is uncertain):

~~**Cardiovascular:** Symptomatic hypotension was seen in 0.3% of patients, postural hypotension in 0.4%, and syncope in 0.1%; these reactions led to discontinuation of therapy in 4 patients who had received benazepril monotherapy and in 9 patients who had received benazepril with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other reports included angina pectoris, palpitations, and peripheral edema.~~

~~**Renal:** Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine.~~

~~**Fetal/Neonatal Morbidity and Mortality:** See WARNINGS, Fetal/Neonatal Morbidity and Mortality.~~

~~**Angioedema:** Angioedema has been reported in patients receiving ACE inhibitors. During clinical trials in hypertensive patients with benazepril, 0.5% of patients experienced edema of the lips or face without other manifestations of angioedema. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, extremities, lips, tongue, or glottis and/or larynx occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately (see WARNINGS).~~

Dermatologic: Stevens-Johnson syndrome, pemphigus, apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash), photosensitivity, and flushing.

Gastrointestinal: Nausea, pancreatitis, constipation, gastritis, vomiting, and melena.

Hematologic: Thrombocytopenia and hemolytic anemia.

Neurologic and Psychiatric: Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia.

Other: Fatigue, asthma, bronchitis, dyspnea, sinusitis, urinary tract infection, frequent urination, infection, arthritis, impotence, alopecia, arthralgia, myalgia, asthenia, sweating.

Another potentially important adverse experience, eosinophilic pneumonitis, has been attributed to other ACE inhibitors.

~~The following adverse events of unknown frequency have been reported during post-marketing use of benazepril: small bowel angioedema, anaphylactoid reactions, hyperkalemia, agranulocytosis, and neutropenia.~~

Pediatric Patients: The adverse experience profile for pediatric patients appears to be similar to that seen in adult patients. ~~Infants below the age of 1 year should not be given ACE inhibitors due to concerns over possible effects on kidney development.~~

~~The long-term effects of benazepril on growth and development have not been studied.~~

Under **CLINICAL LABORATORY TEST FINDINGS** the following have been added or ~~deleted~~

~~**Creatinine and Blood Urea Nitrogen:** Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).~~

~~**Potassium:** Since benazepril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently (see PRECAUTIONS).~~

Hemoglobin: Decreases in hemoglobin (a low value and a decrease of 5 g/dL) were rare, occurring in only 1 of 2,014 patients receiving Lotensin alone and in 1 of 1,357 patients receiving Lotensin plus a diuretic. No U.S. patients discontinued treatment because of decreases in hemoglobin.

Other (causal relationships unknown): ~~Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration~~. Elevations of uric acid, blood glucose, serum bilirubin, and liver enzymes (see WARNINGS) have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, ~~leukopenia~~, eosinophilia, and proteinuria. ~~In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.~~

Under **OVERDOSAGE** the following has been added or ~~deleted~~

Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been

reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension, which can be associated with electrolyte disturbances and renal failure.

Laboratory determinations of serum levels of benazepril and its metabolites are not management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazepril is only slightly dialyzable, but dialysis might be considered in overdosed patients with severely impaired renal function (see WARNINGS).

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

If ingestion is recent, activated charcoal should be considered. Gastric decontamination (e.g., vomiting, gastric lavage) may be considered in individual cases, in the early period after ingestion.

Patients should be closely monitored for blood pressure and clinical symptoms. Supportive management should be employed to ensure adequate hydration and to maintain systemic blood pressure.

In the case of marked hypotension, physiological saline solution should be administered intravenously; depending on the clinical situation the use of vasopressors (e.g., catecholamines i.v.) may be considered.

We have completed our review of this supplemental application. 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).

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, MS, RAC, 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
05/17/2012