Subject: Buprenorphine/Naloxone and Buprenorphine for Opioid Dependence • **Buprenorphine/Naloxone** ▪ Bunavail™ ▪ Suboxone Film® ▪ Zubsolv® ▪ generic Buprenorphine/Naloxone sublingual tablet • **Buprenorphine**	**Original Effective Date:** 8/26/09
Policy Number: MCP-072	**Revision Date(s):** 2/25/13; 4/4/17
Review Date(s): 12/16/15; 6/15/2016, 4/4/2017, 7/10/2018	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Buprenorphine/Naloxone and buprenorphine is indicated for the treatment of opioid dependence** when appropriate criteria are met. The intent of the Molina Clinical Policy (MCP) is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

Suboxone Film, Zubsolv® (buprenorphine/naloxone), Bunavail™, buprenorphine/naloxone, and buprenorphine are **Schedule III** narcotic medications available under the Drug Abuse Treatment Act (DATA) of 2000 for the treatment of opioid dependence. Only qualified physicians with the necessary DEA (Drug Enforcement Agency) identification number can prescribe or dispense buprenorphine products for opioid addiction therapy.

- **PREFERRED: Generic buprenorphine/naloxone sublingual tablets** are the preferred buprenorphine/naloxone product with the EXCEPTION of pregnancy. Due to the potential for naloxone to precipitate withdrawal in both mother and fetus, pregnant women who are deemed to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy.

- **Buprenorphine-naloxone** combines buprenorphine, a long-acting synthetic opioid and partial mu (μ) opioid receptor agonist, and naloxone, an opioid antagonist whose inclusion is intended to limit tampering, non-medical injection, and the potential for diversion. This is an abuse deterrent strategy as buprenorphine-naloxone combination preparations are less likely to be injected than mono preparations containing only buprenorphine.
- **Buprenorphine** is a partial mu opioid receptor agonist[E]

- The naloxone component of buprenorphine-naloxone has limited sublingual and oral bioavailability and is inactive when buprenorphine-naloxone is taken as prescribed.[9] However, if buprenorphine/naloxone is misused by injection, naloxone may block the effects of buprenorphine, or precipitate opioid withdrawal in an opioid dependent person.[9,8] However, blockade may be moderate, and brief relative to the duration of action of buprenorphine.[8]

⌘ **Buprenorphine monotherapy versus Buprenorphine/Naloxone**

- Buprenorphine/naloxone combination is recommended for induction, stabilization, and maintenance treatment for most patients (SAMHSA).[B]
- Sublingual buprenorphine monotherapy for pregnant women is recommended due to concerns that naloxone may cause withdrawal in the woman and fetus.[B,D] Although there is some evidence that the combination is safe in pregnancy, evidence is insufficient to recommend it in pregnancy at this time.[A]
- Other patients who are inducted on monotherapy should be switched to combination therapy as soon as possible to minimize the possibility of diversion and abuse of buprenorphine.
- The use of buprenorphine for unsupervised administration during maintenance therapy should be limited to those patients who cannot tolerate naloxone, for example individuals who have been shown to have a hypersensitivity to naloxone have moderate or severe hepatic impairment, and pregnant women.

⌘ **Adjunctive non-pharmacologic treatment required**

Effective treatment requires comprehensive attention to the individual's medical and psychosocial co-morbidities; pharmacological therapy alone rarely achieves long-term success.[B]

⌘ **DURATION OF TREATMENT:** Treatment may be indefinite.[B]

CLASSIFICATION: Opioid Agonist-Antagonist Analgesics

FDA INDICATIONS

Opioid dependence: For the treatment of opioid dependence[a,b,c,d,i]

- *Prescription use of buprenorphine and naloxone is limited under the Drug Addiction Treatment Act*[i]
- *Orphan drug designation: Treatment of opiate addiction in opiate users*[i]

General information: Buprenorphine/naloxone should be used as part of a complete treatment plan to include counseling and psychosocial support.[e]

FDA APPROVED INDICATIONS		
Product Name	**Opioid Dependence and Induction Treatment**	**Maintenance Treatment of Opioid Dependence**
buprenorphine sublingual tablet ***Generic available*** *Brand Subutex no longer available.*	✓	
Bunavail™ (buprenorphine/naloxone buccal film)		✓
Buprenorphine-Naloxone (buprenorphine/naloxone sublingual tablet) ***Generic available***	✓	✓
Suboxone (buprenorphine/naloxone sublingual film)	✓	✓
Zubsolv (buprenorphine/naloxone sublingual tablet)	✓	✓

Bunavail™ buccal film may contain saccharin. Suboxone sublingual film may contain maltitol. Zubsolv sublingual tablets may contain mannitol and sucralose.
Bunavail™ buccal film is not bioequivalent to Suboxone® SL tabs. Refer to product labeling for further information.[c]
Zubsolv® is not bioequivalent to Suboxone®. Refer to product labeling for further information.[d]

Approved by the FDA

- October 2002: A buprenorphine; naloxone sublingual tablet (Suboxone) was FDA-approved for the maintenance treatment of opioid dependence
- August 2010: A buprenorphine; naloxone sublingual film (Suboxone) was FDA-approved for the maintenance treatment of opioid dependence
- April 2014: **Suboxone sublingual film** was approved for induction treatment in patients dependent on heroin or other short-acting opioid products who are in opioid withdrawal
- June 2014: **Bunavail** buccal film for the maintenance treatment of opioid dependence was FDA-approved
  According to the manufacturer, the drug has a unique adhesive "inside the cheek" delivery system that improves absorption and plasma concentrations of buprenorphine and therefore can be delivered at a lower dose, which may help reduce the potential for misuse and diversion and lessen the incidence of side effects. Approval was based on a phase III, 12-week, clinical trial of 249 patients that were converted to the buccal film from the sublingual tablet (Suboxone). The film was shown to be safe and effective with less constipation than with Suboxone.[c]
- July 2013: **Zubsolv** sublingual tablet was initially approved for the maintenance treatment of opioid dependence
- August 2015: **Zubsolv** was also approved for induction treatment of opioid withdrawal due to heroin or other short-acting opioids.
  Zubsolv: *The new formulation has high bioavailability, a fast dissolve time, a small tablet size, and a menthol flavor to encourage patient adherence with treatment.*[d] *Zubsolv's indication was expanded to include induction dosing for patients dependent on short-acting opioids (e.g., heroin) in August 2015. For patients dependent on long-acting opioids (e.g., methadone), buprenorphine monotherapy is recommended for induction.*

Product	Available Dosage Strengths

buprenorphine sublingual tablets *Generic only; brand no longer available	2 mg; 8 mg
buprenorphine/naloxone sublingual tablet *Generic only; brand no longer available	2 mg/0.5 mg; 8 mg/2 mg
Suboxone (buprenorphine/naloxone) sublingual film	2 mg/0.5 mg; 4 mg/1 mg; 8 mg/2 mg; 12 mg/3 mg
Bunavail (buprenorphine/naloxone) buccal film	2.1 mg/0.3 mg; 4.2 mg/0.7 mg; 6.3 mg/1 mg
Zubsolv (buprenorphine/naloxone) sublingual tablets	0.7 mg/0.18 mg; 1.4 mg/0.36 mg; 5.7 mg/1.4 mg; 8.6 mg/2.1 mg; 11.4 mg/2.9 mg

Refer **to APPENDIX 5** for additional information on Buprenorphine/Naloxone and Buprenorphine Product Availability

Black Box Warnings: *None at the time of this writing*

REMS To mitigate the risk of accidental overdose, misuse, and abuse and to inform prescribers, pharmacists, and patients of risks associated with buprenorphine-containing products, the FDA-approved REMS program includes a Medication Guide, Elements to Assure Safe Use (letters, brochures, appropriate use checklist), and an Implementation System.

