ANDA 213947

ANDA APPROVAL/TENTATIVE APPROVAL

Nexus Pharmaceuticals Inc.
400 Knightsbridge Parkway
Lincolnshire, IL 60069
Attention: Jagdeep Kaur
Regulatory Affairs Lead

Dear Jagdeep Kaur:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on August 29, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL) and 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the complete response letter issued by this office on August 23, 2021, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. We have determined your Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL) and 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Aggrastat Injection, 5 mg/100 mL (50 mcg/mL) and 12.5 mg/250 mL (50 mcg/mL), of Medicure International Inc. (Medicure International).

However, we are unable to grant final approval to your Tirofiban Hydrochloride Injection, 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers, at this time because of the exclusivity issue noted below. Therefore, your ANDA is **approved** insofar as it pertains to Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL), Single-Dose Containers. Your Tirofiban Hydrochloride Injection, 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers, is **tentatively approved**. This determination is based upon information available to the Agency at this time (e.g., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacturing and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention.

The RLD upon which you have based your ANDA, Aggrastat Injection, 5 mg/100 mL

(50 mcg/mL) and 12.5 mg/250 mL (50 mcg/mL), of Medicure International, is subject to a period of patent protection. The following patent and expiration date is currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,770,660 (the '660 patent)	May 1, 2023

Your ANDA contains a paragraph IV certification to the '660 patent under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL) and 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers, under this ANDA. You have notified the Agency that Nexus Pharmaceuticals Inc. (Nexus Pharmaceuticals) complied with the requirements of section 505(j)(2)(B) of the FD&C Act. Litigation was initiated within the statutory 45-day period against Nexus Pharmaceuticals for infringement of the '660 patent in the United States District Court for the Northern District of Illinois Eastern Division [Medicure International, Inc. v. Nexus Pharmaceuticals, Inc., Civil Action No. 19-07979]. You have also notified the Agency that the court entered a consent judgment, pursuant to the parties' agreement "to settle all claims arising out of the pleadings," which states "nothing herein shall prohibit or restrict the Food and Drug Administration from reviewing or approving Nexus's ANDA No. 213947."[1]

However, we are unable to grant final approval to with respect to the 12.5 mg/250 mL (50 mcg/mL) strength product at this time. Prior to the submission of your ANDA, another applicant or applicants submitted a substantially complete ANDA providing for Tirofiban Hydrochloride Injection, 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers, and containing a paragraph IV certification. Your ANDA for this strength will be eligible for final approval on the date that is 180 days after the commercial marketing date identified in section 505(j)(5)(B)(iv) of the FD&C Act.

Upon the foregoing, your ANDA is **approved** insofar as it pertains to the 5 mg/100 mL (50 mcg/mL) product. Your 12.5 mg/250 mL (50 mcg/mL) product, is **tentatively approved**.

I. Approval of Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL), Single-Dose Containers

With respect to 180-day generic drug exclusivity, we note that Nexus Pharmaceuticals was the first ANDA applicant for Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL), Single-Dose Containers, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Nexus Pharmaceuticals may be eligible for 180 days of generic drug exclusivity for Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL), Single-Dose Containers. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the

commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Nexus Pharmaceuticals failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of Nexus Pharmaceuticals' eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Nexus Pharmaceuticals begins commercial marketing of Tirofiban Hydrochloride Injection, 5 mg/100 mL (50 mcg/mL), Single-Dose Containers, or (b) at any time prior to the expiration of the '660 patent if Nexus Pharmaceuticals has not begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts; therefore, we remind you that you must comply with the postmarketing safety reporting requirements for an approved combination product (21 CFR Part 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. 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 (PI), 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

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: https://www.fda.gov/media/128163/download)

You must also submit final promotional materials and package insert(s), 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 https://www.fda.gov/media/73013/download. Information and Instructions for completing the form can be found at https://www.fda.gov/media/132152/download. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/opdp-ectd.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of

misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). 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 https://www.fda.gov/media/71211/download. The SPL will be accessible via publicly available labeling repositories.

We remind you that you must continually monitor available labeling resources such as DRUGS@FDA for changes to your reference listed drug's labels and labeling and make any necessary revisions to your labels and labeling. More information on post-approval labeling changes may be found in the guidance for industry titled "Changes to an Approved NDA or ANDA" at https://www.fda.gov/media/71846/download.

II. Tentative Approval of Tirofiban Hydrochloride Injection, 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers

Our decision to tentatively approve your Tirofiban Hydrochloride Injection, 12.5 mg/250 mL (50 mcg/mL), Single-Dose Containers, is based upon information currently available to the agency (i.e., date in your ANDA and the status of current good manufacturing practice (cGMP) of the facilities used in the manufacture and testing of the drug product). This decision is subject to change on the basis of new information that may come to our attention.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

RESUBMISSION

To request final approval, please submit an amendment titled "FINAL APPROVAL REQUESTED" with enough time to permit FDA review prior to the date you believe that your ANDA will be eligible for final approval. A request for final approval that contains no new data, information, or other changes to the ANDA generally requires a period of 3 months for Agency review. Accordingly, such a request for final approval should be submitted no later than 3 months prior to the date on which you seek approval. A request for final approval that contains substantive changes to this ANDA or changes in the status of the manufacturing and testing facilities' compliance with cGMPs will be classified and reviewed according to OGD policy in effect at the time of receipt. Applicants should review available agency guidance for industry related to amendments under the generic drug user fee program to determine the duration of Agency review needed to review the changes submitted. As part of this consideration, applicants should monitor any changes to the RLD that occur after tentative approval, including changes in labeling, patent or exclusivity information, or marketing status. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

The amendment requesting final approval should provide the legal/regulatory basis for your request for final approval and should include a copy of a court decision, settlement or licensing agreement, or other information described in 21 CFR 314.107, as appropriate. It should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a "MINOR/MAJOR AMENDMENT TO ORIGINAL #2 – FINAL APPROVAL REQUESTED."

In addition to the amendment requested above, the Agency may request, at any time prior to the date of final approval, that you submit an additional amendment containing information as specified by the Agency. Failure to submit either or, if requested, both types of amendments described above may result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 301 of the FD&C Act. Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505(j) of the FD&C Act, and will not be listed in the Orange Book.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and

payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms or active pharmaceutical ingredients manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Adil Merchant, Regulatory Project Manager, at (240) 402 - 3505.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

---

[1] Medicure International, Inc. v. Nexus Pharmaceuticals, Inc., Civil Action No. 19-07979, DKt. 87 (N.D. Ill. Nov. 20, 2020).

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

John Ibrahim

Digitally signed by John Ibrahim
Date: 2/07/2023 10:11:14AM
GUID: 542af06d0124375c12e8c1d9fc86e87c