



NDA 209449/S-005

SUPPLEMENT APPROVAL

Cycle Pharmaceuticals Ltd.
C/O: ICON Clinical Research LLC
Attention: Reiner Elsner, PhD
Director, Regulatory Affairs, International Strategic Regulatory Services
79 T.W. Alexander Dr.
4401 Research Commons, Suite 300, PO Box 14353
Durham, NC 27709

Dear Dr. Elsner:

Please refer to your supplemental new drug application (sNDA) dated and received February 6, 2018, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nityr (nitisinone) tablets.

We acknowledge receipt of your amendment dated July 2, 2020, which constituted a complete response to our December 6, 2018, action letter.

This Prior Approval supplemental new drug application provides for revisions to the Dosage and Administration section of the Prescribing Information (PI) to add a once-daily dosing option for patients 5 years of age and older who have undetectable serum and urine succinylacetone concentrations after a minimum of 4 weeks on a stable dosage of nitisinone, in addition to the currently labeled twice-daily dosing regimen. Additional revisions were also made throughout the PI, including to the Warnings and Precautions and Drug Interactions sections.

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.

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 FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use), with the addition of any labeling

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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 *SPL Standard for Content of Labeling Technical Qs and As*.²

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(I)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 (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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric study for ages less than 5 years for this application because a pediatric study has not been completed in this age group to provide efficacy for approval of the new dosage change.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act (FDCA). This required study is listed below.

- 3926-1 Long-term assessment of PD response and PK of Nityr given under a once-daily dosage regimen in treatment-experienced pediatric patients less than 5 years old with HT-1.

Collect observational data in HT-1 patients to characterize the pharmacodynamic response (urine and blood succinylacetone),

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

pharmacokinetics (plasma nitisinone concentration), tolerability, and safety of Nityr treatment given under a once-daily dosing regimen.

Measurements of succinylacetone (urine and blood) and nitisinone concentration (blood) can follow routine clinical practice. The duration of such study should be at least 6 months to enable characterization of the tolerability and safety of the once-daily dosage regimen and to provide repeated measures of succinylacetone levels and nitisinone concentrations on once-daily dosage regimen over an extended period of time. The patient population should include treatment-experienced pediatric patients less than 5 years of age diagnosed with HT-1 (biochemically, molecularly, or both).

The timetable you submitted on September 2, 2020, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2021

Study Completion: 03/2023

Final Report Submission: 03/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.³

Submit the protocol(s) to your IND 121021, with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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*.⁴

³ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ 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.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

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 CAPT Mimi Phan, Regulatory Project Manager, at (301) 796-5408.

Sincerely,

{See appended electronic signature page}

Rachel Witten, MD
Associate Director, Acting
Division of Rare Diseases and Medical Genetics
Office of Rare Diseases, Pediatrics, Urologic and
Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Instructions for Use

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RACHEL WITTEN
09/02/2020 06:59:29 PM