RECOMMENDATIONS/COVERAGE CRITERIA

Buprenorphine/Naloxone [Bunavail, Suboxone Film, Zubsolv, generic Buprenorphine/Naloxone] may be authorized for members meeting ALL of the following criteria: [ALL]

1. Prescriber specialty [ALL]

- ❑ Prescriber meets the qualification certification criteria in the Drug Addiction Treatment Act (DATA) of 2000 and has been issued a unique DEA identification number by the DEA, an "X" waivered DEA license to prescribe buprenorphine products [buprenorphine, Bunavail, Suboxone, buprenorphine/naloxone, or Zubsolv]

  MOLINA REVIEWER: Verify Prescriber's "X" waivered DEA license number via The Substance Abuse and Mental Health Services Administration (SAMHSA) Buprenorphine Physician Locator Web site: http://www.samhsa.gov/bupe/lookup-form
  - *A provider listed on the site can be considered to have a valid DATA 2000 waiver.*
  - *This list is not complete; a provider with a valid waiver may choose not to be listed on the site. These providers will need to provide verification of their DATA 2000 waiver to Molina Healthcare.*
  - *Molina Healthcare will not recognize any "Immediate" providers as an authorized provider.*
  - *Refer to **'Appendix 1'** for additional information on DATA 2000*

2. Diagnosis/Indication [ALL]

- ❒ Diagnosis clinically based on history and physical exam findings that support Diagnostic and Statistical Manual of Mental Disorders, 5th ed**. DSM-V-TR criteria for Opiate Abuse and Dependence** and/or **DSM-IV-TR criteria for opioid dependence**. [DOCUMENTATION REQUIRED]
  - *Refer to 'Appendix 2' for additional information on DSM-5 or ICD-10 diagnostic criteria[6]*
  - *Buprenorphine is <u>not</u> FDA-approved for the treatment of chronic pain. Buprenorphine/naloxone is not appropriate for pain management; deaths have been reported in opioid-naive patients receiving oral buprenorphine for analgesia.[a-e]*

3. Age/Gender/Other restrictions [ONE]

- ❑ 16 years of age or older
  - *The safety and efficacy of buprenorphine/naloxone in patients 15 years and younger has not been established.[a-e]*
  - *Buccal mucosa route: The safety and effectiveness of buccal film not been established in pediatric patients. Not intended for treatment of neonatal abstinence syndrome; naloxone and buprenorphine may precipitate opiate withdrawal.[a-h]*
  - *Sublingual route: The safety and effectiveness of buprenorphine/naloxone have not been established in pediatric patients. Not intended for treatment of neonatal abstinence syndrome; naloxone and buprenorphine may precipitate opiate withdrawal.[a-h]*

- ❑ Negative pregnancy test (for women, ages 16-45). If positive test, "Exceptions Request" for pregnancy must be met.

- ❑ **ONE (1)** of the following as applicable in accordance to State regulations: **[ONE]**

  - ❍ **FOR STATES WITH PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs):** Prescriber utilized (and will continue to utilize) the applicable State PDMP prior to issuance of a prescription or continuation of therapy request to ensure the member is not concurrently utilizing opioids, benzodiazepines or sedative/hypnotic agents. **NOTE:** PDMP check is required on date of request. Prescriber to confirm PDMP was checked today. [DOCUMENTATION REQUIRED]
    - *PDMPs are databases of all controlled substance prescriptions dispensed in a particular state and should be used to confirm opioid abstinence.*
    - *Refer to 'Appendix 3' or the following website for more further information on PDMPs: https://www.deadiversion.usdoj.gov/faq/rx_monitor.htm#1*

  - ❍ **FOR STATES WITHOUT PDMPs:** Prescriber agrees to review member's records AND/OR perform drug screens on a periodic basis or as necessary to ensure no abuse or diversion of the buprenorphine/naloxone or buprenorphine [DOCUMENTATION REQUIRED]
    - *The recommended clinical guidelines for the use of buprenorphine in the treatment of opioid addiction suggest that physicians periodically and regularly screen all patients for substance use and substance related problems.*

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❍ Prescriber recommends a comprehensive rehabilitation program that includes psychosocial support provided by a program counselor qualified by education, training, or experience to assess the psychological and sociological background of individuals receiving treatment (*not an all-inclusive list*): [ANY]
  - ❍ Outpatient drug addiction treatment programs or formal counseling
  - ❍ 12-Step programs focused on "drug" addiction such as Narcotics Anonymous (N.A.)
  - ❍ Behavioral Health Treatment Services listed on https://findtreatment.samhsa.gov/locator/home
    NOTE: Many different types of behavioral therapies (e.g., Motivational Enhancement Therapy, self-help programs) have been used successfully for substance abuse disorders. The SAMHSA Treatment Improvement Protocol (TIP) series (U.S.) [http://store.samhsa.gov/list/series?name=TIP-Series-Treatment-Improvement-Protocols-TIPS-] includes best-practice guidelines for the provision of interventions and therapies for individuals with substance abuse disorders.

❍ Prescriber agrees to administer random clinical drug testing a **minimum of eight times per year** (*or more frequently as appropriate for member) [DOCUMENTATION REQUIRED]

MOLINA REVIEWER: Verify utilization of the listed drugs in member's prescription claims history

EXCEPTION: If drug screen is **POSITIVE** for ANY of the above substances, Prescriber must submit an acknowledgement and rationale for requesting continued therapy despite a positive drug screen. Continuation of therapy will not be authorized unless written documentation is submitted for Molina Pharmacy/Medical Director Review [DOCUMENTATION REQUIRED]

NOTE: Molina Healthcare reserves the right to request supporting documentation and/or cancel an authorization at any point if the member no longer meets the continuation of therapy coverage criteria (such as filling a narcotic agent, failure to adhere to a counseling program, or if drug screens are positive for other abuse substances).

