ANDA 213267

ANDA APPROVAL/TENTATIVE APPROVAL

Teva Pharmaceuticals USA, Inc.
U.S. Agent for Natco Pharma Limited
400 Interpace Parkway, Building A
Parsippany, NJ 07054
Attention: Elisabeth Gray
Regulatory Affairs, U.S. Agent

Dear Elisabeth Gray:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 11, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Thalidomide Capsules USP, 50 mg, 100 mg, 150 mg, and 200 mg.

Reference is also made to the complete response letter issued by this office on August 31, 2020, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. We have determined your Thalidomide Capsules USP, 50 mg, 100 mg, 150 mg, and 200 mg to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Thalomid Capsules, 50 mg, 100 mg, 150 mg, and 200 mg, of Bristol-Myers Squibb Company (Bristol-Myers).

However, we are unable to grant final approval to your Thalidomide Capsules USP, 50 mg, 100 mg and 200 mg, at this time because of the patent issue noted below. Therefore, your ANDA is **approved** insofar as it pertains to Thalidomide Capsules USP, 150 mg. Your Thalidomide Capsules USP, 50 mg, 100 mg and 200 mg, are **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug (RLD) upon which you have based your ANDA, Thalomid Capsules, 50 mg, 100 mg, 150 mg, and 200 mg, of Bristol-Myers, is subject to a period of patent protection. The following patent and expiration date is currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
7,230,012 (the '012 patent)	December 9, 2023*

* 50 mg, 100 mg and 200 mg

With respect to the '012 patent, your ANDA contains a paragraph III certification to the patent under section 505(j)(2)(A)(vii)(III) of the FD&C Act stating that Natco Pharma Limited will not market Thalidomide Capsules USP, 50 mg, 100 mg, and 200 mg prior to the expiration of the patent. Therefore, final approval of your ANDA with respect to the 50 mg, 100 mg, and 200 mg strength products may not be granted pursuant to section 505(j)(5)(B)(ii) of the FD&C Act until the '012 patent has expired, currently December 9, 2023.

Upon the foregoing, your ANDA is **approved** insofar as it pertains to the 150 mg product. Your 50 mg, 100 mg, and 200 mg products, are **tentatively approved**.

I. Approval of Thalidomide Capsules USP, 150 mg

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a) of the FD&C Act]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) of the FD&C Act is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated February 6, 2020.

Your final proposed REMS, received on March 24, 2023, is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

The Thalidomide Shared System REMS consists of Elements to Assure Safe Use (ETASU) and an implementation system.

Your REMS must be fully operational before you introduce thalidomide to interstate commerce.

Your REMS, known as the Thalidomide REMS Program, is approved as a separate REMS program from that of the reference listed drug, using a different, comparable aspect of the ETASU. Pursuant to section 505-1(i)(3) of the FD&C Act, FDA is requiring that this REMS Program can be used with respect to any other drug that is the subject

of an application under section 505(j) or 505(b) of the FD&C Act that references the same listed drug.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

FDA has determined that assessments are needed for the Thalidomide REMS Program. Re-submit your full audit plan and Compliance Committee and Action Plan within 90-days post-approval as a REMS Assessment Methodology.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **ANDA 213267 REMS CORRESPONDENCE**
> (insert concise description of content in bold capital letters, e.g.,
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY**)

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) of the FD&C Act could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 213267 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR ANDA 213267/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 213267/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 213267/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 213267

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For additional information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

II. Tentative Approval of Thalidomide Capsules USP, 50 mg, 100 mg and 200 mg

Our decision to tentatively approve your Thalidomide Capsules USP, 50 mg, 100 mg and 200 mg, is based upon information currently available to the Agency (i.e., data in your ANDA and the status of current good manufacturing practice (cGMP) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 3 months for Agency review. Accordingly, such a request for final approval should be submitted no later than 3 months prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available Agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. As part of this consideration, applicants should monitor any changes to the RLD that occur after tentative approval, including changes in labeling, patent or exclusivity information, or marketing status. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "MINOR/MAJOR AMENDMENT TO ORIGINAL #2 – FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior December 9, 2023, you should amend your ANDA accordingly.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Olga Salis, Regulatory Project Manager, at (301) 796 - 0837.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: REMS Assessment Plan

APPENDIX 1: REMS Assessment Plan

The Thalidomide Shared System REMS Applicant(s) will submit Thalidomide REMS assessments to the FDA annually from the date of initial approval of the Thalidomide Shared System REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that REMS assessment. The Thalidomide Shared System REMS Applicant(s) will submit each REMS assessment so that it will be received by the FDA on or before the due date.

For each annual Thalidomide REMS assessment report, the following information will be provided. A tabular format will be utilized when appropriate.

