or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Authority: 6 U.S.C. 279; 8 U.S.C. 1232; 45 CFR 410; 45 CFR 411.

Mary C. Jones,

ACF/OPRE Certifying Officer.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2024–N–5381]

Modifications to Labeling of Buprenorphine-Containing Transmucosal Products for the Treatment of Opioid Dependence

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing that we have concluded that certain statements set forth in the FDA-approved labeling for buprenorphine-containing transmucosal products for the treatment of opioid dependence (BTODs) related to the recommended maintenance dosage and dosage adjustments during pregnancy can be modified. We believe that certain statements in BTOD labeling can be modified because the labeling for these products may be misinterpreted by some as establishing a maximum dosage when none exists. FDA is concerned that misinterpretation of these labeling statements may be adversely impacting patients' access to BTODs. We encourage sponsors of approved applications for BTODs to submit supplemental new drug applications (NDAs) (labeling supplements) to modify these labeling statements as described in this notice.

FOR FURTHER INFORMATION CONTACT: Kimberly Compton, Center for Drug Evaluation and Research (HFD–170), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 3168, Silver Spring, MD 20993, 301–796–1191, *kimberly.compton@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

A. FDA-Approved BTODs

Buprenorphine is a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist. BUPRENEX (buprenorphine hydrochloride (HCl)) injection (under NDA 018401) is a schedule III controlled substance under the Controlled Substances Act (CSA) and was the first buprenorphine product to be approved in the United States (approved in 1981) for management of moderate to severe pain. Other buprenorphine products were subsequently approved for the treatment of opioid use disorder (OUD) [1] and are also controlled under schedule III of the CSA.[2] BTODs have been approved by FDA since 2002. BTODs are available both as products containing buprenorphine alone and as fixed combination drug products containing buprenorphine and naloxone. BTODs include ZUBSOLV (buprenorphine HCl and naloxone HCl) sublingual tablets; SUBOXONE (buprenorphine HCl and naloxone HCl) sublingual film (for sublingual or buccal use); Buprenorphine and Naloxone Sublingual Film; and Buprenorphine and Naloxone Sublingual Tablets.

The first BTODs approved were SUBUTEX (buprenorphine HCl) sublingual tablets (NDA 020732)and SUBOXONE (buprenorphine HCl and naloxone HCl) sublingual tablets (NDA 020733).[3] Approval of these products was based, in part, on clinical studies of Buprenorphine Sublingual Tablets with and without Naloxone Sublingual Tablets, and on studies of sublingual administration of a more bioavailable ethanolic solution of buprenorphine (Ref. 1). Dosing recommendations were based on data from one trial of both buprenorphine products and two trials of the ethanolic solutions. In a double-blind, parallel-group, 16-week study, 731 subjects were randomized to receive 1 of 4 dosages of buprenorphine ethanolic solution: 1 milligram (mg), 4 mg, 8 mg, and 16 mg. For comparison purposes 1 mg of solution would be equivalent to less than 2 mg of buprenorphine in sublingual tablets; 4 mg, 8 mg, and 16 mg of buprenorphine in the solution would be roughly equivalent to 6 mg, 12 mg, and 24 mg of buprenorphine in sublingual tablets, respectively. Buprenorphine (administered once daily) was titrated to a maintenance dosage over 1 to 4 days and continued for 16 weeks. Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, the three highest tested dosages of the ethanolic solution (*i.e.,* 4 mg, 8 mg, and 16 mg once daily dosages) were superior to the 1 mg once daily dosage. This study and the additional information submitted to support the approval of SUBUTEX and SUBOXONE demonstrated Buprenorphine Sublingual Tablets are effective from 4 mg to 24 mg once daily. The ''Dosage and Administration'' section of the original labeling for these products in describing the appropriate maintenance dosage read, in part:

The dosage of SUBOXONE should be progressively adjusted in increments/decrements of 2 mg or 4 mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4 mg to 24 mg per day depending on the individual [Ref. 1].

