DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 06188/S-021 and S-022

SUPPLEMENT APPROVAL
RELEASE REMS REQUIREMENT

DAVA Pharmaceutical, Inc.
Attention: Susan F. Hamet
Vice President, Regulatory Affairs
400 Kelbey Street, 10th Floor
Fort Lee, NJ 07024

Dear Ms. Hamet:

Please refer to your Supplemental New Drug Applications (sNDA) dated February 9, 2011, received February 10, 2011 (S-021) and dated July 5, 2011, received July 6, 2011 (S-022) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Propylthiouracil Tablets, USP, 50 mg.

We also refer to our letter dated December 30, 2010, notifying you of new safety information that we believe should be included in the labeling for Propylthiouracil. This information pertains to the safe and effective use of the drug in geriatric patients.

We also refer to your risk evaluation and mitigation strategy (REMS) assessment dated July 5, 2011.

The "Prior Approval" supplemental new drug application (S-021) provides for revisions to the labeling for Propylthiouracil, consistent with our December 30, 2010, letter, which requested the following changes to the PRECAUTIONS section of the package insert:

1. Under DOSAGE AND ADMINISTRATION, addition of the following text:

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

2. Under DOSAGE AND ADMINSTRACTION, addition of a new subsection entitled "Geriatric Use", which includes the following paragraph:

   Clinical studies of propylthiouracil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease of other drug therapy.

Additional editorial changes were made to the package insert and Medication Guide.

The "Prior Approval" supplemental new drug application (S-022) proposes to eliminate the requirement for the approved Propylthoiuracil REMS.

We have completed our review of these supplemental applications. 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, text for Medication Guide) 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/UCMO72392.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 with the revisions listed above 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).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Propylthiouracil was originally approved on April 1, 2010. The REMS consists of a Medication Guide, and a timetable for submission of assessments of the REMS.

You propose that FDA no longer require a REMS for Propylthiouracil.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Propylthiouracil outweigh its risks.

Therefore, we agree with your proposal, and a REMS for Propylthiouracil is no longer required.

We remind you that the Medication Guide will continue to be part of the approved labeling for Propylthiouracil in accordance with 21 CFR 208.

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, call Linda Galgay, Regulatory Project Manager, at (301) 796-5383

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

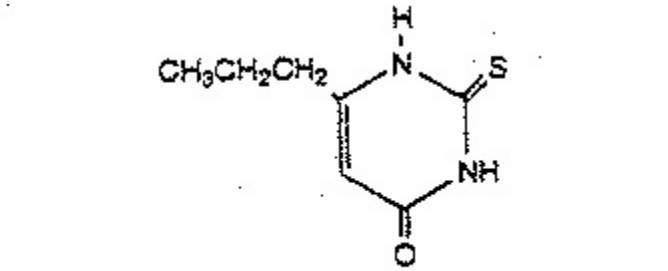
ENCLOSURE:
Content of Labeling

PROPYLTHIOURACIL - propylthiouracil tablet
DAVA International Inc.

WARNING: Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients. Propylthiouracil should be reserved for patients who can not tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.
Because of the risk of fetal abnormalities associated with methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (see Warnings and Precautions).

DESCRIPTION

Propylthiouracil is one of the thiocarbamide compounds. It is a white, crystalline substance that has a bitter taste and is very slightly soluble in water. Propylthiouracil is an antithyroid drug administered orally. The structural formula is:



Molecular Weight: 170.23 $C_7H_{10}N_2OS$

Each tablet contains propylthiouracil 50 mg and the following inactive ingredients: corn starch, docusate sodium, magnesium stearate, microcrystalline cellulose, modified food starch, sodium benzoate, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Propylthiouracil inhibits the synthesis of thyroid hormones and thus is effective in the treatment of hyperthyroidism. The drug does not inactivate existing thyroxine and triiodothyronine that are stored in the thyroid or circulating in the blood, nor does it interfere with the effectiveness of thyroid hormones given by mouth or by injection. Propylthiouracil inhibits the conversion of thyroxine to triiodothyronine in peripheral tissues and may therefore be an effective treatment for thyroid storm.
Propylthiouracil is readily absorbed and is extensively metabolized. Approximately 35% of the drug is excreted in the urine, in intact and conjugated forms, within 24 hours.