For Continuation of Therapy: Urine drug screening (UDS) must be obtained and documented as it provides information about current substance use, which aids in the diagnosis and the treatment planning process (i.e. an opioid-dependent patient who is currently abstinent but at high risk of relapse may require more frequent monitoring)

- *42 CFR § 8.12(f) (6). Drug abuse testing services. Opioid treatment programs (OTPs) must provide adequate testing or analysis for drugs of abuse, including at least eight random drug abuse tests per year, per patient, in maintenance treatment, in accordance with generally accepted clinical practice. For patients in short-term detoxification treatment, the OTP shall perform at least one initial drug abuse test. For patients receiving long-term detoxification treatment, the program shall perform initial and monthly random tests on each patient (SAMHSA 2015. Federal Guidelines for Opioid Treatment Programs).*[C]
- ***The appropriate frequency of urine drug screening is not readily determined and is likely to change in the course of treatment. As such the frequency of urine drug screening is primarily based on the judgment of the prescribing doctor. An intermittent schedule of random testing is adequate for program requirements and patient safety, the uncertainty and unpredictability of screening is likely to ensure more useful information than a system of frequent screening.*

❍ No more than **TWO (2)** failures of buprenorphine/naloxone or buprenorphine treatment requiring a restart within the previous 12 months
EXCEPTIONS: Exceptions may be made on a case-by-case basis by a Molina Pharmacy/Medical Reviewer.
NOTE: After TWO (2) or more treatment failures warrant further assessment of the member. A higher level care, such as a methadone treatment program, may be recommended by Molina Pharmacy/Medical Reviewer. Molina Healthcare may contact the Prescriber for further discussion of treatment plan and review on a case-by-case basis.

❑ **Members with Behavioral Health Disorders ONLY:** Prescriber agrees to coordinate or oversee ongoing behavioral health care for co-existing behavioral health disorders [DOCUMENTATION REQUIRED]

5. Contraindications/Exclusions to buprenorphine/naloxone therapy [ANY]

Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

- ❍ Non-FDA approved indications
- ❍ Hypersensitivity to buprenorphine or naloxone or any component of the formulation[a-e]
  - ◆ *Bronchospasm, angioneurotic edema, and anaphylactic shock, have been reported.*[a-e]

<u>Exclusions</u> [Refer to Appendix 4]

- ❍ Concurrent treatment of pain with an additional opioid analgesic
  - ◆ *Buprenorphine/naloxone is not appropriate for pain management; deaths have been reported in opioid-naive patients receiving oral buprenorphine for analgesia*[a-e]
- ❍ Moderate to severe hepatic impairment (Child-Pugh B to C)
  - ◆ *Buprenorphine-naloxone may be ineffective in patients with severe liver impairment due to increased bioavailability of naloxone. For this reason, use of buprenorphine-naloxone is not recommended in patients with severe liver impairment.*[k]
  - ◆ *Use with caution in patients with moderate hepatic impairment for maintenance treatment; due to reduced clearance of naloxone and potential for reduced buprenorphine efficacy, use may not be appropriate.*[a-e]
- ❍ Decreased level of consciousness
- ❍ Inability to provide informed consent

<u>Warnings/Precautions</u> [NOT AN EXCLUSION; however Prescriber and Molina Reviewer should 'note' for further discussion on case-by case basis as necessary]

- Concurrent treatment with other opioids [Appendix 4]
- Concomitant use of alcohol and sedatives, hypnotics, or anxiolytics with opioids*

  **May contribute to respiratory depression. Patients with significant co-occurring substance use disorders, especially severe alcohol or sedative, hypnotic, or anxiolytic use, may require a higher level of care.*
- Untreated or unstable psychiatric conditions that may interfere with buprenorphine/naloxone compliance
- Acute severe respiratory distress, significant respiratory depression
  - ◆ *Use with caution in patients with preexisting respiratory compromise (hypoxia and/or hypercapnia), chronic obstructive pulmonary disease or other obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve and kyphoscoliosis or other skeletal disorder that may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.*[a-e]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- ❑ Treatment plan for the member, including the following information:
  - ❍ Frequency of office visits
  - ❍ Plan for psychosocial counseling
  - ❍ Precautions that will be taken to ensure that medications are not diverted for abuse such as drug screens, pill counts, and use of a prescription drug monitoring program

EXCEPTION REQUESTS

All 'Initiation of Treatment' criteria above must be met **in addition to** the following criteria specific to member's condition: [AS APPLICABLE]

FOR NON-PREFERRED PRODUCT REQUESTS ONLY

Rationale for **not** using the generic sublingual tablets and request for non-preferred agent [ALL]

FOR SUBOXONE SL FILM

Rationale for inability to use the **preferred Buprenorphine-Naloxone (generic SL tablet)** due to:

- ❑ Allergic or hypersensitivity reaction to the generic buprenorphine/naloxone tablets
- ❑ Adverse reaction that cannot be managed with the generic buprenorphine/naloxone tablets

FOR BUNAVAIL OR ZUBSOLV REQUESTS

- ❑ Documented trial of the preferred alternative (buprenorphine-naloxone SL tablet) AND Suboxone SL film

NOTE:

- *No evidence that one transmucosal buprenorphine product (Zubsolv or Bunavail) is more effective than another.*
- *The tablets may be abused by crushing and snorting (faster "high" than sublingual despite some naloxone absorption).*[7] *Both tablets and film can be abused by injection.*[8]

FOR BUPRENORPHINE REQUESTS ONLY

Member is unable to take buprenorphine/naloxone as documented by **ONE (1)** of the following: [ONE]

- ❑ **Pregnancy or Breastfeeding:** Anticipated date of delivery [DOCUMENTATION REQUIRED]
  NOTE: Member may initiate or continue on buprenorphine monotherapy for the duration of the pregnancy OR may transfer to methadone maintenance therapy at the discretion of the Prescriber and/or Molina Medical Director.
  - *Pregnant women who are physically dependent on opioids should receive treatment using methadone or buprenorphine monoproduct rather than withdrawal management or abstinence (ASAM 2015).*[A] *There is some evidence suggesting that buprenorphine/ naloxone is equivalent in safety and efficacy to the monoproduct for pregnant women. At present, however, this evidence is insufficient to recommend the combination buprenorphine/naloxone formulation in this population. The buprenorphine monoproduct should be used instead (ASAM 2015).*[A]
  - *Buprenorphine monoproduct is a reasonable and recommended alternative to methadone for pregnant women. Whereas there is evidence of safety, there is insufficient evidence to recommend the combination buprenorphine/ naloxone formulation (ASAM 2015).*[A]
  - *For women who are pregnant or breastfeeding, opioid agonist treatment with methadone or buprenorphine is seen as the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on perinatal care and parenting of young children.*

- ❑ **Moderate to severe hepatic impairment (Child-Pugh B to C)** [DOCUMENTATION REQUIRED]

