CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-774/S009

Trade Name: Tev Tropin

Generic Name: (somatropin for injection)

Sponsor: Savient Pharmaceuticals, Inc

Approval Date: March 16, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-774/S009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-774/S009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-774/S-009

Savient Pharmaceuticals, Inc.
Attention: Briti Kundu
Senior Director, Regulatory Affairs
One Tower Center, 14th Floor
East Brunswick, NJ 08816

Dear Ms. Kundu:

Please refer to your supplemental new drug application dated November 11, 2004, received November 12, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tev-Tropin (somatropin for injection).

We acknowledge receipt of your submission dated February 3, 2005.

This "Changes Being Effected" supplemental new drug application provides for revisions to the CONTRAINDICATIONS and WARNINGS sections of the package insert regarding use in Prader-Willi patients, in response to our letter dated August 2, 2004.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on November 11, 2004 (vial labels for growth hormone, vial labels for diluent, patient package insert, carton for 2-vial presentation, carton for 6 X 2-vial presentation) and February 3, 2005 (package insert).

However, at the next printing, please correct the following errors in the package insert:
-In CONTRAINDICATIONS, the first sentence, "inpatients" should be "in patients".
-In WARNINGS, the first sentence, "Prader-willi" should be "Prader-Willi", "sybdrome" should be "syndrome", and "sever" should be "severe".

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Kati Johnson, Chief, Project Management Staff, at (301) 827-6380.

Sincerely,

{See appended electronic signature page}

David G. Orloff, MD
Director
Division of Metabolic & Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure (package insert)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
3/16/05 01:29:20 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-774/S009

LABELING

GATE
713

TEV-TROPIN™
[somatropin (rDNA origin) for injection]
5 mg (15 IU)

℞ only

DESCRIPTION

TEV-TROPIN™ (somatropin, rDNA origin, for injection), a polypeptide of recombinant DNA origin, has 191 amino acid residues and a molecular weight of about 22,124 daltons. It has an amino acid sequence identical to that of human growth hormone of pituitary origin. TEV-TROPIN™ is a strain of *Escherichia coli* modified by insertion of the human growth hormone gene.

TEV-TROPIN™ is a sterile, white, lyophilized powder, intended for subcutaneous administration, after reconstitution with bacteriostatic 0.9% sodium chloride injection, USP, (normal saline) (benzyl alcohol preserved). The quantitative composition of the lyophilized drug per vial is:

5 mg (15 IU) vial:

Somatropin	5 mg (15 IU)
Mannitol	30 mg

The diluent contains bacteriostatic 0.9% sodium chloride injection, USP, (normal saline), 0.9% benzyl alcohol as a preservative, and water for injection. A 5 mL vial of the diluent will be supplied with each dispensed vial of TEV-TROPIN™.

TEV-TROPIN™ is a highly-purified preparation. Reconstituted solutions have a pH in the range of 7.0 to 9.0.

CLINICAL PHARMACOLOGY

Clinical trials have demonstrated that TEV-TROPIN™ is equivalent in its therapeutic effectiveness and in its pharmacokinetic profile to those of human growth hormone of pituitary origin (somatropin). TEV-TROPIN™ stimulates linear growth in children who lack adequate levels of endogenous growth hormone. Treatment of growth hormone-deficient children with TEV-TROPIN™ produces increased growth rates and IGF-1 (Insulin-Like Growth Factor/Somatomedin-C) concentrations that are similar to those seen after therapy with human growth hormone of pituitary origin.

Both TEV-TROPIN™ and somatropin have also been shown to have other actions including:

A. *Tissue Growth*

1. Skeletal Growth. TEV-TROPIN™ stimulates skeletal growth in patients with growth hormone deficiency. The measurable increase in body length after administration of TEV-TROPIN™ results from its effect on the epiphyseal growth plates of long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth hormone-deficient children but increase during treatment with TEV-TROPIN™. Mean serum alkaline phosphatase concentrations are increased.
2. Cell Growth. It has been shown that there are fewer skeletal muscle cells in short statured children who lack endogenous growth hormone as compared with normal children. Treatment with somatropin results in an increase in both the number and size of muscle cells.
3. Organ Growth. Somatropin influences the size of internal organs and it also increases red cell mass.

B. *Protein Metabolism*
Linear growth is facilitated, in part, by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, results from treatment with somatropin.

C. *Carbohydrate Metabolism*
Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. Large doses of somatropin may impair glucose tolerance.

D. *Lipid Metabolism*
Administration of somatropin to growth hormone-deficient patients mobilizes lipid, reduces body fat stores, and increases plasma fatty acids.

E. *Mineral Metabolism*
Sodium, potassium and phosphorous are conserved by somatropin. Serum concentrations of inorganic phosphates increased in patients with growth hormone deficiency after therapy with TEV-TROPIN™ or somatropin. Serum calcium concentrations are not significantly altered in patients treated with either somatropin or TEV-TROPIN™.