In 2011, the Agency took several actions including the approval of two additional strengths, updates to the labeling, and modifications to the risk evaluation and mitigation strategy (REMS) for SUBUTEX and SUBOXONE sublingual tablets (Refs. 2, 3, 4, 5). The goals of the REMS for SUBUTEX and SUBOXONE were to mitigate the risks of accidental overdose, particularly in the pediatric population, and to mitigate the risks of misuse and abuse, as well as to inform patients of the serious risks associated with use of these products (Refs. 2, 4*).* It was at this time and within the context of addressing these concerns that the application holder for SUBUTEX and SUBOXONE proposed changes to the ''Dosage and Administration'' section of the approved labeling. For SUBOXONE, FDA approved the following language related to the maintenance dosage in the ''Dosage and Administration'' section of the labeling (SUBUTEX shares similar language in its labeling (Ref. 5)):

- SUBOXONE sublingual tablet is indicated for maintenance treatment.
- The recommended target dosage of SUBOXONE sublingual tablet is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose.
- The dosage of SUBOXONE sublingual tablet should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose of SUBOXONE sublingual tablet is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been

[1] For the purposes of this notice, the terms *opioid dependence* and *opioid use disorder* are used interchangeably.

[2] 21 CFR 1308.13(e).

[3] Approvals of Subutex and Suboxone sublingual tablets were withdrawn on September 15, 2022 (87 FR 50337, August 16, 2022).

demonstrated to provide any clinical advantage.

Relevant to this notice is the inclusion of the statement, ''Dosages higher than [24 mg/6 mg buprenorphine/naloxone per day] have not been demonstrated to provide any clinical advantage'' in the BTOD labeling (Ref. 5). This language is consistent with 21 CFR 201.57(c)(3)(i)(B) and conveys, in part, that clinical trial data support the safety and effectiveness of buprenorphine dosages up to 24 mg once daily. Although clinical trial data support the effectiveness of buprenorphine dosages ranging from 4 mg to 24 mg once daily for maintenance treatment, this statement may be misconstrued by some as imposing a maximum dosage beyond which buprenorphine may not be prescribed. Further, although the labeling for SUBUTEX and SUBOXONE has always referred to the 16 mg buprenorphine dosage and 16 mg/4 mg buprenorphine and naloxone dosage, respectively, as the ''target'' dosage, we understand that this too may be misinterpreted as a maximum dosage.

The labeling for these products has changed since the inclusion of the 2011 statement, but the maintenance dosage recommendations in the ''Dosage and Administration'' section of the SUBUTEX and SUBOXONE labeling have largely remained the same (Refs. 6, 7). Additionally, labeling for other BTODs includes similar language as the labeling for SUBUTEX and SUBOXONE regarding maintenance dosage and treatment (Refs. 8, 9).

B. Perceived Dosage Maximums for BTODs

In recent years, a number of interested parties have raised concerns that the labeling for BTODs, in particular the maintenance dosage recommendations in the ''Dosage and Administration'' section, may be adversely impacting patient access to this OUD treatment. In August 2022, FDA received a citizen petition submitted by the Colorado Society of Addiction Medicine, in which the petitioner raised concerns that the current labeling for BTODs may be perceived as a barrier to prescribing buprenorphine dosages higher than 24 mg once daily [4] for certain patients, and even dosages higher than 16 mg once daily, and that the language in the labeling may have other implications, such as being used to limit insurance coverage for higher dosages (Ref. 10).[5] The citizen petition specifically cited the maintenance dosage recommendations in the ''Dosage and Administration'' section of the SUBOXONE labeling and asserted that these recommendations do not recognize the needs of certain patients for buprenorphine dosages higher than 24 mg once daily (Ref. 10). In May 2023, the Reagan-Udall Foundation hosted a 2-day public meeting with FDA and the Substance Abuse and Mental Health Services Administration (SAMHSA), entitled ''Considerations for Buprenorphine Initiation and Maintenance Care'' (Ref. 11). Some interested parties attending the public meeting expressed concerns similar to those raised in the citizen petition about perceived buprenorphine maximum dosages (Refs. 12, 13). Additionally, on December 11, 2023, SAMHSA, FDA, and the National Institute on Drug Abuse, hosted a listening session to discuss the medical need, emerging data, and barriers to accessing higher doses of buprenorphine in the context of high potency synthetic opioid exposure and concerns were raised about a perceived dosage ''cap at 24 mg/day'' that is ''set to the FDA label'' for BTODs (Ref. 14).

