NDA 008085/S-071

SUPPLEMENT APPROVAL

DAVA Pharmaceutical, Inc.
Attention: Erin Abdallah, M.S.
Associate Director, Regulatory Affairs
Vintage Pharmaceuticals LLC
1400 Atwater Drive
Malvern, PA 19355

Dear Ms. Abdallah:

Please refer to your supplemental new drug application (sNDA) dated July 9, 2019, received July 9, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methotrexate Tablets, 2.5 mg.

This Prior Approval supplemental new drug application provides for the following:

- to revise the Indication and Usage and Recommended Dosage sections to remove the approved indications and approved recommended dosage regimens, respectively, for chorioadenoma destruens, hydatidiform mole gestational choriocarcinoma, breast cancer, epidermoid cancers of the head and neck, and lung cancer;
- to revise the Indication and Usage section to expand the approved indications for rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis;
- to revise the Dosage and Administration section to remove the recommended dosage for acute lymphoblastic leukemia administered for remission induction:
- to revise the Dosage and Administration section to modify the recommended dosage for rheumatoid arthritis/juvenile idiopathic arthritis; and
- to revise the Dosage and Administration section to modify the recommended dosages mycosis fungoides, non-Hodgkin's lymphoma, and acute lymphoblastic leukemia administered as maintenance.

In addition to these changes, additional changes were made to remove contraindications for nursing mothers; and patients with psoriasis or rheumatoid arthritis who have alcoholism, alcoholic liver disease or other chronic liver disease; overt or laboratory evidence of immunodeficiency syndromes; and preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia or significant anemia. Finally, new sections were added and existing sections were modified throughout the PI to ensure the labeling is compliant with PLR, including PLLR requirements, and FDA guidances for product labeling.

APPROVAL LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the submitted carton and container labeling submitted on March 16, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 008085/S-071**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for ages 0 to 16 years for

- the treatment of mycosis fungoides (cutaneous T-cell lymphoma) as a single agent or as part of a combination chemotherapy regimen;
- the treatment of relapsed or refractory non-Hodgkin lymphomas as part of a combination chemotherapy regimen; and
- the treatment of adults with severe psoriasis

because necessary studies are impossible or highly impracticable. This is because the prevalence of these diseases in pediatric patients is very low.

We are deferring submission of your pediatric studies for ages 0 to 16 years for this application for

- the treatment of acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen and
- the treatment of adults with rheumatoid arthritis

because this product is ready for approval for use in adults and the pediatric assessments have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

3849-1 Conduct an assessment based on available literature of the safety and effectiveness of methotrexate tablets in pediatric patients with acute lymphoblastic leukemia treated with methotrexate tablets as part of a combination chemotherapy maintenance regimen and submit the final report.

The timetable you submitted on April 23, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	07/2020
Final Report Submission:	08/2020

3849-2 Conduct an assessment based on available literature of the safety and effectiveness of methotrexate tablets in pediatric patients with rheumatoid arthritis and juvenile polyarticular idiopathic arthritis in part based on extrapolation of efficacy in adults with rheumatoid arthritis and submit the final report.

The timetable you submitted on April 23, 2020, states that you will conduct this study according to the following schedule:

Study Completion:	09/2020
Final Report Submission:	10/2020

Reports of these required pediatric postmarketing studies must be submittedas a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and*

Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

If you have any questions, call Anuja Patel, Lead Regulatory Project Manager, at 301-796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Associate Director for Medical Policy
Oncology Center for Excellence
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICIA KEEGAN
05/04/2020 04:31:52 PM