- ❑ **Maintenance therapy:** Unable to take naloxone-containing products due to a **documented** hypersensitivity to naloxone or naltrexone; intolerance, FDA-labeled contraindication, drug-drug interaction, history of toxic side effects that caused immediate or long-term damage
  NOTE: GI intolerance is not considered an allergy or intolerance. Symptoms of withdrawal induced by taking narcotics and buprenorphine/naloxone in combination are not considered a naloxone allergy.
- ❑ **Prescribed for buprenorphine induction**
  - *Buprenorphine/naloxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy under supervision. Patients should be switched to the combination product for maintenance and unsupervised therapy.*[e]
  - *The goal of induction is to safely suppress opioid withdrawal as rapidly as possible with the minimum dose of buprenorphine-naloxone or buprenorphine monotherapy and experiences no withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. This phase is to help a patient begin the process of switching from the opioids of abuse to buprenorphine.*

CONTINUATION OF THERAPY

Continuation of Therapy of Buprenorphine/Naloxone [Bunavail, Suboxone Film, Zubsolv, generic buprenorphine/naloxone] may be authorized for members meeting ALL of the following criteria: [ALL]

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria
  NOTE: Requests from a new/different Prescriber requires submission of ALL required documentation

2. Compliance [ALL]

- ❍ Compliance with Buprenorphine/Naloxone therapy since previous authorization [VERIFIED BY PRESCRIBER SUBMITTED DOCUMENTATION OR PHARMACY CLAIMS DATA]

  NOTE: If pharmacy claims data demonstrates non-compliance or inconsistent use, a written explanation to support the rationale for requesting continuation of therapy despite apparent non-compliance [MOLINA MEDICAL DIRECTOR REVIEW REQUIRED]

- ❍ Prescriber recommends a rehabilitation program that may include psychosocial support provided by a program counselor qualified by education, training, or experience to assess the psychological and sociological background of individuals receiving treatment (not an all-inclusive list): [ANY]
  - ❍ Outpatient drug addiction treatment programs or formal counseling
  - ❍ 12-Step programs focused on "drug" addiction such as Narcotics Anonymous (N.A.)
  - ❍ Behavioral Health Treatment Services listed on https://findtreatment.samhsa.gov/locator/home
  - ❍ Other (i.e., SMART recovery, SOS, LifeRing and other mutual-help groups)

    NOTE: Many different types of behavioral therapies (e.g., Motivational Enhancement Therapy, self-help programs) have been used successfully for substance abuse disorders. The SAMHSA Treatment Improvement Protocol (TIP) series (U.S.) (http://store.samhsa.gov/list/series?name=TIP-Series-Treatment-Improvement-Protocols-TIPS-) includes best-practice guidelines for the provision of interventions and therapies for individuals with substance abuse disorders.

TWO (2) or more failures of buprenorphine/naloxone or buprenorphine treatment requiring a re-start within the previous 12 months **NOTE:** TWO (2) or more treatment failures warrant further assessment of the member. A higher level care, such as a methadone treatment program, may be recommended by Molina Pharmacy/Medical Reviewer. Molina Healthcare may contact the Prescriber for further discussion of treatment plan and review on a case-by-case basis. [MOLINA MEDICAL DIRECTOR REVIEW MAY BE REQUIRED]

EXCEPTIONS: Exceptions may be made on a case-by-case basis by a Molina Pharmacy/Medical Reviewer.

- Urine Drug Screen/Test (UDS/UDT) for continuation of therapy **randomly every 1 to 3 months (*minimum of eight times per year*) OR as frequently as appropriate** [DOCUMENTATION REQUIRED]

AND

UDS/UDT is **NEGATIVE** for the following drugs dated *within 30 days* of this request [DOCUMENTATION REQUIRED] **[ANY]**

- Amphetamines [i.e. amphetamine, methamphetamine, ecstasy (MDMA)]
- Benzodiazepines [Appendix 4]
- Illicit substances [i.e. Cocaine (benzoylecgonine: cocaine metabolite); Methylenedioxymethamphetamine (MDMA)(Ecstasy); Hallucinogens (e.g. PCP)]
- Marijuana (THC)
- Muscle Relaxants (i.e. carisoprodol)
- Opioids [morphine, codeine, monoacetylmorphine (heroin metabolite), hydrocodone, hydromorphone, oxymorphone, oxycodone, methadone, and buprenorphine or norbuprenorphine; tramadol]
  NOTE: Monitor opioid use in accordance to respective State prescription drug monitoring program
- Sedative/hypnotic agents (i.e. non-benzodiazepine hypnotics and phenobarbital containing agents

MOLINA REVIEWER: Verify utilization of the listed drugs in member's prescription claims history

EXCEPTION: If drug screen is POSITIVE for ANY of the above substances, Prescriber must submit an acknowledgement and rationale for requesting continued therapy despite a positive drug screen. Continuation of therapy will not be authorized unless written documentation is submitted for Molina Pharmacy/Medical Director Review [DOCUMENTATION REQUIRED]

NOTE: Molina Healthcare reserves the right to request supporting documentation and/or cancel an authorization at any point if the member no longer meets the continuation of therapy coverage criteria (such as filling a narcotic agent, failure to adhere to a counseling program, or if drug screens are positive for other abuse substances).

Note: UDS/UDT must be obtained, interpreted and documented at the initial assessment as it provides information about current substance use, which aids in the diagnosis and the treatment planning process (i.e. an opioid-dependent patient who is currently abstinent but at high risk of relapse may require more frequent monitoring)

- UDS/UDT is **POSITIVE*** for buprenorphine and/or norbuprenorphine [DOCUMENTATION REQUIRED]
  *Presence of norbuprenorphine indicated by a POSITIVE result indicates that the member is taking drug as opposed to adulterating urine sample with tablets or films.

NOTE: A NEGATIVE UDS/UDT for buprenorphine alerts the Prescriber to possible non-compliance or possible diversion. Steps such as discontinuance of buprenorphine prescriptions should be addressed and considered in written documentation to Molina Healthcare. Continuation of therapy will not be authorized unless written documentation is submitted for Molina Pharmacy/Medical Director Review [DOCUMENTATION REQUIRED]

- ❑ Substance abuse disorders, untreated or unstable psychiatric conditions, or co-morbid conditions that may interfere with buprenorphine/naloxone compliance are being evaluated/monitored
  - *Untreated or inadequately treated psychiatric disorders can interfere with the effective treatment of addiction (Ziedonis et al.,2003; Khalsa et al., 2008).*
  - *Patients should achieve clinical stability before starting buprenorphine therapy. Patients should demonstrate social, cognitive and emotional stability. This may include: the absence of suicidal ideation and psychosis, attending scheduled appointments, no missed doses, improved social relationships, stable housing, and/or returning to work or school.*

- ❑ **Members with Behavioral Health Disorders ONLY:** Prescriber continues to oversee and monitor member's behavioral health care for co-existing behavioral health disorders [DOCUMENTATION]

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❑ Continuation of therapy based on the Prescriber's evaluation of positive outcomes and objectives, including but not limited to [ALL]
  - ❍ Achieved risk reduction for opioid overdose
  - ❍ Achieved risk reduction in associated adverse behavioral and/or medical comorbidities related to drug use
  - ❍ Compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
  - ❍ Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

  NOTE: If treatment goals are not being achieved, appropriateness of continuing the current treatment must be re-evaluated. Peer-to-Peer with Prescriber and Medical Director is recommended.