The reported reluctance of some healthcare practitioners to prescribe buprenorphine daily dosages of 24 mg or higher, and even 16 mg in some instances, may be based on a misinterpretation of the labeling that 16 mg or 24 mg once daily dosages are a required ''dosage limit.'' Some publications have incorrectly interpreted BTOD labeling as imposing ''dosage limits'' or ''dose limits'' of 16 mg or 24 mg once daily (Ref. 15). Moreover, the Agency is aware that some States' Medicaid plans require prior authorization as a condition of reimbursement, to include such requirements as documentation of medical necessity for buprenorphine daily dosages of 16 mg or 24 mg and higher, before buprenorphine is dispensed to the patient (Ref. 16). Additionally, we understand that some States impose additional requirements on healthcare practitioners who prescribe buprenorphine dosages higher than 16 mg/day.[6] States have authority to regulate the activities of doctors and pharmacists within their jurisdictions. However, we want to minimize the possibility that the approved labeling for BTODs is misinterpreted in a way that results in stakeholders believing that such labeling recommendations reflect dosage limitations. The labeling, which states that dosages higher than 24 mg daily ''have not been demonstrated to provide any clinical advantage,'' or that 16 mg/day is the ''recommended target dose,'' are not buprenorphine dosage caps.

The inclusion of a buprenorphine ''target'' dosage in BTOD labeling reflects the need to move quickly from the very low dosages recommended for treatment initiation (to reduce the risk of precipitation of opioid withdrawal) to dosages that are effective for the treatment of opioid dependence. BTOD labeling recommends a ''target'' buprenorphine daily dosage of 16 mg, which is not a maximum dosage. The labeling for these products recommends that the buprenorphine dosage should be progressively adjusted in increments or decrements to a level that holds the patient in treatment and suppresses opioid withdrawal. The labeling further provides a general range of daily maintenance buprenorphine dosages of 4 mg to 24 mg per day, depending on the individual patient and clinical response.

The labeling also includes the statement ''Dosages higher than 24 mg/day have not been demonstrated to provide a clinical advantage.'' This statement informs healthcare practitioners regarding the limitations of data available at the time of approval of the application from adequate and well-controlled studies evaluating safety and efficacy beyond a buprenorphine dosage of 24 mg/day. In other words, higher daily dosages have not been subjected to evaluation 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. The labeling does not include any recommended maximum daily buprenorphine dosage.

II. Proposed Revisions to the Labeling for BTODs

A. Ways in Which Labeling May Be Revised

Labeling, including the Prescribing Information (PI), must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading (21 CFR 201.56(a)(2)). An applicant may, on its own initiative, submit a supplemental NDA (labeling supplement) to propose

[4] The dosages of buprenorphine listed herein are based on the bioavailability of SUBUTEX and SUBOXONE sublingual tablets. Some fixed combination products containing buprenorphine and naloxone may provide equivalent buprenorphine exposure at alternate dosages due to differences in formulation. Refer to the product labeling for these products, as appropriate, for equivalent dosing to SUBOXONE.

[5] Issues concerning insurance coverage and reimbursement are outside FDA's regulatory purview.

[6] See Tennessee Code Annotated section 53–11–311 (d) (requiring the healthcare provider to document rationale for prescribing higher than 16 mg/day); Ohio Administrative Code 4731–33–03 (same).

changes to the PI based on new information to satisfy this requirement. FDA may also ask applicants to voluntarily update the PI with information, such as safety information or how to safely use the medication, by sending applicants a letter requesting them to submit a labeling supplement. FDA can also require applicants make safety labeling changes if FDA becomes aware of new safety information or information related to reduced effectiveness (pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(o)(4))) that it determines should be included in the labeling of the drug. Less commonly, FDA has encouraged application holders to submit labeling supplements to modify the approved labeling of drug products by announcing recommended changes to the labeling through a **Federal Register** notice.[7] We are issuing this notice today because we believe that the recommended clarifications to BTOD labeling would benefit the public health by providing clearer dosage and administration recommendations for these important OUD treatments.

