CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761068Orig1s000

Trade Name:	CRYSVITA
Generic or Proper Name:	(burosumab-twza)
Sponsor:	Ultragenyx Pharmaceutical, Inc.
Approval Date:	April 17, 2018
Indication:	Treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

CENTER FOR DRUG EVALUATION AND RESEARCH

761068Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761068

BLA APPROVAL

Ultragenyx Pharmaceutical, Inc.
Attention: Monica Sandberg, Ph.D., RAC
Director, Regulatory Affairs
60 Leveroni Court, Suite 200
Novato, CA 94949

Dear Dr. Sandberg:

Please refer to your Biologics License Application (BLA) dated and received August 17, 2017, and your amendments, submitted under section 351(a) of the Public Health Service Act for CRYSVITA (burosumab-twza) injection.

LICENSING

We have approved your BLA for CRYSVITA (burosumab-twza) injection effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, CRYSVITA (burosumab-twza) under your existing Department of Health and Human Services U.S. License No. 2040. CRYSVITA (burosumab-twza) is indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 1 year of age and older.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture CRYSVITA (burosumab-twza) at Kyowa Hakko Kirin Co., Takahashi Plant, 100-1, Hagiwara-machi, Takasaki-shi, Gunma, Japan. You may label your product with the proprietary name, CRYSVITA, and market it in 10 mg/ 1 mL, 20 mg/ 1 mL, or 30 mg/ 1 mL single-dose vial.

DATING PERIOD

The dating period for CRYSVITA (burosumab-twza) shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of CRYSVITA (burosumab-twza) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of CRYSVITA (burosumab-twza), or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

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 text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, 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). 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/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761068**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761068. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for CRYSVITA (burosumab-twza) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, mitigation, treatment, or prevention of a disease.

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(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 Federal Food, Drug, and Cosmetic Act (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 unexpected serious risks of nephrocalcinosis, renal failure, and spinal stenosis (Study 3370-1), breast-fed infant exposure to burosumab and potential attendant adverse events (Study 3370-2), and immunogenicity-related safety outcomes (Study 3370-3).

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.

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

3370-1 A post-approval surveillance program with safety objectives of evaluating the potential association between burosumab treatment and the risks of nephrocalcinosis, renal failure, and spinal stenosis. Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. This program will be incorporated into the X-linked Hypophosphatemia Disease Monitoring Program (study UX023-CL401) that collects information on the disease for up to 10 years. Safety data collection will begin within 90 days of protocol agreement. After marketing starts, submit progress reports to the FDA at six months, one year, and annually thereafter, with an evaluation of the effectiveness of meeting the surveillance program's safety objectives. Collect surveillance data from a minimum of 500 subjects, 200 of whom will be pediatric patients, and approximately two-thirds will be treated with burosumab.

The timetable you submitted on March 30, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2018
Final Protocol Submission:	08/2018
Study Completion:	12/2028
Final Report Submission:	08/2029

3370-2 In XLH patients enrolled in the prospective, longitudinal, surveillance study, perform a lactation sub-study in lactating women who have received therapeutic doses of burosumab using a validated assay to assess concentrations of burosumab in breast milk, the effects on milk composition (to include calcium and phosphorus levels), and the effects on the breastfed infant

The timetable you submitted on March 30, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2018
Final Protocol Submission:	08/2018
Study Completion:	12/2028
Final Report Submission:	08/2029

3370-3 Conduct a study to reanalyze banked immunogenicity serum samples from XLH clinical trials including Study UX023-CL205, Study UX023-CL201, and Study UX023-CL303 to determine the presence of anti-drug antibodies (ADA) using a validated ADA assay with improved drug tolerance. Characterize the neutralizing activity of ADA for samples tested positive for ADA. Evaluate the impact of immunogenicity on pharmacokinetics, efficacy and safety in adult and pediatric

subjects with XLH based on the ADA data generated with the newly validated assay.

The timetable you submitted on March 30, 2018, states that you will conduct this study according to the following schedule:

Study Completion:	12/2018
Final Report Submission:	06/2019

Submit clinical protocol(s) to your IND 076488 with a cross-reference letter to this BLA. 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 601.70 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 601.70 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 601.70. 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.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3370-4 Conduct studies to further characterize the burosumab master cell bank (MCB) and to support the monoclonality of the MCB.

The timetable you submitted on March 30, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2018
Final Report Submission: 06/2020

3370-5 Conduct studies to evaluate effector functions (i.e., antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity) of burosumab. The final Post Marketing Commitment report should be submitted based on the outcome of the studies per 21 CFR 601.12.

The timetable you submitted on March 30, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 12/2018
Final Report Submission: 12/2019

Submit clinical protocols to your IND 076488 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. 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.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80. We also request that you submit all postmarketing reports of nephrocalcinosis, renal failure, and spinal stenosis in tabular form on a quarterly basis in your periodic adverse experience reports. We further request that you submit these reports for a period of 3 years following launch of CRYSVITA (burosumab-twza) in the US.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Samantha Bell, Regulatory Project Manager, at (301) 796-9687.

Sincerely,

{See appended electronic signature page}

Victor Crentsil, MD, MHS
Acting Deputy Director
Office of Drug Evaluation III
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 and this page is the manifestation of the electronic signature.

/s/

VICTOR CRENTSIL
04/17/2018