- ❑ Confirmation of abstinence from opioid medications (including tramadol) via **ONE (1)** of the following as applicable in accordance to State regulations: **[ONE]**

  - ❍ **FOR STATES WITH PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs):** Prescriber utilized (and will continue to utilize) the applicable State PDMP prior to issuance of a prescription or continuation of therapy request to ensure the member is not concurrently utilizing opioids, benzodiazepines or sedative/hypnotic agents. **NOTE:** PDMP check is required on date of request. Prescriber to confirm PDMP was checked today. [DOCUMENTATION REQUIRED]
    - *PDMPs are databases of all controlled substance prescriptions dispensed in a particular state and should be used to confirm opioid abstinence.*
    - *Refer to 'Appendix 3' or the following website for more further information on PDMPs: https://www.deadiversion.usdoj.gov/faq/rx_monitor.htm#1*

  - ❍ **FOR STATES WITHOUT PDMPs:** Prescriber agrees to review member's records AND/OR perform drug screens on a periodic basis or as necessary to ensure no abuse or diversion of the buprenorphine/naloxone or buprenorphine [DOCUMENTATION REQUIRED]
    - *The recommended clinical guidelines for the use of buprenorphine in the treatment of opioid addiction suggest that physicians periodically and regularly screen all patients for substance use and substance related problems.*

  NOTE: Buprenorphine/naloxone therapy may be discontinued due to compliance issues or poor adherence upon agreement with the Prescriber and/or Medical Director and should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the buprenorphine/dose may be progressively decreased over time in favorable cases until treatment can be discontinued. The decision to taper should be made by the prescriber, patient, and counsellor/support staff and communicated/discussed with Molina Medical Director. The risk of relapse following withdrawal of treatment should be considered.

4. FOR BUPRENORPHINE CONTINUATION OF TREATMENT REQUESTS ONLY

Member is unable to take buprenorphine/naloxone and meets the initial therapy 'Exception' criteria, documentation (medical records, chart notes, clinical/laboratory reports) supporting medical necessity for continuation of treatment is required **[ALL APPLICABLE]**

- ❑ **Pregnancy or Breastfeeding** [DOCUMENTATION REQUIRED]
  - *For women who are breastfeeding, opioid agonist treatment with methadone or buprenorphine is seen as the most appropriate treatment, taking into consideration effects on the fetus, neonatal abstinence syndrome, and impacts on perinatal care and parenting of young children.*

- ❑ **Prescribed for Buprenorphine Induction** [DOCUMENTATION REQUIRED]
  - *Buprenorphine/naloxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy under supervision. Patients should be switched to the combination product for maintenance and unsupervised therapy.*[e]

5. DISCONTINUATION OF THERAPY [ANY]

Molina Healthcare may request supporting documentation and/or cancel an authorization at any point if the member no longer meets the continuation of therapy coverage criteria.

- ❑ **Failure to meet ANY of the criteria** outlined in the 'Continuation of Treatment' section

- ❑ **Non-compliance** with clinically indicated supportive care or other ancillary services related to therapy for opioid dependence (diagnosis in current version of DSM)

- ❑ **Repeated misuse, abuse, or diversion** of buprenorphine, buprenorphine/naloxone or other controlled prescription medications

- ❑ **Inadequate response.** Maximum dose of 32 mg daily (*after* the induction phase) does not suppress physiologic signs and symptoms of withdrawal.
  - *Prescriber should re-evaluate treatment plan (e.g., for appropriateness of methadone treatment or injectable naltrexone) and a more intensive level of care considered.*

- ❑ **Goal of therapy met.** Although members may require long-term maintenance therapy, after a period of medical, psychiatric, social and substance abstinence stability, Prescriber and member may consider a monitored taper of buprenorphine or buprenorphine/naloxone therapy. Individual response to therapy should guide the determination to discontinue opioid substitution therapy.

- ❒ **Contraindications/Exclusions to buprenorphine/naloxone therapy [ANY]**

  Authorization will not be granted if ANY of the following conditions apply [ANY]
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity to buprenorphine or naloxone or any component of the formulation[a-e]
    - *Bronchospasm, angioneurotic edema, and anaphylactic shock, have been reported.*[a-e]

  Exclusions
  - ❍ Concurrent treatment of pain with an additional opioid analgesic
    - *Buprenorphine/naloxone is not appropriate for pain management; deaths have been reported in opioid-naive patients receiving oral buprenorphine for analgesia*[a-e]
  - ❍ Moderate to severe hepatic impairment (Child-Pugh B to C)
    - *Buprenorphine-naloxone may be ineffective in patients with severe liver impairment due to increased bioavailability of naloxone. Therefore therapy is not recommended in patients with severe liver impairment.*[k]
    - *Use with caution in patients with moderate hepatic impairment for maintenance treatment; due to reduced clearance of naloxone and potential for reduced buprenorphine efficacy, use may not be appropriate.*[a-e]
  - ❍ Decreased level of consciousness
  - ❍ Inability to provide informed consent

WARNINGS/PRECAUTIONS [NOT AN EXCLUSION; however Prescriber and Molina Reviewer should 'note' for further discussion on case-by case basis as necessary]

- Concurrent treatment with other opioids [Refer to Appendix 4]
- Concomitant use of alcohol and sedatives, hypnotics, or anxiolytics with opioids*
  **May contribute to respiratory depression. Patients with significant co-occurring substance use disorders, especially severe alcohol or sedative, hypnotic, or anxiolytic use, may require a higher level of care.*
- Untreated or unstable psychiatric conditions that may interfere with buprenorphine/naloxone compliance
- Acute severe respiratory distress, significant respiratory depression
  - *Use with caution in patients with preexisting respiratory compromise (hypoxia and/or hypercapnia), chronic obstructive pulmonary disease or other obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve and kyphoscoliosis or other skeletal disorder that may alter respiratory function; critical respiratory depression may occur, even at therapeutic dosages.*[a-e]

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

- ❑ Treatment plan for the member, including the following information:
  - ❍ Taper strategy/Drug Tapering Schedule: Only required for doses of greater than 16 mg
  - ❍ Frequency of office visits
  - ❍ Plan for psychosocial counseling
  - ❍ Precautions that will be taken to ensure that medications are not diverted for abuse such as drug screens, pill counts, and use of a prescription drug monitoring program

1. **Recommended Dosing Regimen [ALL]**
   Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

TABLE 1. Bunavail, Suboxone, buprenorphine/naloxone, Zubsolv

Initial Therapy: 3months (EXCEPT buprenorphine SL); Continuation of Therapy: 6 months