INDICATIONS AND USAGE

Propylthiouracil is indicated:

- in patients with Graves' disease with hyperthyroidism or toxic multinodular goiter who are intolerant of methimazole and for whom surgery or radioactive iodine therapy is not an appropriate treatment option

- to ameliorate symptoms of hyperthyroidism in preparation for thyroidectomy or radioactive iodine therapy in patients who are intolerant of methimazole

CONTRAINDICATIONS

Propylthiouracil is contraindicated in patients who have demonstrated hypersensitivity to the drug or any of the other product components.

WARNINGS

Liver Toxicity

Liver injury resulting in liver failure, liver transplantation, or death, has been reported with propylthiouracil therapy in adult and pediatric patients. No cases of liver failure have been reported with the use of methimazole in pediatric patients. For this reason, propylthiouracil is not recommended for pediatric patients except when methimazole is not well-tolerated and surgery or radioactive iodine therapy are not appropriate therapies.
There are cases of liver injury, including liver failure and death, in women treated with propylthiouracil during pregnancy. Two reports of *in utero* exposure with liver failure and death of a newborn have been reported. The use of an alternative antithyroid medication (e.g., methimazole) may be advisable following the first trimester of pregnancy (see Precautions, Pregnancy).
Biochemical monitoring of liver function (bilirubin, alkaline phosphatase) and hepatocellular integrity (ALT, AST) is not expected to attenuate the risk of severe liver injury due to its rapid and unpredictable onset. Patients should be informed of the risk of liver failure. Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain,

etc.), particularly in the first six months of therapy. When these symptoms occur, propylthiouracil should be discontinued immediately and liver function tests and ALT and AST levels obtained.

Agranulocytosis
Agranulocytosis occurs in approximately 0.2% to 0.5% of patients and is a potentially life-threatening side effect of propylthiouracil therapy. Agranulocytosis typically occurs within the first 3 months of therapy. Patients should be instructed to immediately report any symptoms suggestive of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. Propylthiouracil should be discontinued if agranulocytosis, aplastic anemia (pancytopenia), ANCA-positive vasculitis, hepatitis, interstitial pneumonitis, fever, or exfoliative dermatitis is suspected, and the patient's bone marrow indices should be obtained.

Hypothyroidism
Propylthiouracil can cause hypothyroidism necessitating routine monitoring of TSH and free T4 levels with adjustments in dosing to maintain a euthyroid state. Because the drug readily crosses placental membranes, propylthiouracil can cause fetal goiter and cretinism when administered to a pregnant woman (see Precautions, Pregnancy).

PRECAUTIONS

General
Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, light colored stools, dark urine, right upper quadrant pain, etc.), particularly in the first six months of therapy. When these symptoms occur, measurement should be made of liver function (bilirubin, alkaline phosphatase) and hepatocellular integrity (ALT/AST levels).
Patients who receive propylthiouracil should be under close surveillance and should be counseled regarding the necessity of immediately reporting any evidence of illness, particularly sore throat, skin eruptions, fever, headache, or general malaise. In such cases, white blood cell and differential counts should be obtained to determine whether agranulocytosis has developed. Particular care should be exercised with patients who are receiving concomitant drugs known to be associated with agranulocytosis.

Information for Patients
Patients should be advised that if they become pregnant or intend to become pregnant while taking an antithyroid drug, they should contact their physician immediately about their therapy.
Patients should report immediately any evidence of illness, in particular sore throat, skin eruptions, fever, headache, or general malaise. They also should report symptoms suggestive of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.).

Laboratory Tests
Because propylthiouracil may cause hypoprothrombinemia and bleeding, monitoring of prothrombin time should be considered during therapy with the drug, especially before surgical procedures.
Thyroid function tests should be monitored periodically during therapy. Once clinical evidence of hyperthyroidism has resolved, the finding of an elevated serum TSH indicates that a lower maintenance dose of propylthiouracil should be employed.

