December 26, 2024

Dear Colleague:

The United States Food and Drug Administration (FDA) is providing additional information on our recent recommendation that applicants of buprenorphine-containing transmucosal products for the treatment of opioid use disorders, also referred to as BTODs, revise the labeling for their products.

Buprenorphine is a safe and effective medication for the treatment of opioid use disorder (OUD) that has been shown to sustain recovery, prevent or reduce opioid overdose, improve patient survival, and allow patients the ability to live a self-directed life.

On December 26, 2024, we issued a Federal Register notice titled, *Modifications to Labeling of Buprenorphine-Containing Transmucosal Products for the Treatment of Opioid Dependence* to encourage the submission of supplemental new drug applications to modify the labeling statements for BTODs. We issued this notice because we have heard from interested parties (e.g., health care practitioners, patients, prescribers, professional societies) that there is a perception by some that labeling for BTODs includes a maximum dose for maintenance treatment when, in fact, the labeling does not specify a maximum dose. We also received similar feedback through several meetings in which FDA participated, including a two-day public meeting with the Reagan-Udall Foundation for the FDA in May 2023 and two listening sessions led by the Substance Abuse and Mental Health Services Administration (SAMHSA) in November and December 2023. For this reason, FDA issued this notice to recommend revisions to BTOD labeling to avoid misinterpretation of dosing information.

Why is FDA encouraging revisions to BTOD labeling?

It is our understanding that certain statements in the current BTOD labeling may be the source of confusion for health care professionals (HCPs), patients, and other interested parties. For example, the language in the current BTOD labeling may be read or misinterpreted as specifying a maximum daily dosage. We are aware that, as a consequence, some insurers may have limited coverage for higher daily dosages. In particular, the current labeling recommends a "target" dose equivalent to 16 mg per day; however, this is not a maximum dose. *The labeling for these products recommends that the dosage should be progressively adjusted in increments/decrements to a level that holds the patient in treatment and suppresses opioid withdrawal. The labeling does not include any maximum dose*, but rather states that patients can have their dose increased to a dosage level that meets their therapeutic need.

The inclusion of a "target dose" is intended to emphasize the need to move quickly from the very low doses recommended for treatment initiation (to prevent precipitation of withdrawal) to the doses that are associated with efficacy. The labeling further provides a general range of daily doses for maintenance, depending on the individual patient and clinical response.

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The current labeling also includes a statement that "Dosages higher than (equivalent to) 24 mg have not been demonstrated to provide a clinical advantage." This informs prescribers of the limitations of currently available data from adequate and well-controlled studies evaluating safety and efficacy beyond a dose of 24 mg per day. This statement reflects that higher daily dosages have not been evaluated in randomized trials; it does not mean that daily dosages higher than 24 mg have been shown to be ineffective or that 24 mg/day is a maximum dosage. Prescribers should recognize that the doses used should be *individualized*—and follow the labeling directions to adjust the dosage based upon their individual patient's therapeutic need.

What are FDA's recommended revisions to BTOD labeling?

In the *Federal Register* notice, we recommend several changes to BTOD labeling to clarify that neither 16 mg/day nor 24 mg/day should be construed as maximum dosages for these medications. FDA's recommended labeling changes include:

- Removal of "target dose;"
- Modification of the statement, "Dosages higher than 24 mg daily have not been demonstrated to provide a clinical advantage" to read, "Dosage higher than 24 mg buprenorphine daily have not been investigated in randomized clinical trials but may be appropriate for some patients"; and
- A minor clarification to the Pregnancy section that would align with the preceding changes above.

To see all of FDA's recommended changes to BTOD labeling, visit https://www.federalregister.gov/d/2024-30776.

Why does this letter focus on transmucosal buprenorphine products indicated for the treatment of OUD?

FDA's recommended labeling changes are only for transmucosal buprenorphine-containing products, including Suboxone, Zubsolv, and generic transmucosal buprenorphine-containing products. Only the transmucosal buprenorphine products indicated for the treatment of OUD have labeling that recommends a "target" maintenance dose and a statement that doses higher than the specified dose in the labeling have not been demonstrated to provide a clinical advantage.

What can health care professionals do?

Until application holders of BTODs make the recommended changes to the labeling, it is important for health care professionals to keep in mind that the labeling for these products does not include a maximum dose. Rather, the labeling provides the following:

- A recommendation that the dosage should be progressively adjusted in increments/decrements to a level that holds the patient in treatment and suppresses opioid withdrawal.
- A recommended "target" dose, which is intended to emphasize the need to move quickly from the very low doses recommended for treatment initiation to doses associated with efficacy, and which should not be interpreted as a maximum dose.

- A general range of effective maintenance daily doses depending on the needs of the individual patient and clinical response.
- A statement that “dosages higher than 24 mg/day or equivalent have not been demonstrated to provide any clinical advantage,” should not be interpreted to mean that daily dosages higher than 24 mg have been shown to be ineffective or that 24 mg/day is a maximum dosage—only that higher doses have not been subjected to evaluation in adequate and well-controlled studies and submitted to FDA.

Further, HCPs should prescribe BTODs based on this understanding of the labeling and their best professional judgment. The dose of buprenorphine should be progressively increased according to the clinical effect in the individual patient, and the dosage may need to be adjusted (up or down) based on reassessments of the patient. As noted in product labeling: It is recommended that an adequate treatment dose, titrated to clinical effectiveness, be achieved as rapidly as possible. In some studies, a too-gradual initiation over several days led to a high drop-out rate of buprenorphine patients during the initiation period. OUD treatment is more likely to be successful when tailored to the needs of the individual patient, including consideration of the appropriate dose of buprenorphine. As with treating any chronic condition, treatment planning should meet people where they are, involve shared decision making, and be supportive and person-centered.

FDA continues to monitor for any adverse events directly related to the use of buprenorphine in treating OUD. We encourage HCPs and patients to report any adverse events associated with buprenorphine use to FDA’s MedWatch Adverse Event Reporting program. Complete and submit the report online at **www.fda.gov/medwatch/report.htm**; or download and complete the form, then submit it via fax at 1-800- FDA-0178.

Sincerely,

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