CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208289Orig1s000

Trade Name:	AKOVAZ injection, 50 mg/mL
Generic Name:	ephedrine sulfate
Sponsor:	Flamel Ireland Limited.
Approval Date:	April 29, 2016
Indication:	For the treatment of clinically important hypotension occurring in the setting of anesthesia.

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208289Orig1s000

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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

NDA 208289

NDA APPROVAL

Flamel Ireland Limited
c/o The Weinberg Group, Inc.
1129 Twentieth St. NW, Suite 600
Washington, DC 20036

Attention: Marla Scarola, MS
Senior Consultant

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated and received June 30, 2015, and your amendments, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for AKOVAZ (ephedrine sulfate) injection, 50 mg/mL.

This new drug application provides for the use of AKOVAZ (ephedrine sulfate) injection for the treatment of clinically important hypotension occurring in the setting of anesthesia.

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 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. 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*, available 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 immediate container labels that are identical to the enclosed carton and immediate container labels submitted on April 12, 2016, 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 Carton and Container Labels for approved NDA 208289**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) 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.

We are waiving the pediatric study requirement for ages 0 to <12 years because necessary studies are impossible or highly impracticable. This is because studying subjects eleven years and under would be difficult because most patients in that age group will not require treatment with ephedrine for hypotension in the setting of anesthesia.

We are deferring submission of your pediatric study for ages 12 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by Section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and Section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3062-1 Conduct a juvenile toxicity study in rats to support treatment of children and adolescents with AKOVAZ (ephedrine sulfate) injection by IV administration.

Final Protocol Submission:	05/2016
Study Completion:	05/2017
Final Report Submission:	11/2017

3062-2 Conduct a single open-label study to evaluate the safety and pharmacodynamics/ pharmacokinetics of intravenous ephedrine dosed on a mg/kg basis with provisions for up-titration (dose or frequency) as clinically indicated in patents 12-16 years.

Final Protocol Submission:	05/2017
Study Completion:	05/2020
Final Report Submission:	05/2021

Submit the protocol(s) to your **IND 116266** with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies 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 these studies. 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.

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 assess reproductive toxicology, embryonic development toxicology, pre- and post-natal development toxicology, and genotoxic potential in appropriate animal species.

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 also required to conduct the following:

3062-3 Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.

The timetable you submitted on March 28, 2016 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2016
Study Completion:	08/2017
Final Report Submission:	05/2018

3062-4 Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.

The timetable you submitted on March 28, 2016 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2016
Study Completion:	05/2017
Final Report Submission:	03/2018

3062-5 Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.

The timetable you submitted on March 28, 2016 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2016
Study Completion:	08/2017
Final Report Submission:	06/2018

3062-6 Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

The timetable you submitted on March 28, 2016 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2016
Study Completion:	07/2018
Final Report Submission:	07/2019

3062-7 Conduct an in vivo micronucleus genotoxicity assay with ephedrine sulfate.

The timetable you submitted on March 28, 2016 states that you will conduct this study according to the following schedule:

Study Completion:	07/2016
Final Report Submission:	01/2017

Submit the protocol(s) to your IND116266 with a cross-reference letter to this NDA. Submit all final report(s) 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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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).

As required under 21 CFR 314.81(b)(3)(i), 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.

EXPIRATION DATING

The drug product is granted an expiry of 24 months, when stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

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 Ayanna Augustus, PhD, RAC, Sr. Regulatory Health Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure(s):
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/

RIGOBERTO A ROCA
04/29/2016