Drug Interactions
Anticoagulants (oral): Due to the potential inhibition of vitamin K activity by propylthiouracil, the activity of oral anticoagulants (e.g., warfarin) may be increased; additional monitoring of PT/INR should be considered, especially before surgical procedures.
Beta-adrenergic blocking agents: Hyperthyroidism may cause an increased clearance of beta blockers with a high extraction ratio. A reduced dose of beta-adrenergic blockers may be needed when a hyperthyroid patient becomes euthyroid.
Digitalis glycosides: Serum digitalis levels may be increased when hyperthyroid patients on a stable digitalis glycoside regimen become euthyroid; a reduced dose of digitalis glycosides may be needed.
Theophylline: Theophylline clearance may decrease when hyperthyroid patients on a stable theophylline regimen become euthyroid; a reduced dose of theophylline may be needed.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Laboratory animals treated with propylthiouracil for >1 year have demonstrated thyroid hyperplasia and carcinoma formation. Such animal findings are seen with continuous suppression of thyroid function by sufficient doses of a variety of *antithyroid* agents, as well as in dietary iodine deficiency, subtotal thyroidectomy, and implantation of autonomous thyrotropic hormone-secreting pituitary tumors. Pituitary adenomas have also been described.

Pregnancy
Because propylthiouracil readily crosses placental membranes and can induce goiter and even cretinism in the developing fetus, it is important that a sufficient, but not excessive, dose be given during pregnancy. In many pregnant women, the thyroid dysfunction diminishes as the pregnancy proceeds; consequently a reduction of dosage may be possible. In some instances, propylthiouracil can be withdrawn several weeks or months before delivery.

If propylthiouracil is used during pregnancy, or if the patient becomes pregnant while taking propylthiouracil, the patient should be warned of the rare potential hazard to the mother and fetus of liver damage.
Since methimazole may be associated with the rare development of fetal abnormalities such as aplasia cutis and choanal atresia, propylthiouracil may be the preferred agent during organogenesis, in the first trimester of pregnancy. Given the potential maternal adverse effects of propylthiouracil (e.g., hepatotoxicity), it may be preferable to switch from propylthiouracil to methimazole for the second and third trimesters.

Pregnancy Category D.
See **WARNINGS.**

Nursing Mothers
Propylthiouracil is transferred to breast milk to a small extent and therefore likely results in clinically insignificant doses to the suckling infant. In one study, nine lactating women were administered 400 mg of propylthiouracil by mouth. The mean amount of propylthiouracil excreted during 4 hours after drug administration was 0.025% of the administered dose.

Pediatric Use
Postmarketing reports of severe liver injury including hepatic failure requiring liver transplantation or resulting in death have been reported in the pediatric population. No such reports have been observed with methimazole. As such, propylthiouracil is not recommended for use in the pediatric population except in rare instances in which methimazole is not well-tolerated and surgery or radioactive iodine therapy are not appropriate.
When used in children, parents and patients should be informed of the risk of liver failure. If patients taking propylthiouracil develop tiredness, nausea, anorexia, fever, pharyngitis, or malaise, propylthiouracil should be discontinued immediately by the patient, a physician should be contacted, and a white blood cell count, liver function tests, and transaminase levels obtained.

