NDA 50722/S-044
NDA 50723/S-044
NDA 50758/S-041
NDA 50759/S-049

SUPPLEMENT APPROVAL

Roche Palo Alto LLC
c/o Genentech Inc.
Attention: Elizabeth Wishart
Regulatory Agent on behalf of Roche
1 DNA Way
South San Francisco, CA 94080-4990

Dear Ms. Wishart:

Please refer to your supplemental new drug application (sNDA) dated and received July 27, 2020 and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA Number	Supplement Number	Drug Name	Submitted and Received
50722	044	CellCept (mycophenolate mofetil) Capsules, 250 mg	July 20, 2020
50723	044	CellCept (mycophenolate mofetil) Tablets, 500 mg	July 20, 2020
50758	041	CellCept (mycophenolate mofetil hydrochloride) Intravenous	July 20, 2020
50759	049	CellCept (mycophenolate mofetil) Oral suspension	July 20, 2020

These Prior Approval supplemental new drug applications provides for proposed modifications to the approved Mycophenolate risk evaluation and mitigation strategy (REMS). These supplements are in response to our August 02, 2019, REMS Modification Notification letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Shared System REMS for the mycophenolate products, of which CellCept (mycophenolic mofetil), is a member, was originally approved on September 25, 2012, and the most recent REMS modification was approved on November 13, 2015. The REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of mycophenolic acid and mycophenolate mofetil outweigh their risks we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated August 2, 2019. In addition, the following modifications were communicated during the course of the review:

- Revisions to the patient-directed goal to make the language more patient-friendly and to align with the Medication Guide
- Elimination of the Patient-Prescriber Acknowledgement Form to reduce burden on stakeholders
- Creation of two versions of the Center & Prescriber Training Confirmation Forms, Healthcare Provider Brochure, Center & Healthcare Provider Letters, & REMS website to address the availability of training prior to and after Continuing Education becomes available
- Inclusion of a list of professional medical societies and publishing schedule for the website banner

Your proposed modified REMS, submitted to Drug Master File (DMF) [redacted] (b) (4) on July 20, 2020, amended and appended to this letter, is approved.

The modified REMS uses a shared system for the elements to assure safe use and a timetable for submission of assessments of the REMS. This shared system, known as the Mycophenolate Shared System REMS, currently includes products listed on the FDA REMS website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=37. Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to require submission of assessments 18 months from the date of this REMS modification approval and every 18 months thereafter.

The revised assessment plan must include, but is not limited to, the following:

Program Outreach and Communication

1) REMS Communication Activities (provide for each reporting period and cumulatively)
   a) For both the Mycophenolate REMS Dear Healthcare Provider (DHCP) Letters (1&2) and the Mycophenolate REMS Dear Healthcare Provider (DHCP) Letter for Centers (1&2), provide the following:
      i) Sources for the distribution lists for healthcare providers
      ii) Number of healthcare providers targeted

iii) The number of REMS materials packets sent by date and method of distribution
iv) The number of mailings successfully delivered and, returned as undeliverable
v) The number of emails successfully delivered, opened, and unopened
vi) Date that the revised materials became available on the website

b) For each professional society, or journal to be sent the banner, provide the following:
i) A summary of the extent to which the banner reached the intended stakeholders.
ii) The number of times the Mycophenolate REMS website was accessed via the banner.

Program Implementation and Operations

2) Status of Grants (provide for each reporting period and cumulatively)
a) The status of the request for proposals for grants for REMS-compliant accredited CE including:
i) Date Request for Application (RFA) issued
ii) Date and number of applications submitted in response to each RFA
iii) RFAs awarded: date, number and name of grantee
iv) Date/timeframe next RFA to be issued.

3) Continuing Education (CE) Program (provide for each reporting period and cumulatively)
a) For CE programs awarded during the assessment period:
i) Description of each grantee and projected number of participants and completers
ii) For the first assessment, the date the first REMS-compliant CE based upon the FDA Mycophenolate REMS Education Blueprint became available.

b) Description of Continuing Education (CE) program:
i) CE format (live, webinar, etc.)
ii) Duration of activity for live or webinar activities
iii) Average duration to complete for internet/enduring activities
iv) Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)
v) A summary of all reports submitted to the Mycophenolate REMS Applicants by CE grantees during the assessment period.

