DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019962/S-042 **SUPPLEMENT APPROVAL**

AstraZeneca LP
Attention: Ian Wogan
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Wogan:

Please refer to your supplemental new drug application dated June 23, 2009, received June 23, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Toprol-XL (metoprolol succinate) 25 mg, 50 mg, 100 mg, and 200 mg Extended Release Tablets.

We acknowledge receipt of your submissions dated July 16 and October 6, 2009.

This "Prior Approval" supplemental new drug application provides for conversion to the Physician Labeling Rule (PLR) format. The following changes were made:

1. In **HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION**, the following text has been added as the third bullet:

   > Hypertension: Usual initial dosage is 25 to 100 mg once daily. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. Dosages above 400 mg per day have not been studied. (2.1)

2. In **HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION**, the following text has been added as the fourth bullet:

   > Angina Pectoris: Usual initial dosage is 100 mg once daily. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is an unacceptable bradycardia. Dosages above 400 mg per day have not been studied. (2.2)

3. In **HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE AND ADMINISTRATION**, the following text has been added as the fifth bullet:

Switching from immediate release metoprolol to TOPROL-XL: use the same total daily dose of TOPROL-XL. (2)

4. **HIGHLIGHTS OF PRESCRIBING INFORMATION/DOSAGE FORMS AND STRENGTHS**, the asterisk and reference have been removed. The first bullet now reads:

   TOPROL-XL Extended Release Tablets (metoprolol succinate): 25mg, 50 mg, 100 mg and 200 mg. (3)

5. **HIGHLIGHTS OF PRESCRIBING INFORMATION/CONTRAINDICATIONS**, the sixth bullet has been changed from:

   Sick sinus syndrome (unless a permanent pacemaker is in place) (4)

   To:

   Sick sinus syndrome without a pacemaker. (4)

6. In **HIGHLIGHTS AND PRECAUTIONS/WARNINGS AND PRECAUTIONS**, the section was reordered and the following added as the sixth bullet:

   Patients with Hepatic Impairment: (5.7)

7. In **HIGHLIGHTS AND PRECAUTIONS/DRUG INTERACTIONS,** the third bullet was changed from:

   Concomitant use of glycosides and beta blockers can increase the risk of bradycardia (7.3)

   To:

   Concomitant use of glycosides, clonidine, and diltiazem and verapamil with beta-blockers can increase the risk of bradycardia (7.3)

8. In **HIGHLIGHTS AND PRECAUTIONS/USE IN SPECIFIC POPULATIONS**, the second bullet was changed from:

   Nursing Mothers: Caution should be exercised when TOPROL XL is administered to nursing women. (8.3)

   To:

   Nursing Mothers: Consider possible infant exposure. (8.3)

9. In **HIGHLIGHTS AND PRECAUTIONS/USE IN SPECIFIC POPULATIONS**, the fourth bullet was changed from:

   Geriatrics: No notable difference in efficacy or safety vs. younger patients, but greater sensitivity of some older individuals cannot be ruled out. (8.5)

   To:

   Geriatrics: No notable difference in efficacy or safety vs. younger patients. (8.5)

10. In **HIGHLIGHTS AND PRECAUTIONS/USE IN SPECIFIC POPULATIONS**, the fifth bullet was changed from:

    Hepatic Impairment: TOPROL XL should be used with caution in patients with impaired hepatic function. (8.6)

    To:

    Hepatic Impairment: Consider initiating TOPROL-XL therapy at low doses and gradually increase dosage to optimize therapy, while monitoring closely for adverse events. (8.6)

11. In **DOSAGE AND ADMINISTRATION/Angina Pectoris**, the text for the first paragraph was converted from passive voice to active voice. The paragraph now reads:

    Individualize the dosage of TOPROL-XL. The usual initial dosage is 100 mg daily, given in a single dose. Gradually increase the dosage at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, reduce the dosage gradually over a period of 1 - 2 weeks *[see Warnings and Precautions (5)]*.

