DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203794/S-005, S-006

SUPPLEMENT APPROVAL

Depo NF SUB, LLC
C/O Assertio Therapeutics, Inc.
100 S. Saunders Road, Suite300
Lake Forest, IL 60045

Attention: Gregg A. Pratt, PhD
Vice President, Regulatory Affairs

Dear Dr. Pratt:

Please refer to the following Supplemental New Drug Applications (sNDAs) dated and received April 25, 2018, and June 12, 2018, and your amendments, submitted under section 505(b)of the Federal Food, Drug, and Cosmetic Act (FDCA) for NUCYNTA (tapentadol) Oral Solution.

We also refer to our letter dated September 28, 2017, notifying you that under section 505-1 of the FDCA, we have determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for certain immediate-release (IR) opioid analgesic products, including NUCYNTA, to ensure the benefits of the drugs outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Finally, we refer to our letter dated June 1, 2018, notifying you, under section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for NUCYNTA. This information pertains to the addition of the REMS program details to product labeling for the class of opioid analgesics intended for use in the outpatient setting.

Supplement S-005 provides for the REMS required under section 505-1 of the FDCA, consistent with our September 28, 2017, letter.

Supplement S-006 provides for revisions to the labeling for NUCYNTA consistent with our June 1, 2018, Safety Labeling Change Notification letter.

APPROVAL & LABELING

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

Note that your approved Medication Guide is now part of the REMS approved in supplement S-006.

WAIVER OF HIGHLIGHTS SECTION

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, 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 titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) post-approval if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of an approved drug outweigh the risks.

The details of the REMS requirements for certain immediate-release (IR) opioid analgesics intended for use in the outpatient setting were outlined in our REMS Notification letter dated September 28, 2017, informing you that a REMS is necessary to mitigate the risks of adverse

outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse of these drugs.

Your proposed REMS, submitted to Drug Master File (DMF) (b) (4) on March 26, 2018, amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

This REMS uses a shared system for the elements to assure safe use and the REMS assessments. This shared system, now known as the Opioid Analgesics REMS Program, includes the products listed on the FDA REMS website, available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Other products may be added in the future if additional NDAs or ANDAs are approved.

The REMS assessment plan must include, but is not limited to, the following:

1. REMS Outreach and Communication

    a. For each healthcare provider (e.g., prescriber, pharmacist) to be sent information regarding REMS-compliant accredited continuing education (CE), provide the date when the letters were sent; the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable

    b. For each professional society, association, and licensing board to be sent information regarding REMS-compliant accredited CE, provide the number of letters electronically sent, received, undeliverable, and opened; and the number of letters mailed and undeliverable

2. REMS Implementation and Operations

    a. Status of grants

        i. The status of the request for proposals for grants for REMS-compliant accredited CE including:

            1. Request for Application (RFA) issued: date and number of applications submitted in response to each RFA
            2. RFAs awarded: date, number, and name of grantee
            3. Date/timeframe next RFA to be issued

        ii. The status of the requests for proposals for any grants to CE Providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct evaluations of health care providers who have taken REMS-compliant accredited CE funded under this REMS.

b. Grant review committee

i. Individuals from the REMS Program Companies (RPC) reviewing grants will include the following clinical licensures: pharmacists, nurses, physicians. Additionally there will be involvement by individuals with regulatory and pharmacovigilance experience. The job title, licensure and professional degree of individuals will be provided for each grant review cycle.

ii. Include any external members (non RPC) involved in the grant review, including those from the broad-based CE community. Provide the job title, licensure and professional degree of the individual for each grant review cycle.

c. For CE programs awarded during the assessment period:

i. Description of each grantee and projected number of completers

ii. For the first assessment, the date the first program based upon the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint"), became available

iii. Description of CE program:

1. Level of outcome the activity[1] is designed to impact
2. CE format (live, webinar, etc.)
3. Duration of activity for live or webinar activities
4. Average duration to complete for internet/enduring activities
5. Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)[2,3]

iv. All reports submitted to the RPC by CE grantees during the assessment period.

[1] Stevenson R, Moore DE. Ascent to the Summit of the CME Pyramid. *JAMA* 2018;319(6):543-544
[2] Cervero R, Gaines J. The Impact of CME on Physician Performance and Patient Health Outcomes: An Updated Synthesis of Systematic Reviews *J Contin Educ Health Prof* 2015;35(2):131–138
[3] Agency for Research Health and Quality. (2007). *Effectiveness of Continuing Medical Education.* Retrieved May 9, 2018, from https://archive.ahrq.gov/downloads/pub/evidence/pdf/cme/cme.pdf

d. Number of participants and completers during the assessment period; provide description of learners by standard learner category data[4].

e. Independent Audit: The results of independent audits of the CE. Audits must be conducted on a random sample of at least 10% of the REMS-compliant accredited CE funded under the Opioid Analgesic REMS and must include/evaluate:

   i. a description of the organization(s) conducting the audit(s)

   ii. whether the content of the REMS-compliant accredited CE covers all elements of the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint") approved as part of the REMS;

   iii. whether the integrated or post-course knowledge assessment measures knowledge of all sections of the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain ("FDA Blueprint"); and

   iv. whether the REMS-compliant accredited CE was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies

f. Concurrent Educational interventions

   i. For the year prior to the assessment period through the assessment period, provide an evaluation of the overall pain/opioid CE landscape including but not limited to:

      1. States requiring prescribers, pharmacists, or nurses to complete opioid or pain management continuing education for licensing/renewal of licensing:

         a. enumeration of these states and their requirements. for continuing education on either pain or safe opioid use,
         b. estimates of annual licensed prescribers in those states
         c. which, if any, opioid analgesic or ER/LA Opioid Analgesic REMS CE were permissible in which states, for prescribers to meet requirements

[4] Standard Continuing Education (CE) learner data to be captured by all CE Providers for Opioid Analgesic REMS includes geographic location (state of primary practice), DEA prescriber status (individual registration or institutional authorization), profession, practice area, and length of time in practice.

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