NDA 203826/S-015
NDA 203826/S-017

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS AND COMMITMENT

Hikma Pharmaceuticals USA, Inc.
2 Esterbrook Lane
Cherry Hill, NJ 08003

Attention: Casey Layton
Associate Director, Regulatory Affairs

Dear Mr. Layton:

Please refer to your supplemental new drug application (sNDA) S-015 dated and received December 11, 2020, and amendments, and sNDA S-017 dated and received December 29, 2022, and amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Phenylephrine hydrochloride injection.

We acknowledge receipt of your amendment dated November 8, 2022, for S-015, which constituted a complete response to our April 9, 2021, action letter.

The Prior Approval Supplement (PAS), S-015, proposes the introduction of a ready to use (RTU) formulation of 100 mcg/mL, packaged as 5 mL and 10 mL vials for Immphentiv (phenylephrine hydrochloride) injection. This proposal for the RTU formulation is intended to satisfy postmarketing commitment (PMC) 1991-2.

The PAS, S-017, provides for updates to the Prescribing Information (PI), specifically to the sections **8.1 Pregnancy** and **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**, based on results from studies conducted under postmarketing requirements (PMRs) 2873-1 through -4. The PI was also updated to comply with Pregnancy Labeling and Lactation Rule (PLLR).

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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) 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 *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(l)(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).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 203826/S-015**." Approval of this submission by FDA is not required before the labeling is used.

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

FULFILLMENT OF POSTMARKETING REQUIREMENTS AND COMMITMENT

We have received your submissions dated September 18, November 10, and December 9, 2015, containing the final study reports for the following PMRs listed in the February 13, 2015, postapproval postmarketing requirement letter:

2873-1 Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride completed via modern reproductive and developmental toxicology studies, as outlined in the guidance for industry, *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)*.

2873-2 Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride completed via modern reproductive and developmental toxicology studies, as outlined in the guidance for industry, *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)*.

2873-3 Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride completed via modern reproductive and developmental toxicology studies, as outlined in the guidance for industry, *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)*.

2873-4 Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride completed via modern reproductive and developmental toxicology studies, as outlined in the guidance for industry, *Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility S5(R2)*.

We have received your submission for PAS S-015 dated November 8, 2022, and amendments, reporting on the following PMC listed in the December 20, 2012, approval letter:

1991-2 The package insert provides dosing for intravenous bolus ranging from 40 mcg to 250 mcg. Currently, only a single concentration of 10 mg/mL is approved. In order to achieve doses as small as 40 mcg to 250 mcg, one or more dilutions would need to be performed by a pharmacist or technician, which introduces opportunity for calculation and compounding confusion that can lead to dosing errors. For this reason, we request that you develop an appropriate

ready-to-use concentration and packaging configuration to administer the approved intravenous bolus doses. A ready-to-use concentration and packaging configuration will help mitigate the risks of calculation and compounding errors as well as unsafe sterile technique and injection practices. In order to guide the development of an appropriate ready-to-use product for intravenous bolus administration, an appropriate methodology such as a risk assessment, utilizing a recognized risk assessment tool (e.g., Failure Mode and Effects Analysis), should be conducted by a multidisciplinary team. Based on your study results, we request you submit a prior approval supplement to support the approval of a ready-to-use formulation and concentration of phenylephrine hydrochloride appropriate for intravenous bolus administration.

We have reviewed your submissions and conclude that the above requirements and commitment were fulfilled.

We remind you that there is a postmarketing requirement listed in the December 20, 2012, approval letter that is still open.

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]

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

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, email the Regulatory Project Manager, Rachel Jang, PharmD, at Rachel.Jang@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURES:

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

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/

RIGOBERTO A ROCA
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