DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 006188/S-020 **SUPPLEMENT APPROVAL**

Dava Pharmaceuticals, Inc.
Attention: Susan F. Hamet
Vice President, Regulatory Affairs
Parker Plaza
400 Kelby Street, 10th Floor
Fort Lee, New Jersey 07024

Dear Ms. Hamet:

Please refer to your supplemental new drug application dated February 4, 2010, received February 5, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for propylthiouracil 50 mg Tablets, USP.

We acknowledge receipt of your submissions dated March 24 and 30, 2010.

SAFETY LABELING CHANGES

Reference is also made to our letter dated December 8, 2009, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for propylthiouracil. This information pertains to the risk of hepatotoxicity with the use of this drug. The decision to require safety labeling changes was based on new safety information about this risk identified since these products were approved. You were directed to submit, within 30 days of the December 8, 2009 letter, a prior approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted. We did not receive any submission from you within the required 30-day time period.

We also refer to our letter dated January 21, 2010, ordering you, under Section 505(o)(4)(E) of the FDCA, to make the safety labeling changes specified in our December 8, 2009 letter.

This supplemental new drug application provides for revisions to the WARNINGS, PRECAUTIONS, CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS, OVERDOSAGE sections of the labeling, to add information pertaining to the risk of hepatotoxicity as well as information about other risks and recommended use of propylthiouracil, consistent with our January 21, 2010 Safety Labeling Change Order letter.

We have completed our review of this supplemental application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

A. At the end of the first paragraph after the boxed warning, add the following:

The structural formula is:

[*STRUCTURAL FORMULA*]

B. The title word of the General subsection of the Precautions section should be on a new line and not in the same line as Precautions.

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, except for including the editorial revisions listed above, the enclosed labeling (text for the package insert and the Medication Guide) and submitted labeling (package insert submitted February 4, 2010, Medication Guide submitted March 30, 2010). The editorial revisions listed above are terms of the NDA approval. For administrative purposes, please designate this submission, "**SPL for approved NDA 006188/S-020**." We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

CONTAINER LABELS

Please note that the statement "CAUTION: Federal law prohibits dispensing without prescription" on the container label is outdated and should be replaced with "Rx only" at the next printing of the label.

Submit final printed container labels (FPL) that are identical (with the minor change noted above) to the enclosed immediate container labels submitted on March 30, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Container Labels for**

approved NDA 006188/S-020." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

If you intend to have a proprietary name for this product, we recommend that you submit a request for a proposed proprietary name review. (See Guidance for Industry, *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

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since propylthiouracil was approved on July 28, 1947, we have become aware of an increased risk of hepatotoxicity with propylthiouracil. We have identified 34 reports in FDA's Adverse Event Reporting System (AERS) database of adult and pediatric patients with serious liver injury associated with propylthiouracil use. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

Your proposed REMS, submitted on March 30, 2010, and appended to this letter, is approved, with a few minor typographical revisions. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of patients' understanding of the serious risks of propylthiouracil
b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to

relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

NDA 006188 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 006188
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT FOR (NEW INDICATION FOR USE)
FOR NDA 006188
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions to 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 following address or by facsimile at 301-847-8444:

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

In addition, as required under 21 CFR 314.81(b)(3)(i), you must submit your updated final promotional materials, and the package insert(s), at the time of initial dissemination or

publication, accompanied by a Form FDA-2253, directly to the above address. For instruction on completing the Form FDA 2253, see 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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important 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 this NDA and a paper copy 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 contact Mehreen Hai, Ph.D., Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
- Package Insert
- Medication Guide
- REMS
- Container Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-6188	SUPPL-20	DAVA PHARMACEUTICALS INC	PROPYLTHIOURACIL TABLETS

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

/s/

AMY G EGAN
04/01/2010
Amy Egan for Mary Parks