F. *Connective Tissue Metabolism*
Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

PHARMACOKINETICS

Following intravenous administration of 0.1 mg/kg of TEV-TROPIN™, the elimination half-life was about 0.42 hours (approximately 25 minutes) and the mean plasma clearance (± SD) was 133 (± 16) mL/min in healthy male volunteers.

In the same volunteers, after a subcutaneous injection of 0.1 mg/kg TEV-TROPIN™ to the forearm, the mean peak serum concentration (± SD) was 80 (± 50) ng/mL which occurred approximately 7 hours post-injection and the apparent elimination half-life was approximately 2.7 hours. Compared to intravenous administration, the extent of systemic availability from subcutaneous administration was approximately 70%.

INDICATION AND USAGE

TEV-TROPIN™ is indicated only for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

CONTRAINDICATIONS

Growth hormone is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see **WARNINGS**). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN™ is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Growth hormone should not be initiated to treat patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or to patients having acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone-deficient adult patients (n = 522) with these conditions revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin treated patients (doses 5.3 to 8 mg/day) compared to those receiving placebo (see **WARNINGS**).

TEV-TROPIN™ should not be used in patients with closed epiphyses.

Patients with evidence of progression of an underlying intracranial lesion should not receive TEV-TROPIN™, intracranial tumors must be inactive and antitumor therapy completed.

TEV-TROPIN™ reconstituted with bacteriostatic 0.9% sodium chloride injection, USP (normal saline) (benzyl alcohol preserved) should not be administered to patients with a known sensitivity to benzyl alcohol.

WARNINGS

See **CONTRAINDICATIONS** for information on increased mortality in patients with acute critical illnesses in intensive care units due to complications following open heart or abdominal surgery, multiple accidental trauma or with acute respiratory failure. The safety of continuing growth hormone treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with growth hormone in patients having acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with growth hormone in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstructions or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with growth hormone. If during treatment with growth hormone, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with growth hormone should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (see **CONTRAINDICATIONS**).

Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN™ is not indicated for the long term treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN™ to newborns, reconstitute with sterile normal saline for injection, USP. WHEN RECONSTITUTING WITH STERILE NORMAL SALINE, USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNUSED PORTION.

PRECAUTIONS

Therapy with TEV-TROPIN™ should be directed by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Patients with growth hormone deficiency secondary to intracranial lesion should be examined frequently for progression or recurrence of the underlying disease process.

Patients should be observed for evidence of glucose intolerance because human growth hormone may induce a state of insulin resistance.

Glucocorticoid therapy may inhibit the growth-promoting effect of human growth hormone. Patients with coexisting ACTH deficiency should have their glucocorticoid replacement dose carefully adjusted to avoid an inhibitory effect on growth.

Hypothyroidism may become manifest during treatment with human growth hormone. Inadequate treatment of hypothyroidism may negate optimal response to human growth hormone. Therefore, patients should have periodic thyroid function tests and be treated with thyroid hormone when indicated.

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders. Physicians and parents should be alert to the development of a limp or complaint of hip or knee pain in patients treated with TEV-TROPIN™.

Intracranial hypertension (IH) has not been reported in any patients treated with TEV-TROPIN™. Nevertheless, IH with papilledema, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with other growth hormone products. Symptoms usually occurred within the first eight (8) weeks of the initiation of growth hormone therapy. In all reported cases, IH-associated signs and symptoms resolved after termination of therapy or a reduction of the growth hormone dose. Funduscopic examination of patients is recommended at the initiation and periodically during the course of growth hormone therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis, mutagenesis and reproduction studies have not been conducted with TEV-TROPIN™ growth hormone.

Pregnancy
Pregnancy Category C
Animal reproduction studies have not been conducted with TEV-TROPIN™ growth hormone. It is not known whether TEV-TROPIN™ growth hormone can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TEV-TROPIN™ growth hormone should be given to a pregnant woman only if clearly needed.

Nursing Mothers
There have been no studies conducted with TEV-TROPIN™ in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEV-TROPIN™ is administered to a nursing woman.

Geriatric Use
The safety and effectiveness of TEV-TROPIN™ in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of TEV-TROPIN™ and may be more prone to develop adverse reactions.

ADVERSE REACTIONS
Utilizing a double-antibody immunoassay, no antibodies to growth hormone could be detected in a group of 164 naive and previously treated clinical trial patients after treatment with TEV-TROPIN™ for up to 40 months. However, utilizing the less specific polyethelene glycol (PEG) precipitation immunoassay, 27 of the 164 patient group were tested after treatment with TEV-TROPIN™ for 4 to 6 months and antibodies to growth hormone were detected in two patients (7.4%). The binding capacity of the antibodies from the two antibody positive patients was not determined.

