DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 011366/S-030

SUPPLEMENT APPROVAL

Taro Pharmaceutical Industries, Ltd.
c/o Taro Pharmaceuticals USA, Inc.
3 Skyline Drive
Hawthorne, NY 10532

Attention: Kavita Srivastava, M.S.
Executive Director, Regulatory Affairs

Dear Ms. Srivastava:

Please refer to your Supplemental New Drug Application (sNDA) dated November 10, 2014, received November 10, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for KEVEYIS (dichlorphenamide), 50 mg tablets.

We acknowledge receipt of your amendments dated:

December 23, 2014	February 4, 2015	April 15, 2015	July 15, 2015
December 29, 2014	February 12, 2015	May 5, 2015	July 27, 2015 (3)
January 5, 2015	February 13, 2015	May 12, 2015	
January 7, 2015	March 3, 2015	May 14, 2015	
January 9, 2015	March 10, 2015	May 29, 2015	
January 26, 2015	March 18, 2015	June 18, 2015	
January 30, 2015	March 26, 2015	July 8, 2015	

This Prior Approval supplemental new drug application provides for a new indication for the use of KEVEYIS for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.

We make reference to your July 27, 2015, amendment which requests withdrawal, under 21 CFR 314.150, of the indication of increased intraocular pressure (IOP) from the prescribing information. We acknowledge this request and agree to its removal from the prescribing information.

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.

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), 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 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 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed immediate container labels 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 *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. 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 011366/S-030**." 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.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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.

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 identify an unexpected serious risk of increased toxicity of KEVEYIS (dichlorphenamide) (including the serious risks of hypokalemia, metabolic acidosis, falls, cognitive impairment, and paresthesias) caused by alterations in P450-mediated metabolism of KEVEYIS (dichlorphenamide) that result from drug-drug interactions.

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 this serious risk.

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

> **2942-1** Identify the in vitro metabolic pathways of dichlorphenamide and characterize the potential for P450-mediated drug interactions due to inhibition or induction of these pathways in vitro. Refer to the draft Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations **(**http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf) regarding conduct of the studies.

The timetable you submitted on July 27, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/15
Study Completion:	02/16
Final Report Submission:	03/16

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to, , identify an unexpected serious risk of increased toxicity of KEVEYIS (dichlorphenamide) (including the serious risks of hypokalemia, metabolic acidosis, falls, cognitive impairment, and paresthesias) related to excessive exposure caused by alterations in the pharmacokinetics of KEVEYIS (dichlorphenamide) .

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

> **2942-2** Conduct a trial to characterize the pharmacokinetics of dichlorphenamide in healthy volunteers, to include a single ascending dose assessment and a multiple ascending dose assessment, using a dose range of 25 to 200 mg. Pharmacokinetic parameters should include AUC, Cmax, and elimination half-life.

The timetable you submitted on July 27, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	11/15
Trial Completion:	03/16
Final Report Submission:	05/16

Submit the protocols to your IND 63921, with a cross-reference letter to this NDA. Submit all final reports 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.

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 package insert(s) 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 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 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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, contact Cathy Michaloski, BSN, MPH, RAC, Sr. Regulatory Project Manager, by email at Cathleen.michaloski@fda.hhs.gov or by phone at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Eric P. Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Container Labeling

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

/s/

ERIC P BASTINGS
08/07/2015