The Thalidomide Shared System REMS Assessment Plan will include, but is not limited to, the following information:

Program Implementation and Operations

1. REMS Program Implementation (1-year assessment only)

    a. Date of first commercial distribution of generic thalidomide

    b. Date when the Thalidomide REMS website became live and fully operational

    c. Date when healthcare providers could become certified

    d. Date when pharmacies could become certified

    e. Date when patients could become enrolled

    f. Date when the REMS Coordinating Center was established and fully operational

2. Certification of healthcare providers (HCPs) (per current and previous two reporting periods and cumulatively)

    a. Number of new certifications of HCPs, indicating whether previously certified or not, stratified by professional designation (i.e., MD, DO, PA, NP), and geographic region (defined by US Census).

    b. Number of active HCPs (have prescribed thalidomide at least once during the reporting period), stratified by professional designation (i.e., MD, DO, PA, NP), and geographic region (defined by US Census).

3. Certification of pharmacies (per current and previous two reporting periods and cumulatively)

    a. Number of new certified pharmacies stratified by geographic region (defined by US Census).

    b. Number of active certified pharmacies (have filled or ordered at least one prescription for thalidomide during the reporting period) stratified by geographic region (defined by US Census).

4. Patient enrollment (per current and previous two reporting periods and cumulatively)

    a. Number of new patients enrolled stratified by age, gender, diagnosis, females of reproductive potential (FRP).

    b. Number of active patients (have received at least one shipment of thalidomide during the reporting period) stratified by age gender, diagnosis, and patient reproductive status (i.e. females of reproductive potential (FRP) and females of non-reproductive potential (FNRP).

5. REMS Utilization Data (per current and previous two reporting periods and cumulatively)

    a. Number and percentage of unique patients who received thalidomide, new and total, stratified by patient type grouped by the following age ranges (i.e., years):

        I. < 10

        II. 10 - < 18

        III. 18 - < 25

        IV. 25 - < 45

        V. 45 - < 53

        VI. 53+

    b. Number and percentage of prescriptions (new and refills) dispensed for females of reproductive potential (FRPs) and females of non-reproductive potential (FNRPs) stratified by:

        i. Healthcare provider specialty

        ii. Reproductive Status (FRP or FNRP)

iii. Patient age as outlined in 5.a above

6. Compliance with the Thalidomide REMS (per current and previous two reporting periods and cumulatively; where applicable)

   a. Provide a report of audit activities for stakeholders (pharmacies, distributors, and the REMS Coordinating Center)

   b. Provide a copy of the non-compliance plan to include the following:

      i. Criteria for non-compliance

      ii. Actions taken to address non-compliance for each event identified

      iii. Criteria for de-certification

   c. Provide a copy of the audit plan.

   d. Report of audit findings.

      i. The number of audits expected, and the number of audits conducted

      ii. The number and type of deficiencies noted

         1. Number that successfully completed a corrective and preventative (CAPA) plan within 30 days of receipt of CAPA

         2. Describe actions taken for any that did not complete the CAPA within 30 days of receipt of CAPA

         3. Include a unique ID for each stakeholder that had deviations to track deviations over time

      iii. Documentation of completion of training for relevant staff

      iv. The existence of documented processes and procedure for complying with the REMS

      v. A comparison of the findings to findings of previous audits and assess whether any trends are noted

   e. Non-compliance events: for each event provide the following:

      i. Source of the report

      ii. Description of the event

1. Indicate the risk category for the patient(s) associated with the event (when applicable)

iii. Cause of the event

iv. Corrective actions taken

v. Event:

1. Number of thalidomide prescriptions dispensed that were written by non-certified prescribers

2. Number of thalidomide prescriptions dispensed by non-certified pharmacies

3. Number of thalidomide prescriptions dispensed to de-enrolled or non-enrolled patients

4. Number of times a thalidomide prescription was dispensed without obtaining a confirmation number

5. Number of prescriptions dispensed of greater than a 28 days' supply

6. Number of shipments sent to non-certified pharmacies, sources of the reports, and actions taken to prevent future occurrences

7. Number of prescribers and pharmacies who were de-certified (suspended or deactivated) for non-compliance and reasons for de-certification

7. REMS Infrastructure and Performance (per current and previous two reporting periods and cumulatively; where applicable)

a. REMS Coordinating Center

i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, wholesaler(s)/distributor(s), other)

ii. Summary of reasons for calls (e.g., enrollment question, location of a pharmacy) and by reporter (authorized representative, pharmacy, healthcare provider, patient, other)

iii. Summary of frequently asked questions (FAQ) by stakeholder type

iv. Summary report of REMS-related problems identified and resulting corrective actions

b. REMS Website

i. Number of visits and unique visits to the REMS website

ii. Number of REMS materials downloaded or printed for each material

Health Outcomes and/or Surrogates of Health Outcomes

8. Pregnancy Metrics (per reporting period and cumulatively)

a. Number of pregnancies reported stratified by the source of the report (spontaneous report, reported via the REMS program, etc.)

b. Pregnancy rate

c. A summary of both US and worldwide pregnancy cases, including but not limited to the following information:

i. Event identification number

ii. Age of the patient

iii. Contraceptive methods used

iv. Outcome of each pregnancy

v. Weeks gestation at termination if pregnancy is terminated

d. Follow-up of outstanding pregnancy reports

e. Root cause analysis of each reported pregnancy

f. Link to most recent Periodic Safety Update Report (PSUR) or Periodic Benefit-Risk Evaluation Report (PBRER) that provides information on worldwide pregnancies. Discussion of any new information provided in the PSUR or PBRER regarding pregnancy.