Drug	Average Daily Dose or Dosage Range	Maximum Daily Dose *buprenorphine component*	Dosage Strength
buprenorphine‡ sublingual tab	Induction Dose (titrated) **Usual maintenance dose: 12-16 mg SL QD**	24 mg	2 mg; 8 mg
Buprenorphine/naloxone‡ sublingual tab	Induction Dose (titrated) **Usual maintenance dose: 12-16 mg SL QD** Maximum dose: 24 mg SL QD **however some may require up to 32 mg QD*	24/6 mg	2 mg/0.5 mg; 8 mg/2 mg
Suboxone (sublingual film/tablet)	Dosing range: 4/1 mg to 24/6 mg SL QD **Usual maintenance dose: 16/4 mg SL QD**	24/6 mg	2mg/0.5mg 4mg/1mg 8mg/2mg 12mg/3mg
Bunavail (buprenorphine/naloxone buccal film)	**Usual maintenance dose: 8.4 mg/1.4 mg**	12.6mg/2.1mg	2.1mg/ 0.3mg, 4.2mg/ 0.7mg, 6.3mg/ 1mg
Zubsolv (buprenorphine/naloxone) sublingual tablet	Dosing range: 1.4-17.1 mg/day **Usual Maintenance Dose: 11.4 mg/2.9 mg SL QD**	17.1 mg /4.2 mg	1.4 mg /0.36 mg; 5.7 mg /1.4 mg

- ‡ = *generic available*
- *Buprenorphine buccal film and Suboxone sublingual (SL) film are not bioequivalent. Dose adjustments may be necessary.*
- *Buprenorphine exposure from buccal films has double the bioavailability of Suboxone tablets and film as a result only half the buprenorphine is required per dose.*
- *The difference in bioavailability of Zubsolv compared to Suboxone tablet requires different tablet strength to be given to the patient. One Zubsolv 5.7/1.4 mg SL tablet provides equivalent buprenorphine exposure to one Suboxone 8/2 mg SL tablet.*

TABLE 2. BUPRENORPHINE SUBLINGUAL TABLET		
ONE TIME INDUCTION FILL: One week (7 days) buprenorphine or buprenorphine/naloxone (maximum: #14 tabs of 8-2mg) available without PA to address urgent inductions needs of Molina members. Prescriber submit authorization request per MCP coverage criteria for Initial Therapy.		
	Initial Therapy	**Continuation of Therapy**
Induction therapy	**Up to 1 month** for the induction phase then should be converted to buprenorphine/naloxone maintenance therapy	A treatment plan of the transition to buprenorphine/naloxone. and agreed to by Prescriber and Molina Medical Director if the plan is longer than **thirty (30)** days for the member to taper off the medication
Pregnancy/Breastfeeding	Duration of pregnancy as deemed appropriate by Molina Clinical Reviewer	For duration of pregnancy/pregnancy as deemed appropriate by Molina Clinical Reviewer
Moderate to severe hepatic impairment (Child-Pugh B to C)	3 months	6 months
Maintenance therapy: For members meeting exception criteria **AND** unable to take naloxone-containing products due to a **documented** hypersensitivity to naloxone or naltrexone; intolerance, FDA-labeled contraindication, drug-drug interaction, history of toxic side effects that caused immediate or long-term damage	3 months	6 months

DOSING CONSIDERATIONS

- Induction protocols vary; the period of induction is incremental. Goal is to use the lowest effective dose that ameliorates symptoms (objectively represented by a low COWS score or may be subjectively reported by patient).
- Most patients will be stabilized on a daily dose of 16 to 24 mg of buprenorphine; however, some may require up to 32 mg daily. Current literature does not support greater efficacy with doses >32 mg/day.[B]
- Some patients can be maintained on a dose every other day or three times weekly.[B]
- TIP 40 recommended a maximum buprenorphine dose on day one of 8 mg. Clinical experience with this protocol suggests that many patients will still experience marked withdrawal symptoms after receiving a total of 8 mg on their first treatment day, and will be quite uncomfortable. Therefore many clinicians give repeated small doses of buprenorphine until the patient is comfortable, up to approximately 16 mg on day one. This is supported by the recently published consensus statement on use of buprenorphine from the American Society of Addiction Medicine (Kraus, J Addict Med, 2011) and the dosing guideline from the Physician Clinical Support System for Buprenorphine (PCSS-B).
- The rationale for exceeding the dosing guidelines from TIP 40 include the patient's likely level of discomfort, the need for using additional medications to help relieve symptoms if 8 mg is the maximum buprenorphine dose used on day one, and the concern that the patient will not persist with treatment if s/he or he does not believe that you are really able to relieve withdrawal symptoms adequately during early therapy (Mattick, 2003; Maremmani, 2010). A number of recent large-scale studies have used 16 mg as the maximum dose on day one of induction (e.g., Nielsen, 2012).

- **Stabilization phase**: focused on finding the optimal dose for the individual patient. This dose should eliminate all withdrawal symptoms, decrease opioid craving, ideally eliminate other opioid use, and provide maximal functional status (Joseph 2000; Baxter, 2009).
- **Most patients stabilize on 8 to 24 mg/day** (Comer et al., 2005a; Comer et al., 2005b). There is no precise way to determine in advance the optimal dose for a particular patient. Because buprenorphine has a long plasma half-life and an even longer duration of action at the mu opioid receptor, ideally approximately five days should be allowed between dose adjustments to assess the effect.
- The need for an increase up to **32 mg** for the highly tolerant patient may occur although it is seldom. If more than 16 mg per day appear to be needed clinically, the possibility of diversion or misuse should be assessed, particularly for patients who appear to need more than 24 mg per day.
    - *Conversely, if there is no diversion or misuse identified after thorough assessment, a recent study found that patients prescribed higher doses of buprenorphine were more clinically stable than those prescribed lower doses (Fareed, 2012).*

2. FOR REQUESTS EXCEEDING QUANTITY LIMITS

Requests that exceed the quantity limit [listed in Table 1] must also meet ALL of the Initial and Continuation of Therapy criteria **[ALL]**

- ❑ Member's medical record indicates that the requested dose is the lowest effective dose
- ❒ Clinical documentation supporting the request for a higher daily dose **up to 24 mg buprenorphine daily** for the management of opiate dependence. Requests for doses greater than 32 mg daily will NOT be authorized.
  NOTE: Current literature does not support greater efficacy with doses >32 mg/day and will NOT be authorized.
    - *The manufacturer of Suboxone (Reckitt-Benckiser Corporation) recommends that doses higher than 16 mg should be used with caution, with particular attention to signs of medication diversion, and that doses higher than 24 mg should be used rarely, if ever (reference REMS).*
- ❑ Complete treatment plan

3. Authorization Limit [ALL]

- ❒ Prescription claims confirm only **ONE (1)** buprenorphine or buprenorphine/naloxone product is authorized.