None of the patients with anti-GH antibodies in the clinical studies experienced decreased linear growth response to TEV-TROPIN™ or any other associated adverse event. Growth hormone antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases, when binding capacity exceeds 2 mg/L, growth attenuation has been observed.

In studies of growth hormone-deficient children, headaches occurred infrequently. Injection site reactions (e.g., pain, bruise) occurred in 8 of the 164 treated patients.

Leukemia has been reported in a small number of patients treated with other growth hormone products. It is uncertain whether this risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors.

OVERDOSAGE
The recommended dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight 3 times per week should not be exceeded. Acute overdose could cause initial hypoglycemia and subsequent hyperglycemia. Long-term repeated use of doses in excess of those recommended could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

DOSAGE AND ADMINISTRATION
A dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight administered 3 times per week by subcutaneous injection is recommended. The dosage schedule for TEV-TROPIN™ should be reconstituted with 1 to 5 mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved).* The stream of normal saline should be aimed against the side of the vial to prevent foaming. Swirl the vial with a GENTLE rotary motion until the contents are completely dissolved and the solution is clear. DO NOT SHAKE. Since TEV-TROPIN™ is a protein, shaking or vigorous mixing will cause the solution to be cloudy. If the resulting solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

* Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN™ to newborns, reconstitute with sterile normal saline for injection, USP.

Occasionally, after refrigeration, some cloudiness may occur. This is not unusual for proteins like TEV-TROPIN™ growth hormone. Allow the product to warm to room temperature. If cloudiness persists or particulate matter is noted, the contents MUST NOT be used.

Before and after injection, the septum of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions. It is recommended that TEV-TROPIN™ be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

STABILITY AND STORAGE
Before Reconstitution – Vials of TEV-TROPIN™ are stable when refrigerated at 36° to 46°F (2° to 8°C). Expiration dates are stated on the labels.

After Reconstitution – Vials of TEV-TROPIN™ are stable for up to 14 days when reconstituted with bacteriostatic 0.9% sodium chloride (normal saline), USP, and stored in a refrigerator at 36° to 46°F (2° to 8°C). Do not freeze the reconstituted solution.

HOW SUPPLIED
TEV-TROPIN™ (somatropin, rDNA origin, for injection) is supplied as 5 mg (15 IU) of lyophilized, sterile somatropin per vial.

Each 5 mg carton contains one vial of TEV-TROPIN™ (5 mg per vial) and one vial of diluent [5 mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved)], and is supplied in single cartons or cartons of six.

Manufactured In Israel By:
BIO-TECHNOLOGY GENERAL (ISRAEL) LTD.
Rehovot, Israel

Distributed By:
GATE PHARMACEUTICALS
div. of Teva Pharmaceuticals USA
Sellersville, PA 18960

Rev. D 9/2004
0082-5008v1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-774/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Metabolic & Endocrine Drug Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 19-774/S-009

Name of Drug: Tev-Tropin [somatropin (rDNA origin) for Injection], 5 mg (15IU)

Applicant: Savient Pharmaceuticals, Inc.

Material Reviewed:

Submission Date(s): November 11, 2004, Final Printed Labeling (FPL) for package insert (PI), patient package insert (PPI), vial, and carton labels

Background and Summary

Tev-Tropin is indicated for the long-term treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone (GH).

The product is marketed as a 2-vial carton containing a vial of Tev-Tropin 5 mg and a vial of diluent. These cartons are sold as single cartons and in cartons of six 2-vial cartons.

Supplement -009, submitted as a Supplement-Changes Being Effected, was submitted in response to our letter dated August 2, 2004 requesting revisions to the CONTRAINDICATIONS and WARNINGS sections of the PI regarding use in Prader- Willi patients. This letter was issued to all sponsors of approved NDAs for GH.

In addition to the revision described above, the firm said that minor editorial revisions were made to the patient package insert (Information for the patient or parent), vial, and carton labels.

Review

Package Insert
The proposed labeling (Rev. D 9/2004, 0082-5008v1) was compared to the approved labeling (0082-5008, Rev. A 7/2001, approved with S-008, Acknowledged and Retained 11/26/03). The requested information with regard to use in Prader-willi patients has been included. In addition, the potency of the drug products has been changed from "5 mg (approximately 15IU)" to "5 mg (15 IU)". According to the firm, this revision was approved with Supplement -007 on April 9, 2002. This wording is consistent with the other marketed growth hormone products.

In reviewing the submission, several spelling errors were noted:
-CONTRAINDICATIONS section: In the first sentence, "Growth hormone is contraindicated inpatients with Prader-Willi syndrome who are severely obese or have severe respiratory…",

"inpatients" should be "in patients".
-WARNINGS section: In the first sentence, the following underlined words have been misspelled and should be corrected at the next printing: "There have been reports of fatalities after initiating therapy with growth hormone in pediatric patients with Prader-willi sybdrome who had one or more of the following risk factors: sever obesity, history of upper airway..."