B. Recommended Changes to the Maintenance Dosage Recommendations in the ''Dosage and Administration'' Section of the Labeling

The ''Dosage and Administration'' section of the most recently approved labeling for BTODs contains the following: (1) ''Dosages higher than 24 mg daily have not been demonstrated to provide a clinical advantage;'' and (2) reference to dosage of 16 mg as a ''target'' dosage.

As stated previously, the statement ''Dosages higher than 24 mg daily have not been demonstrated to provide a clinical advantage'' was added to the labeling to convey, in part, that clinical trial data support the safety and effectiveness of buprenorphine daily dosages up to 24 mg. However, this statement should not be construed as a buprenorphine maximum dosage, and its inclusion is not a recommendation against healthcare practitioners prescribing buprenorphine daily dosages higher than 24 mg.

Regarding the reference in the labeling to a buprenorphine daily dosage of 16 mg as a ''target'' dosage, the ''target'' dosage is to emphasize the need to move quickly from the very low dosages recommended for treatment initiation (to reduce the risk of precipitation of opioid withdrawal) to the dosages that are effective for the treatment of opioid dependence. For example, patients generally begin at a low buprenorphine dosage and titrate upward, which allows the healthcare practitioner to monitor for effectiveness and adverse reactions, such as precipitated opioid withdrawal. During this time of titration, the ''target'' buprenorphine dosage provides healthcare practitioners with a dosage to aim for because most patients can be stabilized at around 16 mg/day, while also recognizing that further upward titration may be necessary. Due to patient variability in response, daily dosages higher or lower than 16 mg/day may be needed, and each patient should be dosed to clinical effect. The ''target'' dosage is not a maximum daily maintenance dosage.

Accordingly, we are announcing that the statements in the labeling that dosages higher than 24 mg daily have not been demonstrated to provide a clinical advantage and the reference to the dosage of 16 mg as a ''target'' dosage can be modified. FDA recommends the following specific changes to the maintenance dosage recommendations in the ''Dosage and Administration'' section of the most recent approved BTOD labeling: [8]

> After treatment induction to the recommended dose of [equivalent 16 mg buprenorphine OR equivalent 16 mg/4 mg buprenorphine/naloxone] per day, dosing should be further adjusted based on the individual patient and clinical response. The maintenance dose of [DRUG NAME] is generally in the range of [equivalent 4 mg buprenorphine OR equivalent 4 mg/1 mg buprenorphine/naloxone] to [equivalent 24 mg buprenorphine OR equivalent 24 mg/6 mg buprenorphine/naloxone] per day. Dosages higher than [equivalent 24 mg buprenorphine OR equivalent 24 mg/6 mg buprenorphine/naloxone] daily have not been investigated in randomized clinical trials but may be appropriate for some patients.

C. Recommended Changes to the ''Pregnancy'' Subsection of the ''Use in Specific Populations'' Section of the Labeling

The ''Pregnancy'' subsection of the ''Use in Specific Populations'' section of the most recently approved BTOD labeling contains the statements ''Dosage adjustments of buprenorphine may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Withdrawal signs and symptoms should be monitored closely, and the dose adjusted as necessary'' (Refs. 6, 7). To better align with the changes that the Agency is recommending for the maintenance dosage recommendations in the ''Dosage and Administration'' section of BTOD labeling, the Agency further recommends that ''dosage adjustments'' be revised in the ''Pregnancy'' subsection of BTOD labeling to qualify that the adjustment is most often a dosage increase. For example, the labeling would read, ''Dosage adjustments of buprenorphine, such as using higher doses, may be required . . . .''

FDA recommends these changes given the concerns raised regarding the maintenance dosage recommendations in the ''Dosage and Administration'' section of BTOD labeling. Specifically, it may not be clear from the most recent approved labeling that certain populations, including pregnant females,[9] may need a higher dosage of buprenorphine. For example, the ''Pregnancy'' subsection of the ''Use in Specific Populations'' section of the labeling discusses the possible need for ''dosage adjustments'' for pregnant females but does not specifically highlight the potential need for higher dosages (Refs. 17, 18, 19, 20). We believe it is important that the labeling clearly communicate that this population may require a higher dosage.