ADVERSE REACTIONS
Major adverse reactions (much less common than the minor adverse reactions) include liver injury resulting in hepatitis, liver failure, a need for liver transplantation or death. Inhibition of myelopoiesis (agranulocytosis, granulopenia, and thrombocytopenia), aplastic anemia, drug fever, a lupus-like syndrome (including splenomegaly and vasculitis), hepatitis, periarteritis, and hypoprothrombinemia and bleeding have been reported. Nephritis, glomerulonephritis, interstitial pneumonitis, exfoliative dermatitis, and erythema nodosum have been reported. Reports of a vasculitis syndrome associated with the presence of anti-neutrophilic cytoplasmic antibodies (ANCA) have also been received. Manifestations of ANCA-positive vasculitis may include rapidly progressive glomerulonephritis (crescentic and pauci-immune necrotizing glomerulonephritis), sometimes leading to acute renal failure; pulmonary infiltrates or alveolar hemorrhage; skin ulcers; and leukocytoclastic vasculitis. Minor adverse reactions include skin rash, urticaria, nausea, vomiting, epigastric distress, arthralgia, paresthesias, loss of taste, taste perversion, abnormal loss of hair, myalgia, headache, pruritus, drowsiness, neuritis, edema, vertigo, skin pigmentation, jaundice, sialadenopathy, and lymphadenopathy.
It should be noted that about 10% of patients with untreated hyperthyroidism have leukopenia (white blood cell count of less than $4{,}000/mm^3$), often with relative granulopenia.

OVERDOSAGE

Signs and Symptoms
Nausea, vomiting, epigastric distress, headache, fever, arthralgia, pruritus, edema, and pancytopenia. Agranulocytosis is the most serious effect. Rarely, exfoliative dermatitis, hepatitis, neuropathies or CNS stimulation or depression may occur.
No information is available on the following: LD50; concentration of propylthiouracil in biologic fluids associated with toxicity and/or death; the amount of drug in a single dose usually associated with symptoms of overdosage; or the amount of propylthiouracil in a single dose likely to be life-threatening.

Treatment
To obtain up-to-date information about the treatment of overdose, a good resource is the certified Regional Poison Control Center. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in the patient.
In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's medical status.

DOSAGE AND ADMINISTRATION
Propylthiouracil is administered orally. The total daily dosage is usually given in 3 equal doses at approximately 8-hour intervals.

Adults
The initial dose is 300 mg daily. In patients with severe hyperthyroidism, very large goiters, or both, the initial dose may be increased to 400 mg daily; an occasional patient will require 600 to 900 mg daily initially. The usual maintenance dose is 100 to 150 mg daily. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric Use
Propylthiouracil is generally not recommended for use in the pediatric patient population except in rare instances in which other alternative therapies are not appropriate options. Studies evaluating appropriate dosing regimen have not been conducted in the pediatric population although general practice would suggest initiation of therapy in patients 6 years or older at a dosage of 50 mg daily with careful upward titration based on clinical response and evaluation of TSH and free T4 levels. Although cases of severe liver injury have been reported with doses as low as 50 mg/day, most cases were associated with doses of 300 mg/day and higher.

Geriatric Use
Clinical studies of propylthiouracil did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

HOW SUPPLIED
Propylthiouracil Tablets, USP, 50 mg, are round, white, scored tablets, engraved LL and P33, supplied as: NDC 67253-651-10 Bottle of 100 NDC 67253-651-11 Bottle of 1000 Store at controlled room temperature 15°-30°C (59° -86°F).

REFERENCE
1. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. 1974; 7; 67-76.

DAVA Pharmaceuticals, Inc.
Fort Lee, NJ 07024
Rev. 2 - February 2010

MEDICATION GUIDE
PROPYLTHIOURACIL TABLETS, USP
(Pro-pil-thi-o-ur-a-sil)
Read this Medication Guide before you start taking Propylthiouracil and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.
What is the most important information I should know about Propylthiouracil?
Propylthiouracil can cause serious side effects, including:
Severe liver problems. In some cases, these liver problems can lead to liver failure, the need for liver transplant, or death.
Stop taking Propylthiouracil and call your doctor right away if you have:
- fever
- loss of appetite
- nausea
- vomiting
- tiredness
- itchiness
- pain or tenderness in your right upper stomach area (abdomen)
- dark (tea colored) urine
- pale or light colored bowel movements (stools)
- yellowing of your skin or whites of your eyes

What is Propylthiouracil?
Propylthiouracil is a prescription medicine used to treat people who have Graves' disease with hyperthyroidism or toxic multinodular goiter. Propylthiouracil is used when:
- certain other antithyroid medicines do not work well.
- thyroid surgery or radioactive iodine therapy is not a treatment option.