NOTE-the revisions are acceptable, however, the firm will be asked to correct the spelling errors at the next printing.

Patient Package Insert (Information for the Patient or Parent)
The proposed labeling (Rev. A 9/2004, 0082-5009v1) was compared to the currently approved labeling (Iss. 6/2001, 0082-50009, approved with S-008, Acknowledged and Retained 11/26/03). The only revision was to the potency of the growth hormone, as described above, located at the top of the labeling.

NOTE: This is an acceptable revision

Vial labels
Growth hormone
The proposed labeling (Rev. A 9/2004, 0082-1016v2) was compared to the currently approved labeling (Iss. 6/2001, 0082-1015v1, approved with S-008, Acknowledged and Retained 11/26/03). The following revisions have been made:
-The potency has been changed from "5 mg (approximately 15 IU)" to "5 mg (15 IU)"
NOTE-This is an acceptable revision, as stated above.
-The NDC number has been changed from "57844-713-41" to 57844-713-46"
NOTE-this is an acceptable editorial revision
-The place of manufacture [redacted] has been deleted.
NOTE-since the name of the distributor (GATE PHARMACEUTICALS) is on the label, the place of manufacture is not required [21 CFR 201.1(a)]. This is an acceptable revision.

Diluent
The proposed labeling (Rev.A 9/2004, 0082-6008v2) was compared to the currently approved labeling (Iss. 6/2001, 0082-6008v1, approved with S-008, Acknowledged and Retained 11/26/03). The following revisions have been made:
-The NDC number has been changed from "57844-713-41" to "57844-103-33".
NOTE-this is an acceptable editorial revision.
-The place of manufacture [redacted] has been deleted.
NOTE-since the name of the distributor (GATE PHARMACEUTICALS) is on the label, the place of manufacture is not required [21 CFR 201.1(a)]. This is an acceptable revision.

2-vial carton label
The proposed labeling (Rev. A 9/2004, 0082-3007v2) was compared to the currently approved labeling (Iss. 6/2001, 0082-3007v1). The following revisions have been made:

-The potency has been changed from "5 mg (approximately 15 IU)" to "5 mg (15 IU)"
NOTE-This is an acceptable revision, as stated above.
-The NDC number has been changed from "57844-713-41" to 57844-713-19"
NOTE-this is an acceptable editorial revision

Six 2-vial carton label
The proposed labeling (Rev. 9/2004, 0082-3008v2) was compared to the currently approved labeling (Iss. 6/2001, 0082-3008v1, approved with S-008, Acknowledged and Retained 11/26/03). The following revision has been made:
-The potency has been changed from "5 mg (approximately 15 IU)" to "5 mg (15 IU)"
NOTE-This is an acceptable revision, as stated above.

Conclusions

An Acknowledge and Retain letter should be drafted.
However, at the next printing, the firm should be requested to correct the following errors in the package insert:
-In CONTRAINDICATIONS, the first sentence, "inpatients" should be "in patients".
-In WARNINGS, the first sentence, "Prader-willi" should be "Prader-Willi", "sybdrome" should be "syndrome", and "sever" should be "severe".

The currently approved labeling for this drug is as follows:

Package Insert: Rev. D 9/2004, 0082-5008v1
Patient package insert: Rev. A 9/2004, 0082-5009v1
Growth hormone vial label: Rev. A 9/2004, 0082-1016v2
Diluent vial label: Rev.A 9/2004, 0082-6008v2
2-vial carton labels: REV. A 9/2004, 0082-3007v2
Six 2-vial carton label: Rev. 9/2004, 0082-3008v2

Reviewed by Kati Johnson
Chief, Project Management Staff
Division of Metabolic & Endocrine Drug Products

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/s/

Kati Johnson
3/16/05 06:53:44 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 19-774/S-009

CBE-0 SUPPLEMENT

Savient Pharmaceuticals, Inc.
Attention: Briti Kundu
Director, Regulatory Affairs
One Tower Center, 14th Floor
Brunswick, NJ 08816

Dear Ms. Kundu:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tev-Tropin (somatropin)

NDA Number: 19-774

Supplement number: 009

Date of supplement: November 11, 2004

Date of receipt: November 12, 2004

This supplemental application, submitted as "Supplement - Changes Being Effected" proposes revisions to the WARNINGS and CONTRAINDICATIONS sections of the package insert regarding the growth hormone treatment of patients with Pradar-Willi syndrome. In addition, revised labeling, with minor editorial changes, for vials and cartons and the patient package insert accompany this supplement.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 11, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be May 12, 2005.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Document Room 8B45
5600 Fishers Lane

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/s/

Monika Johnson
12/14/04 02:46:04 PM