Further, these changes are consistent with the data submitted to support the initial inclusion of the ''dosage adjustment'' statement to the ''Pregnancy'' subsection of BTOD labeling (Ref. 21). When the statement on ''dosage adjustments'' for pregnant females was first added to BTOD labeling, FDA reviewed data showing that this population may need higher

[7] See 78 FR 19718 (April 2, 2013), 66 FR 55679 (November 2, 2001).

[8] Some BTOD products contain buprenorphine only and others are fixed combination products containing buprenorphine and naloxone. Further, as discussed in footnote 2, some products containing buprenorphine may provide equivalent buprenorphine exposure at alternate doses (*e.g.,* equivalent to 16 mg or equivalent to 24 mg buprenorphine in SUBUTEX and SUBOXONE) due to differences in formulation. Accordingly, where this notice recommends changes to the labeling, application holders of these BTOD products should update the labeling with appropriate product-specific information, including the appropriate dose(s) specific to their products.

[9] For purposes of this notice, ''sex'' is a biological construct based on anatomical, physiological, hormonal, and genetic (chromosomal) traits, and is generally assigned based on anatomy at birth typically categorized as male or female, but variations occur. Variations of sex refers to differences in sex development or intersex traits. See Measuring Sex, Gender Identity, and Sexual Orientation (2022). National Academies of Science, Engineering, and Medicine. Washington, DC: The National Academies Press. FDA recognizes that sex and gender are distinct terms, with sex defined as a biological construct and gender as a social construct. For more information, see the guidance for industry Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020) available at: *https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.*

dosages. This labeling statement was supported, in part, by a retrospective case review of buprenorphine dosage adjustments for 45 adult females maintained on buprenorphine during pregnancy, in which 89 percent of all patients required an increase of buprenorphine dosage during pregnancy (Ref. 17). Pharmacokinetic data submitted at the time the ''dosage adjustment'' statement was added to the ''Pregnancy'' subsection is also consistent with the changes that are being proposed in this notice. A study of nine pregnant females, where pharmacokinetic data were collected on three subjects, reported a trend suggesting a lower buprenorphine and norbuprenorphine (major metabolite) maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve ($AUC_{0–24hrs}$) over the last 24-hour dosing interval during the third trimester of pregnancy than after delivery (Ref. 22). The magnitude of this exposure reduction was highly variable; however, the study authors found that lower C_{max} and $AUC_{0–24hrs}$ suggest ''pregnant opioid-dependent women may require increased [buprenorphine] dose during gestation and decreased dose postpartum'' (Ref. 22).

Accordingly, we are announcing that the statement in BTOD labeling regarding the potential need for dosage adjustments during pregnancy can be modified as described below. FDA recommends the following specific change under the ''Dose Adjustment during Pregnancy and the Postpartum Period'' subheading under the ''Clinical Considerations'' heading in the ''Pregnancy'' subsection of the ''Use in Specific Populations'' section in BTOD labeling:

> Dosage adjustments of buprenorphine, such as using higher doses, may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Dosing should be based on individual response, and withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.

D. Summary of Proposed Labeling Revisions

To clarify that the recommendations in the current BTOD labeling do not reflect a maximum buprenorphine dosage of 16 mg or 24 mg once daily, FDA recommends changes to the maintenance dosage recommendations in the ''Dosage and Administration'' section of BTOD labeling as noted in table 1.