4) Audit: The aggregate results of independent audits of the CE. Audits must include/evaluate:
a) a description of the organization(s) or independent auditors (accreditation bodies of CE Providers are considered independent and eligible to conduct the audits)

conducting the audit(s)

b) whether the content of the REMS-compliant accredited CE covers all elements of the FDA Blueprint approved as part of the REMS;
c) whether the integrated or post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint;
d) whether the REMS compliant accredited CE was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies

5) Healthcare Provider Training (provide for each reporting period and cumulatively)
   a) The number of healthcare providers who completed the Mycophenolate REMS Prescriber Training Confirmation Form in the Single Shared System (SSS) Mycophenolate REMS, stratified by specialty.

   b) A summary of the methods used to complete the Mycophenolate REMS Prescriber Training Confirmation Form (i.e., online, phone, fax,).

   c) The number of healthcare providers who have confirmed training through the Mycophenolate REMS website and were actively prescribing mycophenolate during the reporting period (i.e., have written at least one prescription in the time period) stratified by specialty.

   d) The number of healthcare providers who have taken REMS compliant accredited CE stratified by specialty, degree, and geographic region (defined by US Census) and those who report prescribing mycophenolate.

   e) Provide an analysis comparing the number of healthcare providers who completed the Mycophenolate REMS Prescriber Training Confirmation Form and/or a REMS compliant accredited CE program to the total number of healthcare providers prescribing a mycophenolate-containing product stratified by specialty and degree.

   f) A description of any activities undertaken during the assessment reporting period to increase training, not identified in other metrics.

6) Center training (provide for each reporting period and cumulatively)
   a) The total number of centers, stratified by type of center, that confirmed training.

   b) A descriptive summary of how newly confirmed centers incorporated the Mycophenolate REMS into their center's practice (as described on the Mycophenolate REMS Center Training Confirmation Form).

   c) Total prescribers confirmed by centers.

7) Mycophenolate Utilization Data (provide for each reporting period and cumulatively)
   a) Healthcare Provider Data
      i) The number and percentage of total prescriptions dispensed, by new and refill, stratified by specialty.
      ii) The number of unique prescribers stratified by specialty

   b) Patient Utilization Data
      i) The number of unique patients receiving mycophenolate stratified by age, gender, and reasons for use/indication.

Health Outcomes and Surrogates of Health Outcomes

8) Pregnancy Exposures (provide for each reporting period and cumulatively)
   a) An analysis of the post-marketing cases of pregnancy reported in association with mycophenolate with attention to but not limited to:
      i) The number of pregnancy exposures* reported and stratified by source (spontaneous report, reported via the Mycophenolate REMS Call Center, enrolled in the Mycophenolate REMS Pregnancy Registry), age, and other demographics, and if the prescriber completed the Mycophenolate REMS Training and/or reports completing REMS compliant CE training.
      ii) The duration of mycophenolate exposure data
      iii) The pregnancy outcome for each exposed pregnancy reported
      iv) The root cause analysis of each pregnancy reported to determine the cause of the pregnancy exposure.
      v) Results of any follow up from previous years' exposures.

*All pregnancy exposures reported to the Applicants from any source should be reported and analyzed as part of the SSS Mycophenolate REMS assessment plan. The cases should be linked to allow matching of the cases reported in the Mycophenolate REMS Pregnancy Registry to cases in the global safety database.

Knowledge

9) Healthcare Provider Knowledge (beginning with the 3-year assessment report and each reporting period thereafter) Stratified by whether the healthcare provider reports training through the REMS website, training through the REMS complaint accredited CE program, neither or both.
   An evaluation of healthcare providers' understanding of:

a. first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy

b. the need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate

c. the need to report pregnancies to the Mycophenolate Pregnancy Registry.

10) Patient Knowledge (beginning with the 3-year assessment report and each reporting period thereafter)

a. An evaluation of patients' understanding and awareness of the increased risks of miscarriage and birth defects when taking mycophenolate during pregnancy, and the importance of pregnancy prevention and planning when taking mycophenolate.

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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, 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 FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.

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:

NDA/BLA ###### REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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

Prominently identify any submission containing the 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 as appropriate:

NDA ###### REMS ASSESSMENT
CROSS REFERENCE TO THE REMS DMF

NEW SUPPLEMENT FOR NDA ###### /S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR NDA ###### /S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR NDA ######/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA ######/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)
CROSS REFERENCE TO THE REMS DMF

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 REVISIONS FOR NDA ######
CROSS REFERENCE TO THE REMS DMF

The Mycophenolate Shared System REMS uses a Type V DMF for shared system REMS submissions. Please refer to the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*,[1] for instructions on how to submit and reference the shared system REMS DMF.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the 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 SPL format using the FDA automated drug registration and listing system (eLIST).

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[2]

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default htm

[2] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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.[3] Information and Instructions for completing the form can be found at FDA.gov.[4]

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).

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 Ms. June Germain, Safety Regulatory Project Manager, at 301-796-4024.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE: REMS

[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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/s/

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