DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022468/S-012
NDA 022468

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your Supplemental New Drug Application (sNDA) dated December 24, 2015, received December 24, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Folotyn® (pralatrexate injection) 20 mg/1 mL and 40 mg/2 mL.

We also refer to your May 15, 2015, submission containing the final study report for PMR 1547-4 "*A Phase 1 Study for the Evaluation of Excretion (Mass Balance) and Pharmacokinetics (PK) of Pralatrexate in Patients with Advanced Cancer*" and your July 27, 2015, submission containing final study report for PMR 1547-3 "*An Open-label, Phase 1 Study to Evaluate the Safety and Pharmacokinetics of Pralatrexate in Relapsed/Refractory Advanced Solid Tumor or Advanced Lymphoma/Myeloma Patients with Mild, Moderate, and Severe Renal Impairment.*"

This Prior Approval supplemental new drug application provides for changes to the package insert based on data reported in the final study reports for PMR 1547-3 and PMR 1547-4, including edits to Dosage and Administration, Sections 2.1 and 2.2, Use in Specific Populations, Section 8.7 and Clinical Pharmacology, Section 12.3.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 the 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 titled "*SPL Standard for Content of Labeling Technical Qs and As*" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes 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).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

We have received your submissions dated May 15, 2015 and July 27, 2015, containing the final reports for the following postmarketing requirements listed in the September 24, 2009 approval letter.

PMR 1547-3 A clinical pharmacokinetic trial in patients with renal impairment to include patients with severe renal impairment.

Description of trial: This will be a Phase 1 clinical trial to evaluate the pharmacokinetics of pralatrexate in relapsed/refractory lymphoma patients (B-cell, T-cell, and Hodgkin's Lymphoma) with mild to severe renal impairment. Three cohorts (N=6 per cohort) will be enrolled in this study for a total of 18 patients. Cohorts will be based on the severity of renal impairment, i.e., cohort A = severely impaired (Creatinine clearance Cockroft-Gault (CrCl C-G) < 30 mL/min), cohort B = moderately impaired (CrCl C-G = 30-50 mL/min), and cohort C = mildly impaired patients (CrCl C-G = 50-80 mL/min). The pralatrexate dose for cohorts A and B will be determined based on the pharmacokinetics experience from the PROPEL study. Cohort C will be dosed at the recommended dose (30 mg/m2) since patients with mild renal impairment were included in the PROPEL trial. Patients will undergo extensive plasma and urine collections following the first dose of FOLOTYN.

The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date:	January 31, 2010
Trial Completion Date:	June 30, 2012
Final Report Submission Date:	January 31, 2013

PMR 1547-4 Completion of the planned mass balance trial. Contingent on FDA review of the mass balance results, a clinical pharmacokinetic trial in patients with hepatic impairment may be required.

Description of trial: This is an ongoing Phase 1 mass balance clinical trial to evaluate the excretion and metabolic profile of pralatrexate. Patients will receive a fixed dose of 225 mg radio-labeled pralatrexate. Patients will undergo intense sampling of blood, urine, feces, expired air, and other incidental excreta as needed for up to 7 days. Analysis of the samples will be done by liquid scintillation counting for mass balance determination and HPLC for metabolite profiling. Pralatrexate diastereomer concentrations in plasma and urine will be determined in parallel using a validated LCMS/MS method.

The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date:	October 29, 2008
Trial Completion Date:	June 30, 2010
Final Report Submission Date:	December 31, 2010.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the September 24, 2009 approval letter and the July 3, 2014 postapproval postmarketing requirement letter that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Folotyn was approved on September 24, 2009, we have become aware that hepatic excretion accounts for a substantial portion of the elimination of Folotyn, based in part on results of the mass balance study. Increased pralatrexate exposure may be observed in patients with hepatic impairment, increasing the risk of adverse reactions, such as mucositis and hematologic toxicities. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks from increased exposure of Folotyn due to hepatic impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

PMR 3086-1 Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of Folotyn (pralatrexate). Submit a complete final report with all supporting datasets.

The timetable you submitted on May 9, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2016
Trial Completion:	12/2020
Final Report Submission:	06/2021

Submit the protocol(s) to your IND 052604, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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 Jessica Boehmer, Regulatory Project Manager, at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

ANN T FARRELL
05/13/2016