NDA 202788/S-021

SUPPLEMENT APPROVAL

BTcP Pharma, LLC
c/o West Therapeutics Development, LLC
1033 Skokie Boulevard
Suite 620
Northbrook, IL 60062

Attention: Mahlaqa Patel
Vice President, Regulatory Affairs and Quality Assurance

Dear Ms. Patel:

Please refer to your supplemental new drug application (sNDA) dated and received July 25, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Subsys (fentanyl sublingual spray).

We also refer to our REMS MODIFICATION NOTIFICATION letter, dated March 27, 2019, informing you that the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) must be modified to ensure that the benefits of the drug outweigh its risks. This determination was based on information contained in the REMS assessment reports suggesting many patients prescribed a TIRF medicine may not have been opioid-tolerant when they received a new prescription for a TIRF medicine, as well as recommendations from the August 3, 2018, joint meeting of the Drug Safety and Risk Management, and the Anesthetic and Analgesic Drug Products advisory committees.

This supplemental new drug application proposes REMS modifications required under section 505-1 of the FDCA, consistent with those outlined in the March 27, 2019, letter.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for TIRF products, of which Subsys is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on September 7, 2017. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Subsys outweigh its risks, we determined that you were required to make the REMS modifications outlined in our REMS Modification letter dated March 27, 2019.

Your proposed modified REMS, submitted to Drug Master File (DMF) [redacted] (b) (4) on December 7, 2020, and appended to this letter, is approved.

The modifications to the approved REMS must be fully implemented within 120 calendar days of the date of this letter.

The REMS uses a shared system for the elements to assure safe use, an implementation system, and a timeable for assessments of the REMS. This shared system, known as the TIRF REMS program, currently includes products listed on the FDA REMS, website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60

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

The timetable for submission of assessments of the REMS must be revised to 12 months from the date of the approval of this REMS modification (December 23, 2020) and annually thereafter.

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

Program Outreach and Communication

1. **Communication (1-year assessment post-modification approval only)**
    a. Sources of the distribution list(s) for the Dear Healthcare Provider Letter to healthcare providers likely to prescribe TIRF medicines
    b. Number of targeted healthcare providers who can prescribe
    c. The number of Dear Healthcare Provider letters sent by date(s), medical specialty, and method of distribution.
        i. The number and percentage of emailed letters successfully delivered, opened, and unopened.
        ii. The number and percentage of mailed letters successfully delivered or returned as undeliverable.
        iii. The number and percentage of faxed letters successfully delivered or returned as undeliverable.
    d. The number of professional societies sent the Dear Healthcare Provider Letter by date(s) and method of distribution. In addition, include which

professional societies distributed the Dear Healthcare Provider Letter or the content of the letter to their respective members.

e. Sources of the distribution list(s) for the Dear Pharmacy Letter to inpatient and outpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines

f. The number of pharmacies sent the Dear Pharmacy Letter date(s), type of pharmacy, and by method of distribution

   i. The number and percentage of emailed letters successfully delivered, opened, and unopened.

   ii. The number and percentage of mailed letters successfully delivered or returned as undeliverable.

   iii. The number and percentage of faxed letters successfully delivered or returned as undeliverable.

g. The number of professional societies sent the Dear Pharmacy by dates(s) and by method of distribution. In addition, include which professional societies distributed the Dear Pharmacy Letter or the content of the letter to their respective members.

h. Date(s) and name(s) of Professional meetings where TIRF REMS materials were disseminated or displayed.

Program Implementation and Operations

2. REMS Program Implementation (1-year assessment post-modification approval only)

a. Date when the modified TIRF REMS website went live and was fully operational

b. Date when healthcare providers who can prescribe could become certified in the modified REMS

c. Date when pharmacies could become certified in the modified REMS

d. Date when patients could be enrolled in the modified REMS

e. Date when distributors/wholesalers could be registered in the modified REMS

f. Date when the REMS Call Center for the modified TIRF REMS program went live and was fully operational

3. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)

a. Patients (number and percent)

   i. For the one-year assessment report only:

1) Patients previously enrolled in the TIRF REMS Access program (i.e. enrolled prior to implementation of the modified REMS)

2) Patients re-enrolled (i.e., previously enrolled in the TIRF REMS Access program and transitioned to new program)

ii. Newly enrolled into the new program

iii. Active patients (i.e., received at least one dispensation of a TIRF product during the reporting period)

iv. For metrics 3.a.i. through iii, stratify by demographics (age, gender, ethnicity, race, and geographic region [as defined by US Census]), around-the-clock opioid(s) (moiety, daily dose, and duration of greater than seven days), medical reasons related to pain (cancer or non-cancer pain), TIRF medicine use in the prior six months, and concomitant benzodiazepines and other central nervous system (CNS) depressants

v. A summary of the methods of patient enrollment (e.g., online, fax)

vi. Number of patients who were unable to become enrolled, accompanied by a summary of the reasons they were unable to be enrolled

b. Healthcare Providers who can Prescribe (number and percent)

i. For the one-year assessment report only:

1) Healthcare providers who can prescribe who previously certified in the TIRF REMS Access program (i.e. enrolled prior to implementation of the modified REMS)

2) Healthcare providers who can prescribe who re-certified (i.e., previously certified in the TIRF REMS Access program and transitioned to new program)

ii. Healthcare providers who can prescribe who are newly certified

iii. Active prescribers (i.e. who have prescribed a TIRF at least once during the reporting period)

iv. For metrics 3.a.i. through iii, stratify by credentials, (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other), medical specialty (e.g., Pain Medicine, Oncology, Internal Medicine, Other, etc.) and geographic region [as defined by US Census])

v. A summary of the methods of healthcare provider certification (e.g., online, fax)

vi. Number of healthcare providers who can prescribe who were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

vii. For the 2-year assessment report, conduct an outreach to healthcare providers that did not re-certify in the REMS to ascertain the reasons why they did not re-certify. Submit the methodology protocol 120 days prior to initiating the outreach.

c. Pharmacies (number and percent)

i. For the one-year assessment report only:

1) Pharmacies previously certified in the TIRF REMS Access program (i.e. enrolled prior to implementation of the modified REMS)

2) Pharmacies re-certified (i.e., previously certified in the TIRF REMS Access program and transitioned to new program)

ii. Pharmacies newly certified into the new program

iii. Active pharmacies (i.e., have dispensed a TIRF at least once during the reporting period)

iv. For metrics 3.a.i. through iii, stratify by pharmacy type (inpatient, chain, independent [retail, mail, institutional], or closed system [provide identity of closed system entities]) and by geographic region [as defined by US Census])

v. A summary of the methods of pharmacy certification (e.g., online, fax)

vi. Number of pharmacies that were unable to become certified, accompanied by a summary of the reasons they were unable to be certified

vii. For the 2-year REMS assessment report, conduct an outreach to pharmacies that did not re-certify in the REMS to ascertain the reasons why they did not re-certify. Submit the methodology protocol 120 days prior to initiating the outreach.

d. Wholesalers-Distributors (number)

i. Previously enrolled (i.e. enrolled prior to implementation of the modified REMS)

ii. Re-enrolled (i.e., enrolled prior to implementation of the modified REMS and transitioned to new program)

iii. Newly enrolled into the new program

iv. Active (i.e., distributed a TIRF product during the reporting period)

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