  MOLINA REVIEWER: All previous authorizations must be terminated prior to entering an authorization for a different product. Molina Healthcare will only authorize ONE (1) drug at a time for the duration authorized; however Prescriber may switch back and forth between different products in this class as deemed clinically appropriate for individual member [TABLE 1 & 2]

- ❑ Continuation of Treatment: ALL authorizations are subject to continued eligibility based on meeting ALL 'Continuation of Therapy' criteria and considered after review of clinical documentation (i.e. medical records, laboratory reports, progress notes, etc.).
- ❑ Quantity/Dosage Limit [ONE]
    - ❍ Dose requested is within the maximum recommended dosage limit [TABLE 1 & 2]
    - ❍ Dose requested exceeds the quantity limit and/or maximum dose recommended in FDA-approved labeling: Documentation in support of therapy with a higher dose for the intended diagnosis for review [Review by Clinical Pharmacist or Medical Director required] **[SEE CRITERIA FOR REQUESTS EXCEEDING QUANTITY LIMITS ABOVE]**

4. Route of Administration [ALL]

- ❑ Buprenorphine and buprenorphine/naloxone are used for **office-based management** treatment of opioid dependence, until information from the manufacturer, scientific literature, practice standards, or governing State or Federal agency indicates otherwise.
  - *The US National Institute on Drug Abuse considers buprenorphine and buprenorphine/naloxone as a first-line option for office-based management of opiate dependency.*[7]

- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy addresses the coverage of **Buprenorphine/Naloxone** for the treatment of **opioid dependence** when appropriate criteria are met.

All other uses of **Buprenorphine/Naloxone** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❍ Pain
  - Buprenorphine/naloxone is not recognized as an option of management of pain by any current treatment guidelines.[C,D] The NCCN, Clinical Practice Guidelines in Oncology, specifically recommends against the use of partial agonists, such as buprenorphine, as well as mixed agonist-antagonists in opioid-dependent patients, due to limited utility for treatment of pain and risk of potentiation of withdrawal.[E]
  - There is no useful evidence supporting the efficacy of buprenorphine/naloxone in the treatment of pain, as there are no studies of buprenorphine/naloxone for treatment of pain.
  - Buprenorphine/naloxone offers no proven additional clinical value over many generic alternatives for treatment of pain.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

SUMMARY OF EVIDENCE/POSITION

Opioid use disorder is '*a problematic pattern of opioid use leading to clinically significant impairment or distress*.'[G] Medication-assisted treatment of opioid use disorder prevents withdrawal, decreases illicit opioid use, reduces criminal activity, and improves social functioning.[H,I]

- Opioid Addiction[F1-F5]
  - Opioids are a class of drugs that include the illicit drug heroin as well as the licit prescription pain relievers oxycodone, hydrocodone, codeine, morphine, fentanyl and others.[F1]
  - Opioids are chemically related and interact with opioid receptors on nerve cells in the brain and nervous system to produce pleasurable effects and relieve pain.[F1]
  - Addiction is a primary, chronic and relapsing brain disease characterized by an individual pathologically pursuing reward and/or relief by substance use and other behaviors.[F2]
  - Of the 20.5 million Americans 12 or older that had a substance use disorder in 2015, 2 million had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin.[F3]
  - It is estimated that 23% of individuals who use heroin develop opioid addiction.[F4]
  - Drug overdose is the leading cause of accidental death in the US, with 55,403 lethal drug overdoses in 2015. Opioid addiction is driving this epidemic, with 20,101 overdose deaths related to prescription pain relievers, and 12,990 overdose deaths related to heroin in 2015.[F5]

- The U.S. National Institute on Drug Abuse has identified the medication as a **first-line treatment for opioid dependence**.[D]

- Pharmacologic treatment options for opioid use disorder
  - **Opioid agonist:** Methadone, morphine, heroin, oxycodone and hydromorphone are all full opioid agonists. These drugs bind to and activate mu opioid receptors in the brain. Increasing doses of full agonists produce increasing effects. [*NOT ADDRESSED IN THIS POLICY]
  - **Opioid antagonists:** Naltrexone and naloxone are examples of opioid antagonists. These drugs also bind to mu opioid receptors in the brain, but do not activate t hem. In binding to the receptors antagonists prevent the receptors from being activate d by agonists. Hence antagonists are blocking agents.
  - **Opioid partial agonists:** buprenorphine, buprenorphine/naloxone

BUPRENORPHINE/NALOXONE

- **Schedule III.** The Drug Enforcement Administration (DEA) categorizes buprenorphine in Schedule III of the Controlled Substances Act. Schedule III substances have a potential for abuse, but it is less than substances in Schedule II that include methadone, morphine, oxycodone, hydrocodone, and cocaine. The abuse of Schedule III substances, however, may still lead to physical dependence or psychological dependence. Review DEA's drug scheduling definitions to learn more.
- Prescription use of buprenorphine and naloxone is limited under the Drug Addiction Treatment Act (DATA)
- Pharmacology of Buprenorphine-naloxone
  - Buprenorphine: Buprenorphine exerts its analgesic effect via high affinity binding to mu opiate receptors in the CNS; displays partial mu agonist and weak kappa antagonist activity.[a-h]
  - Naloxone: Pure opioid antagonist that competes and displaces opioids at opioid receptor sites.[a-h]
- Due to extensive first-pass liver metabolism, oral dosing of buprenorphine is not feasible. Thus, buprenorphine is intended for sublingual administration, by which its bioavailability is relatively high (35–55%) while that of naloxone is low (10%). This contrast in properties allows the combination product of buprenorphine/naloxone (Suboxone®) to deliver the effects of the opioid without those of the antagonist.

- **Phases of Treatment**

Current maintenance treatment with buprenorphine consists of 3 phases: induction, stabilization, and maintenance.

1) **Induction:** Induction is the process of transferring a patient from other opioids onto buprenorphine. It is complicated by the fact that a patient must be in a state of mild-to-moderate withdrawal from the opioid s/he have been using (e.g. heroin or oxycodone) before s/he can safely be transferred onto buprenorphine. The reason for this is the very high affinity of buprenorphine for the opioid mu receptor in the brain. This phase consists of finding the minimum dose of buprenorphine at which the patient stops or significantly lessens use of other opioids and experiences no withdrawal symptoms, minimal or no side effects, and no craving for the drug(s) of abuse.
2) **Stabilization:** The stabilization phase is focused on finding the optimal dose for the individual patient. This dose should eliminate all withdrawal symptoms, decrease opioid craving, ideally eliminate other opioid use, and provide maximal functional status (Joseph, 2000; Baxter, 2009). The stabilization phase begins when a patient experiences no withdrawal symptoms, minimal or no side effects, and no uncontrollable cravings. Adjusting the dose of buprenorphine or naloxone may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance.
3) **Maintenance:** A stabilization period. The patient remains on the lowest effective dose for an indefinite amount of time, to suppress signs and symptoms of the disease of addiction. This allows the patient to prepare and make the necessary changes that would otherwise make long-term addiction remission unlikely.