12. In **DOSAGE AND ADMINISTRATION/Heart Failure**, the text for the first paragraph was converted from passive voice to active voice. The paragraph now reads:

    Dosage must be individualized and closely monitored during up-titration. Prior to initiation of TOPROL-XL, stabilize the dose of other heart failure drug therapy. The recommended starting dose of TOPROL-XL is 25 mg once daily for two weeks in patients with NYHA Class II heart failure and 12.5 mg once daily in patients with more severe heart failure. Double the dose every two weeks to the highest dosage level tolerated by the patient or up to 200 mg of TOPROL- XL. Initial difficulty with titration should not preclude later attempts to introduce TOPROL-XL. If patients experience symptomatic bradycardia, reduce the dose of TOPROL-XL. If transient worsening of heart failure occurs, consider treating with increased doses of diuretics, lowering the dose of TOPROL-XL or

temporarily discontinuing it. The dose of TOPROL-XL should not be increased until symptoms of worsening heart failure have been stabilized.

13. In **WARNINGS AND PRECAUTIONS/Ischemic Heart Disease**, the text for the first paragraph was converted from passive voice to active voice. The paragraph now reads:

    Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered TOPROL-XL, particularly in patients with ischemic heart disease gradually reduce the dosage over a period of 1 - 2 weeks and monitor the patient. If angina markedly worsens or acute coronary ischemia develops, promptly reinstate TOPROL-XL, and take measures appropriate for the management of unstable angina. Warn patients not to interrupt therapy without their physician's advice. Because coronary artery disease is common and may be unrecognized, avoid abruptly discontinuing TOPROL-XL in patients treated only for hypertension.

14. In **WARNINGS AND PRECAUTIONS/Heart Failure**, the text for the first paragraph was converted from passive voice to active voice. The paragraph now reads:

    Worsening cardiac failure may occur during up-titration of TOPROL-XL. If such symptoms occur, increase diuretics and restore clinical stability before advancing the dose of TOPROL-XL *[see Dosage and Administration (2)]*. It may be necessary to lower the dose of TOPROL-XL or temporarily discontinue it. Such episodes do not preclude subsequent successful titration of TOPROL-XL.

15. In **WARNINGS AND PRECAUTIONS/Bronchospastic Disease,** the third sentence of the first paragraph was changed from:

    Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly and the lowest possible dose of TOPROL-XL should be used [*see Dosage and Administration* (2)].

    To:

    Because $beta_1$-selectivity is not absolute, use the lowest possible dose of TOPROL-XL. Bronchodilators, including $beta_2$-agonists, should be readily available or administered concomitantly *[see Dosage and Administration (2)]*.

16. In **WARNINGS AND PRECAUTIONS/Major Surgery**, the first and second paragraphs were changed from:

    The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Acute initiation of high-dose metoprolol to patients undergoing non-cardiac surgery should be avoided, since it has been associated with bradycardia, hypotension and stroke including fatal outcome in patients with cardiovascular risk factors.

TOPROL-XL, like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with betablockers

To:

Avoid initiation of a high-dose regimen of extended release metoprolol in patients undergoing non-cardiac surgery, since such use in patients with cardiovascular risk factors has been associated with bradycardia, hypotension, stroke and death. Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

17. In **WARNINGS AND PRECAUTIONS/Diabetes and Hypoglycemia,** the first sentence of the first paragraph has been deleted. The paragraph now reads:

    Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

18. In **WARNINGS AND PRECAUTIONS/Hepatic Impairment**, the first paragraph was changed from:

    TOPROL-XL should be used with caution in patients with impaired hepatic function.

    To:

    Consider initiating TOPROL-XL therapy at doses lower than those recommended for a given indication; gradually increase dosage to optimize therapy, while monitoring closely for adverse events.

19. In **WARNINGS AND PRECAUTIONS/Thyrotoxicosis**, the first paragraph was changed from:

    Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of

hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm

To:

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may precipitate a thyroid storm.

20. In **WARNINGS AND PRECAUTIONS/Anaphylactic Reaction**, the first paragraph was changed from:

    While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

    To:

    While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge and may be unresponsive to the usual doses of epinephrine used to treat an allergic reaction.

