NDA 020732/S-023
NDA 020733/S-027
NDA 022410/S-039

SUPPLEMENT APPROVAL

Indivior Inc.
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Attention Rachel Capone
Manager, Regulatory Affairs

Dear Ms. Capone:

Please refer to your supplemental new drug applications (sNDAs) dated and received June 18, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SUBUTEX (buprenorphine) sublingual tablets (NDA 020732/S-023), SUBOXONE (buprenorphine and naloxone) sublingual tablets (NDA 020733/S-027), and SUBOXONE (buprenorphine and naloxone) sublingual film (NDA 022410/S-039).

These Prior Approval sNDAs proposed modifications to the approved risk evaluation and mitigation strategy (REMS) for SUBUTEX sublingual tablets, SUBOXONE sublingual tablets, and SUBOXONE sublingual film.

We have completed our review of these supplemental applications, as amended and they are approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for SUBOXONE (buprenorphine and naloxone) sublingual film was originally approved on August 30, 2010. The REMS for SUBUTEX (buprenorphine) sublingual tablets and the REMS for SUBOXONE (buprenorphine and naloxone) sublingual tablets were originally approved on December 22, 2011. The most recent modification was approved on October 26, 2018. 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. Your proposed modification to the REMS consists of modifying the REMS Document to the new format in accordance with the October 2017 *Draft Guidance: Format and Content of a REMS Document Guidance for Industry*. In addition to the modification described above, changes to the supporting document and assessment plan were also included in the submission.

Your proposed modified REMS, submitted on June 18, 2019, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS remains the same as that approved on August 31, 2012.

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

1. An evaluation of patients' understanding of the serious risks of SUBOXONE sublingual film.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements for the Medication Guide, and corrective actions taken to address noncompliance.
4. A survey of prescribers' understanding of the serious risks of SUBOXONE sublingual film and the:

    a) need for appropriate patient monitoring
    b) need for patient adherence to conditions of safe use
    c) need to check that patients are using the drug appropriately and making adequate progress towards treatment goals
    d) need to make sure prescriptions are provided in amounts commensurate with patient stability
    e) importance of psychosocial support services
    f) The results of the prescriber survey will be stratified by stage of treatment (i.e., those initiating treatment [month 1] vs. established patients [month 2+]). The stratification will be applied to the analysis of the 12 possible steps prescribers use to reduce inappropriate use or diversion in their practices.
    g) Specific measures that will be taken to increase awareness if surveys of prescribers indicate that prescriber awareness is not adequate

5. A survey of pharmacists' understanding of the serious risks of SUBOXONE sublingual film and the need for patient adherence to conditions of safe use.
6. An analysis to evaluate SUBOXONE sublingual film utilization patterns including frequency of office visits, amount dispensed in prescriptions to new patients and other indicators of adherence to practices important to safe use. The analysis of utilization patterns (frequency of office visits per patient, amount of medication dispensed in prescriptions, etc.) will be stratified by stage of treatment (i.e., new [month 1] vs. established patients [month 2+]).
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose and addiction and any intervention taken resulting from signals of abuse, misuse, overdose and addiction. Surveillance data are to be drawn from multiple sources and are to place a special focus on pediatric exposures.

The SUBOXONE/SUBUTEX REMS will undergo periodic review to evaluate the effectiveness of the strategies and tools in accomplishing the goals and objectives of the REMS. Appropriate revisions to the REMS will be proposed based on the evaluations. Based on the monitoring and evaluation of these elements to assure safe use, Indivior will take reasonable steps to improve implementation of these elements, such as suggesting changes to the prescriber or pharmacist brochures or mailing an additional letter to healthcare providers (HCPs) based on which specific risks messages seem to have low understanding.