TABLE 1—RECOMMENDED CHANGES TO MAINTENANCE DOSAGE RECOMMENDATIONS IN THE ''DOSAGE AND ADMINISTRATION'' SECTION OF BTOD LABELING

Most recently approved labeling	Proposed labeling
2 DOSAGE AND ADMINISTRATION . . . After treatment induction and stabilization, the maintenance dose of [DRUG NAME] is generally in the range of [equivalent 4 mg buprenorphine OR equivalent 4 mg/1 mg buprenorphine/naloxone] to [equivalent 24 mg buprenorphine OR equivalent 24 mg/6 mg buprenorphine/naloxone] per day depending on the individual patient. The recommended target dosage of [DRUG NAME] is [equivalent 16 mg buprenorphine OR equivalent 16 mg/4 mg buprenorphine/naloxone] as a single daily dose. Dosages higher than [equivalent 24 mg buprenorphine OR 24 mg/6 mg buprenorphine/naloxone] have not been demonstrated to provide any clinical advantage.	2 DOSAGE AND ADMINISTRATION . . . After treatment induction to the recommended dose of [equivalent 16 mg buprenorphine OR equivalent 16 mg/4 mg buprenorphine/naloxone] per day, dosing should be further adjusted based on the individual patient and clinical response. The maintenance dose of [DRUG NAME] is generally in the range of [equivalent 4 mg buprenorphine OR 4 mg/1 mg buprenorphine/naloxone] to [equivalent 24 mg buprenorphine OR equivalent 24 mg/6 mg buprenorphine/naloxone] per day. Dosages higher than [equivalent 24 mg buprenorphine OR equivalent 24 mg/6 mg buprenorphine/naloxone] mg daily have not been investigated in randomized clinical trials but may be appropriate for some patients.

Additionally, to align with the changes that the Agency is recommending for the maintenance information in the ''Dosage and Administration'' section of BTOD labeling, FDA recommends changes to the ''Dose Adjustment during Pregnancy and the Postpartum Period'' subheading under the ''Clinical Considerations'' heading in the ''Pregnancy'' subsection of the ''Use in Specific Populations'' section of BTOD labeling as noted in table 2.

TABLE 2—RECOMMENDED CHANGES TO THE ''PREGNANCY'' SUBSECTION OF THE ''USE IN SPECIAL POPULATIONS'' SECTION OF BTOD LABELING

Most recently approved labeling	Proposed labeling
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Clinical Considerations . . . *Dose Adjustment during Pregnancy and the Postpartum Period.* Dosage adjustments of buprenorphine may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.	8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Clinical Considerations . . . *Dose Adjustment during Pregnancy and the Postpartum Period.* Dosage adjustments of buprenorphine, such as using higher doses, may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Dosing should be based on individual response, and withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.

We have determined that these labeling revisions may be addressed through a supplement submitted under 21 CFR 314.70(c)(6). Any labeling revisions submitted pursuant to this notice should reflect changes to all of

the relevant sections of the labeling identified in this notice, which include the ''Dosage and Administration'' and ''Use in Specific Populations'' sections of BTOD labeling.

III. Electronic Submissions

Submit any draft labeling as a prior approval supplement to your NDA. Any labeling supplement must be submitted in the electronic common technical document (eCTD) standard format. The eCTD is the standard format for electronic regulatory submissions to FDA's Center for Drug Evaluation and Research. The FDA Electronic Submissions Gateway (available at: *https://www.fda.gov/industry/electronic-submissions-gateway)* is the central transmission point for sending information electronically to FDA and enables the secure submission of regulatory information for review.

IV. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at *https://www.regulations.gov.* References without asterisks are not on public display at *https://www.regulations.gov* because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

1. * Labeling for SUBUTEX (buprenorphine HCl) (NDA 020732) and SUBOXONE (buprenorphine HCl and naloxone HCl) (NDA 020733) sublingual tablets, Oct. 8, 2002, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20732,20733lbl.pdf.*
2. * Supplement Approval for SUBUTEX (buprenorphine HCl) sublingual tablets (NDA 020732), Dec. 22, 2011, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020732s006,s007ltr.pdf.*
3. * Labeling for SUBUTEX (buprenorphine HCl) sublingual tablets (NDA 020732), Dec. 22, 2011, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf.*
4. * Supplement Approval for SUBOXONE (buprenorphine HCl and naloxone HCl) sublingual tablets (NDA 020733), Dec. 22, 2011, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020733s007,s008ltr.pdf.*

