



NDA 022314/S-013

**SUPPLEMENT APPROVAL**

Novartis Pharmaceuticals Corporation  
Attention: Ms. Nancy Price  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms Price:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 9, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exforge HCT (amlodipine/valsartan/hydrochlorothiazide) 5/160/12.5 mg, 10/160/12.5 mg, 5/160/25 mg, 10/160/25 mg, and 10/320/25 mg Tablets.

We acknowledge receipt of your amendment dated June 29, 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:

Indications and Usage: Benefits of lowering blood pressure ( <u>1</u> )	12/2011
<u>Contraindications: Known hypersensitivity (4)</u>	<u>XX/2012</u>
Boxed Warning: Fetal Toxicity	01/2012
Warnings and Precautions: Fetal Toxicity (5.1)	01/2012

2. In **HIGHLIGHTS/CONTRAINDICATIONS**, the following bullet was added:

- Anuria
- Hypersensitivity to sulfonamide-derived drugs (4)
- Known hypersensitivity to any component (4)

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

- Hypotension: Correct volume depletion prior to initiation (5.2)
- Increased angina and/or myocardial infarction (5.3)
- Monitor renal function and potassium in susceptible patients (5.4, 5.5)
- Exacerbation or activation of systemic lupus erythematosus (5.7)
- Observe for signs of fluid or electrolyte imbalance (5.9)
- Acute angle-closure glaucoma (5.10)

4. Under **CONTRAINDICATIONS**, the following text was added:

Because of the hydrochlorothiazide component, Exforge HCT is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs. Do not use in patients with anuria, hypersensitivity to other sulfonamide-derived drugs or hypersensitivity to any component of this product.

5. Under **WARNINGS AND PRECAUTIONS**, the following text was added/deleted:

### ***5.3 Increased Angina and/or Myocardial Infarction***

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration or severity of angina or acute myocardial infarction upon starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

### **~~5.5 Heart Failure~~**

~~Exforge HCT has not been studied in patients with heart failure.~~

**Studies with amlodipine:** In general, calcium channel blockers should be used with close monitoring, including close follow up of fluid status, electrolytes, renal function, and blood pressure in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1,153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

**Studies with valsartan:** Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuation due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

### **5.59 Potassium abnormalities ~~Electrolytes and Metabolic Imbalances~~**

In the controlled trial of Exforge HCT in moderate to severe hypertensive patients, the incidence of hypokalemia (serum potassium <3.5 mEq/L) at any time post-baseline with

the maximum dose of Exforge HCT (10/320/25 mg) was 10% compared to 25% with HCTZ/amlodipine (25/10 mg), 7% with valsartan/HCTZ (320/25 mg), and 3% with amlodipine/valsartan (10/320 mg). One patient (0.2%) discontinued therapy due to an adverse event of hypokalemia in each of the Exforge HCT and HCTZ/amlodipine groups. The incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4% with Exforge HCT compared to 0.2-0.7% with the dual therapies.

Some patients with heart failure have developed increases in potassium on valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required.

Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically.

If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), Exforge HCT should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.

~~Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients. Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Exforge HCT.~~

### **5.9 Metabolic Imbalances**

Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides.

Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving Exforge HCT.

6. Under **ADVERSE REACTIONS/Post-Marketing Experience**, the following text was added/deleted:

#### **Valsartan**

The following additional adverse reactions have been reported in post-marketing experience with valsartan or valsartan/hydrochlorothiazide:

Blood and Lymphatic: ~~There are very rare reports of thrombocytopenia.~~ Decrease in hemoglobin, decrease in hematocrit, neutropenia

Hypersensitivity: There are rare reports of angioedema. Some of these patients previously experience angioedema with other drugs including ACE inhibitors. Exforge HCT should not be re-administered to patients who have had angioedema.

Digestive: Elevated liver enzymes and very rare reports of hepatitis

Renal: Impaired renal function, renal failure

Clinical Laboratory Tests: Hyperkalemia

Dermatologic: Alopecia

Vascular: Vasculitis

Nervous System: Syncope

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

7. Under **DRUG INTERACTIONS**, the following text was added/deleted:

### **Amlodipine**

~~In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.~~

~~Cimetidine: Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.~~

~~Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.~~

~~Magnesium and aluminum hydroxide (antacid): Co-administration of the magnesium and aluminum hydroxide antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.~~

~~Sildenafil: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.~~

~~Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.~~

~~Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.~~

~~Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.~~

**Simvastatin:** ~~Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone.~~ Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

**CYP3A4 Inhibitors:** Co-administration with CYP3A inhibitors (moderate and strong) result in increased systemic exposure to amlodipine warranting dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A4 inhibitors to determine the need for dose adjustment.

**CYP3A4 Inducers:** No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be monitored when amlodipine is co-administered with CYP3A4 inducers.

### **Valsartan**

No clinically significant pharmacokinetic interactions were observed when valsartan was co-administered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

In vitro metabolism studies have indicated that CYP450 mediated drug interaction between valsartan and co-administered drugs are unlikely because of the low extent of metabolism [see *Pharmacokinetics – Valsartan*, (12.3)].

Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

**Potassium:** Concomitant use of valsartan with other agents that block the renin-angiotensin system, potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advisable. ~~As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.~~

**Non-Steroidal Anti-Inflammatory Agents 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 angiotensin II receptor antagonists, including valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including valsartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

8. Under **USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

### 8.5 Geriatric Use

Exposure to amlodipine is increased in elderly patients, thus consider lower initial doses of Exforge HCT [see Clinical Pharmacology (12.3)].

In controlled clinical trials, 82 hypertensive patients treated with Exforge HCT were <sup>365</sup> years and 13 were <sup>375</sup> years. No overall differences in the efficacy or safety of Exforge HCT were observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

### 8.7 Hepatic Impairment

#### Amlodipine

Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of Exforge HCT [see Clinical Pharmacology (12.3)].

~~Amlodipine is extensively metabolized by the liver and the plasma elimination half life ( $t_{1/2}$ ) is 56 hours in patients with impaired hepatic function.~~

#### Valsartan

No dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with severe liver disease.

#### Hydrochlorothiazide

Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

9. Under **OVERDOSAGE**, the following text was added/deleted:

#### **Amlodipine**

Single oral doses of amlodipine maleate equivalent to 40 mg/kg and 100 mg/kg amlodipine in mice and rats, respectively, caused deaths. Single oral doses equivalent to 4 or more mg/kg amlodipine in dogs (11 or more times the maximum recommended human dose on a mg/m<sup>2</sup> basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. ~~Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) who was hospitalized underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.~~

If massive overdose should occur, initiate active cardiac and respiratory monitoring ~~should be instituted~~. Frequent blood pressure measurements are essential. Should

hypotension occur, initiate cardiovascular support including elevation of the extremities and the judicious administration of fluids ~~should be initiated~~. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. ~~Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade.~~ As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

10. Under **CLINICAL PHARMACOLOGY/Pharmacodynamics**, the following text was added:

**Hydrochlorothiazide**

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

**Drug Interactions**

**Hydrochlorothiazide:**

~~*Alcohol, barbiturates, or narcotics:* Potentiation of orthostatic hypotension may occur.~~

~~*Skeletal muscle relaxants:* Possible increased responsiveness to muscle relaxants such as curare derivatives.~~

~~*Digitalis glycosides:* Thiazide induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.~~

11. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted:

**Special Populations**

~~*Geriatric:* Elderly patients have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40%–60% peak plasma levels, elimination half-life and AUC. Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. Limited amount of data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.~~

**Drug Interactions**

**Amlodipine:**

~~*In vitro* data in human plasma indicate that amlodipine has no effect on the protein binding of digoxin, phenytoin, warfarin, and indomethacin.~~

~~*Cimetidine:* Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.~~

~~*Grapefruit juice:* Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.~~

~~*Maalox® (antacid):* Co-administration of the antacid Maalox with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.~~

~~*Sildenafil:* A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and~~

sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

CYP3A4 Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent.

#### **Hydrochlorothiazide:**

*Drugs that alter gastrointestinal motility:* The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.

*Cholestyramine:* In a dedicated drug interaction study, administration of cholestyramine 2 hours before hydrochlorothiazide resulted in a 70% reduction in exposure to hydrochlorothiazide. Further, administration of hydrochlorothiazide 2 hours before cholestyramine resulted in 35% reduction in exposure to hydrochlorothiazide.

*Antineoplastic agents (e.g. cyclophosphamide, methotrexate):* Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Skeletal muscle relaxants: Possible increased responsiveness to muscle relaxants such as curare derivatives.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may predispose the patient to digoxin toxicity.

12. Under **PATIENT COUNSELING INFORMATION/Information for Patients/What Should I tell my doctor before taking EXFORGE HCT?**, the following Bullets were added:

Especially tell your doctor if you take:

- simvastatin or other cholesterol lowering medicine
- other medicines for high blood pressure or a heart problem
- water pills (“diuretics”)
- potassium supplements. Your doctor may check the amount of potassium in your blood periodically.
- salt substitute containing potassium. Your doctor may check the amount of potassium in your blood periodically.
- diabetes medicine including insulin
- narcotic pain medicines
- sleeping pills and anti-seizure medicines called barbiturates
- lithium, a medicine used to treat some types of depression
- aspirin or other medicines called non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen or naproxen
- steroids
- alcohol
- digoxin or other digitalis glycosides (a heart medicine)
- muscle relaxants (medicines used during operations)
- certain cancer medicines, like cyclophosphamide or methotrexate
- medicines used to prevent and treat fungal infections (such as ketoconazole, intraconazole).
- medicines used to treat bacterial infections (such as clarithromycin, telithromycin).
- certain antibiotics (rifamycin group), a drug used to protect against transplant rejection (cyclosporin) or an antiretroviral drug used to treat HIV/AIDS infection (ritonavir). These drugs may increase the effect of valsartan.

13. 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, as amended, 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, Pharm.D.  
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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARY R SOUTHWORTH  
09/28/2012