Safe-Use Behaviors

9. Change in Reproductive Status as reported via the required prescriber survey (per current and previous two reporting periods and cumulatively)

a. Number of status changes to a female of reproductive potential, including:

i. Number of times thalidomide was dispensed prior to the patient getting her first pregnancy test following the status change, any resulting adverse events, and corrective actions

b. Number of status changes to a female of non-reproductive potential, including rationale for the change as indicated on the survey.

i. Number of female patients for whom pregnancy testing can be discontinued because the patient has had a natural menopause for at least 24 consecutive months, a hysterectomy, and/or a bilateral oophorectomy

10. Documentation of safe-use conditions (per current and previous two reporting periods and cumulatively, where applicable)

Based on information collected from the mandatory surveys (used to document safe-use conditions) provide information that could represent potential fetal exposure or that might result in a delay or interruption in treatment.

Provide the following in a tabular format:

a. The total number of authorization numbers issued

b. The number and proportion of failed authorizations intended for an FRP due to responses in the mandatory surveys related to pregnancy testing that did not meet the REMS requirements

c. The number and proportion of failed authorizations that caused a delay in treatment initiation or a gap in therapy for patients due to REMS processes related to the mandatory surveys compared to the total authorization numbers. Include the time to resolution of failed authorizations in days (mean, minimum, maximum) for the reporting period and for each previous reporting period. Include the number of patients with a delay in treatment or a gap in therapy due to REMS processes related to the mandatory surveys.

Knowledge

11. Inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for thalidomide (per current and previous two reporting periods and cumulatively, where applicable)

a. Ensure that thalidomide will only be dispensed to patients enrolled in the Thalidomide REMS with evidence or other documentation of safe-use conditions

i. Number of patient surveys that met the REMS requirements relating to knowledge compared to the total number of patient surveys submitted per patient risk category

ii. Number of patient surveys that did not meet the REMS requirements related to knowledge as compared to the total number of patient surveys submitted per patient risk category. Include the time to resolution in days (mean, minimum, maximum) for the reporting period and for each previous reporting period. Include outreach strategies taken by the REMS Coordinating Center to resolve unacceptable safe-use survey responses.

b. Ensure healthcare providers counsel patients on the benefits and risks of thalidomide therapy, including risks described in the boxed warnings

i. Number of prescriber surveys that met the REMS requirements reported per risk category

ii. Number of prescriber surveys that did not meet the REMS requirements reported per risk category. Include the time to resolution in days (mean, minimum, maximum) for the reporting period and for each previous reporting period. Include outreach strategies taken by the REMS Coordinating Center to resolve unacceptable safe-use survey responses.

c. Educate pharmacies on the risks and safe-use conditions of thalidomide

i. Total number of pharmacy certification quizzed administered

ii. Number of pharmacies with a passing rate/total number of certified pharmacies on the last day of the reporting period

12. Thalidomide REMS Knowledge, Attitudes, and Behavior Survey (KAB) (beginning with the 1-year assessment report and annually thereafter with each assessment report)

The first KAB assessment of prescribers, pharmacists and patients will be completed for inclusion in the 1-year FDA Assessment Report, and will be repeated annually. The KAB surveys will assess the following:

a. Patient understanding of:

i. The risks associated with the use of thalidomide

ii. The importance of regular pregnancy testing as described in the ***Patient Guide***

b. Prescriber understanding of:

i. The risks associated with the use of thalidomide

ii. The requirements for monitoring reproductive status and pregnancy status described in the ***Prescriber Guide***

iii. The need to counsel patients about the risks associated with the use of thalidomide and the need for monitoring as described in the ***Prescriber Guide***

c. Pharmacist understanding of:

i. The risks associated with the use of thalidomide

ii. The training and dispensing procedures for thalidomide as described in the ***Pharmacy Guide***

iii. The need to counsel patients on the benefits and risks of thalidomide using the ***Education and Counseling Checklist for Pharmacies***

Overall Assessment of REMS Effectiveness

13. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

John Ibrahim

Digitally signed by John Ibrahim
Date: 4/27/2023 09:50:02AM
GUID: 542af06d0124375c12e8c1d9fc86e87c