21. In **WARNINGS AND PRECAUTIONS/Peripheral Vascular Disease**, the second sentence in the first paragraph was deleted. The paragraph now reads:

    Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

22. In **ADVERSE REACTIONS**, the following text was added:

    The following adverse reactions are described elsewhere in labeling:
    - Worsening angina or myocardial infarction. *[see Warnings and Precautions (5)]*
    - Worsening heart failure. *[see Warnings and Precautions (5)]*
    - Worsening AV block. *[see Contraindications (4)]*

23. In **ADVERSE REACTIONS/Clinical Trials Experience**, the following text was added as the first paragraph:

    Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however,

provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

24. In **ADVERSE REACTIONS/Clinical Trials Experience/Heart Failure**, the first and second paragraphs were changed from:

> In the MERIT-HF study, serious adverse reactions and adverse reactions leading to discontinuation of study medication were systematically collected. In the MERIT-HF study comparing TOPROL-XL in daily doses up to 200 mg (mean dose 159 mg once-daily)
> (n=1990) to placebo (n=2001), 10.3% of TOPROL-XL patients discontinued for adverse reactions vs. 12.2% of placebo patients.
>
> The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of equal to or greater than 1% in the TOPROL-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.
>
> To:
>
> In the MERIT-HF study comparing TOPROL-XL in daily doses up to 200 mg (mean dose 159 mg once-daily; n=1990) to placebo (n=2001), 10.3% of TOPROL-XL patients discontinued for adverse reactions vs. 12.2% of placebo patients.
>
> The table below lists adverse reactions in the MERIT-HF study that occurred at an incidence of ≥ 1% in the TOPROL-XL group and greater than placebo by more than 0.5%, regardless of the assessment of causality.

25. In **ADVERSE REACTIONS/Clinical Trials Experience/Heart Failure**, the following text was deleted:

> Other adverse reactions with an incidence of > 1% on TOPROL-XL and as common on placebo (within 0.5%) included myocardial infarction, pneumonia, cerebrovascular disorder, chest pain, dyspnea/dyspnea aggravated, syncope, coronary artery disorder, ventricular tachycardia/arrhythmia aggravated, hypotension, diabetes mellitus/diabetes mellitus aggravated, abdominal pain, and fatigue.

26. In **ADVERSE REACTIONS/Post-Marketing Experience**, the section was changed from:

> Cardiovascular: 2nd and 3rd degree heart block, cardiogenic shock in patients with acute
> myocardial infarction.
>
> Gastrointestinal: hepatitis, vomiting.

Hematologic: thrombocytopenia.

Musculoskeletal: arthralgia.

Nervous System/Psychiatric: anxiety/nervousness, hallucinations, paresthesia.

Reproductive, male: impotence.

Skin: increased sweating, photosensitivity, urticaria.

Special Sense Organs: taste disturbances.

To:

*Cardiovascular*: Cold extremities, arterial insufficiency (usually of the Raynaud type), palpitations, peripheral edema, syncope, chest pain and hypotension.

*Respiratory:* Wheezing (bronchospasm), dyspnea.

*Central Nervous System*: Confusion, short-term memory loss , headache, somnolence, nightmares, insomnia. anxiety/nervousness, hallucinations, paresthesia.

*Gastrointestinal*: Nausea, dry mouth, constipation, flatulence, heartburn, hepatitis, vomiting.

*Hypersensitive Reactions*: Pruritus.

*Miscellaneous*: Musculoskeletal pain, arthralgia, blurred vision, decreased libido, male impotence, tinnitus, reversible alopecia, agranulocytosis, dry eyes, worsening of psoriasis, Peyronie's disease, sweating, photosensitivity, taste disturbance.

27. In **ADVERSE REACTIONS/Clinical Trials Experience/ Potential Adverse Reactions**:, the following text was changed from:

In addition, there are a variety of adverse reactions not listed above, which have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to TOPROL-XL.

*Central Nervous System*: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

*Cardiovascular*: Intensification of AV block [*see Contraindications* (4)].

*Hematologic*: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

*Hypersensitive Reactions*: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

To:

In addition, there are adverse reactions not listed above that have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to TOPROL-XL.

*Central Nervous System*: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, clouded sensorium, and decreased performance on neuropsychometrics.

*Hematologic*: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

*Hypersensitive Reactions*: Laryngospasm, respiratory distress.

28. In **DRUG INTERACTIONS/Catecholamine Depleting Drugs**, the first paragraph was changed from:

    Catecholamine-depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with TOPROLXL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension

    To:

    Catecholamine-depleting drugs (eg, reserpine, monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Observe patients treated with TOPROL-XL plus a catecholamine depletory for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

29. In **DRUG INTERACTIONS/Digitalis, Clonidine and Calcium Channel Blockers**, the following text was changed from:

    Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta-blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

To:

Digitalis glycosides, clonidine, diltiazem and verapamil slow atrioventricular conduction and decrease heart rate. Concomitant use with beta blockers can increase the risk of bradycardia.