Medication Guide Distribution Audits

Indivior will periodically assess the distribution and dispensing of the SUBOXONE sublingual film, Authorized Generic of SUBOXONE sublingual film, SUBOXONE sublingual tablet, and SUBUTEX sublingual tablet Medication Guide in accordance with 21 CFR 208.24. Periodic audits of the packaging facility will be conducted to monitor compliance with inclusion of the Medication Guide within the product packaging. The Knowledge, Attitudes, and Behavior (KAB) surveys described in Section 4.2.12 below will also assess this by querying patients about whether they received a Medication Guide when their prescription for SUBOXONE Sublingual film and Authorized Generic of SUBOXONE sublingual film was dispensed. Failures to adhere to Medication Guide distribution and dispensing requirements will be identified and appropriate actions will be implemented to address non-compliance. This information will be provided in the regular assessment reports for the REMS.

Surveillance and Epidemiology

Epidemiology and surveillance data reporting reflects emails Indivior received from the FDA on 14 JAN 2019, 19 MAR 2019, 24 SEP 2019, and 22 NOV 2019, and referenced in the REMS Assessment Acknowledgement Letter received on 02 AUG 2019.

Data Sources

As part of the REMS program, Indivior will conduct analysis and summary of surveillance/epidemiologic data on abuse, misuse, overdose (mortality), and addiction.

These data sources include:

- Researched Abused, Diversion and Addiction-Related Surveillance (RADARS®) System:
  - Poison Control Centers
  - Treatment Centers - Survey of Key Informants' Patients (SKIP)/Opioid Treatment Program (OTP)

- Drug Diversion

- National Forensic Laboratory Information System (NFLIS)
- National Survey of Drug Use (NSDUH)
- National Survey of Substance Abuse Treatment Services (N-SSATS)
- Treatment Episodes Dataset (TEDS)
- Medical Examiners Data
- Assessment of Adherence in Medical Records/Administrative Claims - Feasibility Assessment
- Literature Review

Researched Abuse, Diversion and Addiction Related Surveillance (RADARS®) System

The RADARS System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The RADARS System is comprised of multiple independent surveillance programs which gather data from several unique populations along the spectrum of the drug abuse pathway.[i]

RADARS System Poison Center

The RADARS System Poison Center Program obtains data from participating poison centers, which manage exposure calls from individuals within the general population and from HCPs who are seeking advice regarding potential toxic exposures, including exposures to prescription opioids.[ii] Poison Center Program data collected through the RADARS System provide an estimate of change in intentional abuse, misuse, and deaths associated with these drugs. The Poison Center Program collects data from 50 of the 55 regional US poison centers in 48 states.

Objective

- To examine trends in buprenorphine and other opioid exposures reported to US Poison Centers.

Outcomes

- Intentional abuse exposures
- Intentional misuse exposures
- Pediatric (ages 0-5 years) unintentional general exposures
- Major medical outcome, hospitalization, or death

Measures

- Rate per population
- Utilization based rate (e.g., dosing unit dispensed)
- Proportion of SUBOXONE intentional cases (i.e., intentional abuse, intentional misuse, suspected suicide, intentional unknown) that also involved benzodiazepines
- Number of unspecified abuse cases for buprenorphine

Buprenorphine Categorizations

- Any buprenorphine (Active Pharmaceutical Ingredient [API])
- All single ingredient tablets
- All combination tablets
- All combination film products
- SUBOXONE sublingual film
- Authorized Generic of SUBOXONE sublingual film
- Suboxone sublingual tablets
- Subutex sublingual tablets

Note: It is not possible to differentiate Authorized Generic of SUBOXONE sublingual film in all RADARS Systems; this category will be included when feasible.

Comparators (API)

- Hydrocodone
- Methadone
- Oxycodone

Analysis

- Quarterly and annual population rates and utilization-based rates will be calculated. Results will be presented graphically with modeled trend lines and 95% confidence intervals going back to 2011; tabular data for case counts and rates will also be provided. No formal statistical comparisons will be conducted. For all tables and figures, the total number of individuals for each data point will be included where applicable. Additionally, case narratives will be provided for all fatal exposure cases involving SUBOXONE in the RADARS Poison Center Program. As appropriate, for utilization-based analyses of methadone, provide a sensitivity analysis that accounts for methadone's unique distribution mechanism.

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