* 5. Labeling for SUBOXONE (buprenorphine HCl and naloxone HCl) sublingual tablets (NDA 020733), Dec. 22, 2011, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020733s007s008lbl.pdf.*

* 6. Labeling for SUBUTEX (buprenorphine HCl) sublingual tablets (NDA 020732), June 17, 2022, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020732s027s028lbl.pdf.*

* 7. Labeling for SUBOXONE (buprenorphine HCl and naloxone HCl) sublingual tablets (NDA 020733), June 17, 2022, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020733s031s032lbl.pdf.*

* 8. ZUBSOLV (buprenorphine HCl and naloxone HCl) sublingual tablets (NDA 204242), Dec. 15, 2023, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/204242s027lbl.pdf.*

* 9. BUNAVAIL (buprenorphine HCl and naloxone HCl) buccal film (NDA 205637), June 17, 2022, available at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/205637s023s024lbl.pdf.*

* 10. Citizen petition submitted by the Colorado Society of Addiction Medicine (FDA–2022–P–1863), posted Aug. 10, 2022, available at: *https://www.regulations.gov/docket/FDA-2022-P-1863.*

11. Reagan-Udall Foundation, virtual public meeting entitled ''Considerations for Buprenorphine Initiation and Maintenance Care,'' May 10–11, 2023, meeting materials and transcripts available at: *https://reaganudall.org/news-and-events/events/considerations-buprenorphine-initiation-and-maintenance-care.*

12. Reagan-Udall Foundation, Meeting Transcript, ''Considerations for Buprenorphine Initiation and Maintenance Care—Day One,'' May 10, 2023, available at: *https://reaganudall.org/sites/default/files/2023-07/Transcript%20-%20Buprenorphine%20Initiation%20-%20Day%201%20-%20REVISED%20FINAL.pdf.*

13. Reagan-Udall Foundation, Meeting Transcript, ''Considerations for Buprenorphine Initiation and Maintenance Care—Day Two,'' May 11, 2023, available at: *https://reaganudall.org/sites/default/files/2023-05/Transcript%20-%20Buprenorphine%20Initiation%20-%20Day%202%20-%20final.pdf.*

* 14. SAMHSA, Meeting Summary, ''Listening Session: Use of High Dose Buprenorphine for the Treatment of Opioid Use Disorder,'' December 11, 2023, available at: *https://store.samhsa.gov/sites/default/files/high-dose-buprenorphine-report-pep24-02-013.pdf.*

15. Grande, LA, D Cundiff, MK Greenwald, et al., 2023, ''Evidence on Buprenorphine Dose Limits: A Review,'' *J Addict Med,* 17(5): 509–516.

16. Tiako, MJN, A Dolan, M Abrams, et al., 2023, ''Thematic Analysis of State Medicaid Buprenorphine Prior Authorization Requirements,'' *JAMA Netw Open,* 6(6):e2318487.

17. Bakaysa, S, S Heil, and M Meyer, 2009, ''833: Buprenorphine Dose Changes During Gestation,'' *Am J Obstet Gynecol,* 201(6):S297–S298.

18. Martin, CE, C Shadowen, B Thakkar, et al., 2020, ''Buprenorphine Dosing for the Treatment of Opioid Use Disorder Through Pregnancy and Postpartum,'' *Curr Treat Options Psychiatry,* 7(3): 375–399.

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* 20. Substance Abuse and Mental Health Services Administration (SAMHSA) Advisory, ''Evidence-Based, Whole-Person Care for Pregnant People Who Have Opioid Use Disorder,'' March 2024, available at: *https://store.samhsa.gov/sites/default/files/whole-person-care-pregnant-people-oud-pep23-02-01-002.pdf.*

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Dated: December 18, 2024.

P. Ritu Nalubola,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Indian Health Service

Request for Public Comment: 60-Day Notice for Extension of the Indian Health Service Loan Repayment Program

AGENCY: Indian Health Service, HHS.

ACTION: Notice and request for comments; request for extension of approval.

SUMMARY: In compliance with the Paperwork Reduction Act of 1995, the Indian Health Service (IHS) invites the general public to take this opportunity to comment on the information collection Office of Management and Budget (OMB) Control Number 0917–