If clonidine and a beta blocker, such as metoprolol are co administered, withdraw the beta-blocker several days before the gradual withdrawal of clonidine because beta-blockers may exacerbate the rebound hypertension that can follow the withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, delay the introduction of beta-blockers for several days after clonidine administration has stopped *[see Warnings and Precautions (5.11)]*.

30. In **USE IN SPECIFIC POPULATIONS/Nursing Mothers,** the following sentence was added to the first paragraph:

    Consider possible infant exposure when TOPROL-XL is administered to a nursing woman.

31. In **USE IN SPECIFIC POPULATIONS/Geriatric Use**, the third paragraph was changed from:

    In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

    To:

    In general, use a low initial starting dose in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

32. In **USE IN SPECIFIC POPULATIONS/Hepatic Impairment**, the first paragraph was changed from:

    TOPROL-XL should be used with caution in patients with impaired hepatic function.

    To:

No studies have been performed with TOPROL XL in patients with hepatic impairment. Because TOPROL-XL is metabolized by the liver, metoprolol blood levels are likely to increase substantially with poor hepatic function. Therefore, initiate therapy at doses lower than those recommended for a given indication; and increase doses gradually in patients with impaired hepatic function.

33. In **USE IN SPECIFIC POPULATIONS/Renal Impairment**, the word "consequently" has been deleted from the second sentence in the first paragraph. The paragraph now reads:

> The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. No reduction in dosage is needed in patients with chronic renal failure *[see Clinical Pharmacology (12.3)]*.

34. In **OVERDOSAGE**, the entire section was changed from:

> Acute Toxicity - There have been a few reports of overdosage with TOPROL-XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since TOPROL-XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to TOPROL-XL.
>
> Signs and Symptoms - Overdosage of TOPROL-XL may lead to severe hypotension, sinus bradycardia, atrioventricular block, heart failure, cardiogenic shock, cardiac arrest, bronchospasm, impairment of consciousness/coma, nausea, vomiting, and cyanosis.
>
> Treatment – In general, patients with acute or recent myocardial infarction or congestive heart failure may be more hemodynamically unstable than other patients and should be treated accordingly. When possible the patient should be treated under intensive care conditions. On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed.
>
> Elimination of the Drug: Gastric lavage should be performed.
>
> Bradycardia: Atropine should be given intravenously. If the response is inadequate, isoproterenol or any other agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.
>
> Hypotension: A vasopressor should be administered, eg, levarterenol or dopamine.

Bronchospasm: A beta2-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered

To:

Signs and Symptoms - Overdosage of TOPROL-XL may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment – Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacologic actions of metoprolol, employ the following measures.

There is very limited experience with the use of hemodialysis to remove metoprolol; however, metoprolol is not highly protein bound.

Bradycardia: Administer intravenous atropine; repeat to effect. If the response is inadequate, consider intravenous isoproterenol or other positive chronotropic agents. Evaluate the need for transvenous pacemaker insertion.

Hypotension: Treat underlying bradycardia. Consider intravenous vasopressor infusion, such as dopamine or norepinephrine.

Bronchospasm: Administer a $beta_2$-agonist, including albuterol inhalation, or an oral theophylline derivative.

Cardiac Failure: Administer diuretics or digoxin for congestive heart failure. For cardiogenic shock, consider IV dobutamine, isoproterenol, or glucagon.

35. In **PATIENT COUNSELING INFORMATION**, the text was converted from passive voice to active voice. The section now reads:

Advise patients to take TOPROL-XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose is missed, the patient should take only the next scheduled dose (without doubling it). Patients should not interrupt or discontinue TOPROL-XL without consulting the physician.

Advise patients (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with TOPROL-XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking TOPROL-XL.

Heart failure patients should be advised to consult their physician if they experience signs or symptoms of worsening heart failure such as weight gain or increasing shortness of breath.

36. The revision date was updated

We have completed our review of this application, as amended, and 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, please submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert). For administrative purposes, please designate this submission, "SPL for approved NDA 019962/S-048.

## LETTERS TO HEALTH CARE PROFESSIONALS

If you 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 an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

## 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
(301) 796-3975

Sincerely,

*{See appended electronic signature page}*

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Agreed-upon labeling text

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-19962 | SUPPL-42 | ASTRAZENECA LP | TOPROL-XL |

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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
01/19/2010