- to decrease symptoms of hyperthyroidism in preparation for a thyroidectomy (removal of the thyroid gland) or radioactive iodine therapy.

Propylthiouracil is not recommended for use in children.
Propylthiouracil may be used when an antithyroid drug is needed during or just before the first trimester of pregnancy.

Who should not take Propylthiouracil?

Do not take Propylthiouracil if you are allergic to Propylthiouracil or any of its ingredients. See the end of this Medication Guide for a complete list of ingredients in Propylthiouracil.

What should I tell my doctor before taking Propylthiouracil?

Before you take Propylthiouracil, tell your doctor if you:

- plan to have surgery.
- have any other medical conditions
- are pregnant or plan to become pregnant. Talk to your doctor right away if you are pregnant or plan to become pregnant.
- Propylthiouracil may cause liver problems, liver failure and death in pregnant women.
- Propylthiouracil may harm your unborn baby.
- are breast-feeding or plan to breast-feed. Propylthiouracil can pass into your breast milk. talk to your doctor about the best way to feed your baby if you take Propylthiouracil.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Propylthiouracil may affect the way other medicines work.
Especially, tell your doctor if you take:

- a blood thinner medicine warfarin sodium (Coumadin, Jantoven)
- medicine for heart problems
- medicine for high blood pressure
- Digoxin (Lanoxicaps, Lanoxin)
- Theophylline (Elixophyllin, Theolair, Theochron, Theo-24, Uniphyl)

Ask your doctor if you are not sure if your medicine is one of these.
Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take Propylthiouracil?

- Take Propylthiouracil exactly as your doctor tells you to take it.
- Your doctor may change your dose if needed.
- Propylthiouracil is usually taken 3 times a day (every 8 hours).
- If you take too much Propylthiouracil, call your Regional Poison Control Center or go to the nearest hospital emergency room right away.
- If you take too much Propylthiouracil you may have the following symptoms:

• nausea	• fever
• vomiting	• joint pain
• upper stomach pain or tenderness	• swelling of your body, arms, and legs
• headache	

- If you miss a dose of Propylthiouracil, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not double your dose.

What are the possible side effects of Propylthiouracil?
Propylthiouracil may cause serious side effects, including:
- **liver problems.** See "What is the most important information I should know about Propylthiouracil?"

- **low white blood cell counts.** This usually happens within the first 3 months of treatment and can be life-threatening. You may have a higher chance of getting an infection when your white blood cell count is low.

Tell your doctor right away if you have:
- a fever

- chills

- sore throat

- **hypothyroidism.** Your doctor should do blood tests regularly during treatment to check your thyroid.

- increased bleeding especially with surgical procedures and particularly if you are taking blood thinners.

The most common side effects of Propylthiouracil include:

- skin rash or hives
- nausea
- vomiting
- upper stomach pain or tenderness
- joint pain
- itching or tingling
- loss or change in taste
- loss of hair
- muscle pain
- headache
- sleepiness
- nerve pain
- swelling (edema)
- dizziness
- enlarged salivary glands or enlarged lymph nodes

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all of the possible side effects of Propylthiouracil. For more information, ask our doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Propylthiouracil?

Store Propylthiouracil at 59ºF to 86º F (15º-30ºC).

Keep Propylthiouracil and all medicines out of the reach of children.

General information about the safe and effective use of Propylthiouracil:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use Propylthiouracil for a condition for which it was not prescribed.

Do not give Propylthiouracil to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Propylthiouracil. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Propylthiouracil that is written for health professionals.

www.davapharma.com

1-877-963-8422

What are the ingredients in Propylthiouracil?

Active ingredient: propylthouracil

Inactive ingredients: corn starch, docusate sodium, magnesium stearate,microcrystalline cellulose, modified food starch, sodium benzoate, and sodium starch glycolate.

DAVA Pharmaceuticals, Inc,

Fort Lee, NJ 07024

This Medication Guide has been approved by the U.S. Food and Drug Administration.

03/2010

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

/s/

MARY H PARKS
07/27/2011