NDA 218980

NDA APPROVAL

Eton Pharmaceuticals, Inc.
Attention: Adam Christensen, MBA, DPT
Senior Director, Regulatory Affairs & Project Management
21925 W. Field Parkway, Suite 235
Deer Park, IL 60010A

Dear Adam Christensen:

Please refer to your new drug application (NDA) received April 29, 2024, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Khindivi (hydrocortisone) oral solution.

We acknowledge receipt of your major amendment dated December 5, 2024, which extended the goal date by three months.

This NDA provides for the use of Khindivi (hydrocortisone) oral solution as replacement therapy in pediatric patients 5 years of age and older with adrenocortical insufficiency.

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 with minor editorial revisions listed below and reflected in the enclosed labeling.

- Abbreviations were defined at first use.
- Changes were made throughout the prescribing information to correct spacing.

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 (Prescribing Information and Medication Guide) as well as annual reportable changes not included in

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed container labeling that is identical to the enclosed container labeling submitted on May 22, 2025, as soon as it is available, but no more than 30 days after it is printed. Please submit this labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218980**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Khindivi (hydrocortisone) oral solution shall be 18 months from the date of manufacture when stored at Store at 2°C to 25°C (36°F to 77°F).

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.

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

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.*[3]

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Khindivi (hydrocortisone) oral solution you submit all serious and non-serious domestic and foreign cases of metabolic acidosis, acute kidney injury, central nervous system (CNS) toxicity, hypoglycemia, and hyperosmolarity as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the 5th year following the initial U.S. approval date.

We also request that you provide a narrative summary including analysis of metabolic acidosis, acute kidney injury, central nervous system (CNS) toxicity, hypoglycemia, and hyperosmolarity as part of your required periodic safety reports (e.g., periodic adverse drug experience report (PADER)/periodic adverse experience report (PAER) required under 21 CFR 314.80(c)(2)), through the 5th year following initial U.S. approval date.

Your analysis should include interval and cumulative data relative to the date of approval of Khindivi (hydrocortisone) oral solution. Your analysis should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, laboratory values at time of the event, confounders, underlying risk factors, treatment given for the event, outcome, and dechallenge/rechallenge.

The goal of this enhanced pharmacovigilance (EPV) plan is to evaluate for possible systemic toxicities of specific inactive ingredients included in your hydrocortisone oral solution formulation.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third

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

parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[6].

If you have any questions, call Meghna M. Jairath, Pharm.D., Senior Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, MD
Director
Division of General Endocrinology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[6] https://www.uspnf.com/

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/

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