ADJUNCT THERAPIES IN DETOXIFICATION

Cochrane review (L. Amato, Minozzi, Davoli, & Vecchi, 2011a) found that adding any psychosocial treatment to any detoxification treatment was beneficial in terms of reduced dropouts, use of opiates during treatment and at follow-up and clinical absences during treatment. However, in the studies included in the review, psychosocial interventions were delivered in conjunction with methadone or buprenorphine over periods ranging from 16 days to 26 weeks. With short-term detoxification (10 day s or less), support is important, but the capacity for psychosocial interventions is doubtful.

TESTING AND SCREENING FOR DRUG USE

- **Substance Abuse and Mental Health Services Administration (SAMHSA 2015)**[C]
  Federal Guidelines for Opioid Treatment Programs. HHS Publication No. (SMA) PEP15-FEDGUIDEOTP.

  Clinical drug testing is used for the purposes of diagnosis, monitoring, and evaluating progress in treatment and the promotion of long-term recovery.[C] Through drug testing, patients' use of specific drugs as well as the absence of prescribed medications, which may be an indication of diversion, can be identified. After the patient's initial drug test at admission, clinicians should determine the frequency of toxicological testing by evaluating the clinical appropriateness in relation to the patient's stage of treatment. All maintenance patients must receive a minimum of eight toxicology tests per year. The results of toxicological tests are an essential component in making decisions regarding take-home medication privileges; however, treatment decisions should not be based solely on toxicology screening results.

  Although testing panels typically include opioids (including prescription opioid analgesic compounds), benzodiazepines, barbiturates, cocaine, marijuana, methadone (and its metabolites), buprenorphine, amphetamines, and alcohol, they are not limited to these substances.[C] Clinicians should determine the drug-testing regimen by analyzing community drug-use patterns and individual medical indications. It is strongly recommended that benzodiazepines, barbiturates, and alcohol (using the ethyl glucuronide test) be included in drug screening and testing panels. Alcohol is the most widely used mood-altering substance in the United States, and benzodiazepines and barbiturates are often prescribed for detoxification and chronic seizure disorders. Detection of benzodiazepines, barbiturates, or alcohol is important in ongoing assessment, treatment planning, and medication management.

Substance Abuse and Mental Health Services Administration (SAMHSA)

- Recommendations for buprenorphine use in treatment of opioid addiction
  - Use buprenorphine/naloxone combination in most patients
  - Use buprenorphine monotherapy in
    - pregnant women for induction and maintenance
    - patients changing from long-acting opioids (methadone, levo-alpha-acetyl-methadol [LAAM]) for induction only
  - If buprenorphine monotherapy used for induction in non-pregnant patients, switch to buprenorphine/naloxone combination as early as possible (within 2 days)
  - Wait until patient is no longer intoxicated or experiencing any residual opioid effect before administering first dose of buprenorphine to avoid precipitated withdrawal syndrome

DEFINITIONS

- **Drug Enforcement Administration (DEA) Registration Number:** The DEA assigns the physician a special identification number. DEA regulations require this ID number to be included on all buprenorphine prescriptions for opioid addiction therapy, along with the physician's regular DEA registration number.

- **DSM-IV-TR:** The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), published by the American Psychiatric Association, is the handbook used most often in diagnosing mental disorders in the United States. The DSM has gone through five revisions (II, III, III-R, IV, IV-TR) since it was first published. The next version will be the DSM V, due in approximately 2011. The International Statistical Classification of Diseases and Related Health Problems (ICD) is a commonly-used alternative internationally.

APPENDIX

APPENDIX 1: DRUG ADDICTION TREATMENT ACT OF 2000 (DATA 2000)

Background: In 2000 Congress passed DATA-2000, a law that allows physicians, to become eligible to prescribe specially approved opioid-based medications specifically for the treatment of opioid addiction. Buprenorphine/naloxone (Suboxone®) and buprenorphine (Subutex®) became the first medications to be approved and affected by this law. If physicians take and pass an 8 hour course and meet other qualifications, they become eligible to apply for a special waiver which allows them to treat addiction with above mentioned medications in an office-based setting. This same law, void of any supporting science, arbitrarily caps the number of addicted patients a physician can treat at any one time to 30 through the first year following certification, expandable to 100 patients thereafter. No other medications have such restrictions, including the prescription drugs people get addicted to and die from. Like many well-intentioned laws, the unintended consequences are significant. https://www.naabt.org/data2000.cfm

Update 7/2016: In 2016 HHS amended the regulation to allow *qualifying* physicians to apply for permission to help up to 275 patients concurrently. Physicians must reapply every 3 years.
https://www.naabt.org/tl/275_patient_limit_increase_HHS_2016.pdf

Update 7/2016: On 7/22/2016 the Comprehensive Addiction and Recovery Act (CARA) of 2016 was signed into law. One of its provisions is to allow Nurse Practitioners and Physician Assistants to obtain a DATA-2000 waiver and prescribe buprenorphine for the treatment of Opioid Use Disorder. Prescribing was previously limited to physicians; however in 2016, Congress passed the Comprehensive Addiction and Recovery Act (CARA) to expand office-based treatment to allow nurse practitioners and physician assistants to prescribe buprenorphine for opioid addiction physician assistants and nurse practitioners to prescribe buprenorphine for addiction if they meet training and state-specific requirements. http://www.asam.org/magazine/read/article/2016/07/13/congress-passes-cara!-asam-applauds-passage-of-historic-addiction-legislation

APPENDIX 2: DEFINITION OF OPIOID USE DISORDER [A]

Diagnoses of opioid abuse and opioid dependence in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) were replaced by opioid use disorder (OUD) in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

DSM-5 OPIOID USE DISORDER[J]

DSM-5 opioid use disorder is defined as follows:[J]

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two (or more) of the following, occurring within a 12-month period:

1) Substance is often taken in larger amounts or over a longer period than was intended
2) There is a persistent desire or unsuccessful efforts to cut down or control opioid use
3) A great deal of time is spent in activities necessary to obtain the opioid, use the opioid or recover from its effects
4) Craving, or a strong desire or urge to use opioids
5) Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home
6) Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
7) Important social, occupational, or recreational activities are given up or reduced because of opioid use
8) Recurrent opioid use in situations in which it is physically hazardous
9) Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been cause or exacerbated by the substance
10) Tolerance, as defined by either of the following:
    a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect
    b) a markedly diminished effect with continued use of the same amount of the opioid; however, this criterion is not considered to be met for those taking opioids solely under appropriate medical supervision
11) Withdrawal, as manifested by either of the following:
    a) the characteristic opioid withdrawal syndrome
    b) opioids (or closely related substance) is taken to relieve or avoid withdrawal symptoms

NOTE: The severity of opioid use disorder at the time of diagnosis can be specified as a subtype based on the number of criteria present

- Mild: Presence of 2-3 symptoms
- Moderate: Presence of 4-5 symptoms
- Severe: Presence of 6 or more symptoms

Reference: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

DSM-IV-TR OPIOID DEPENDENCE

DSM-IV-TR opioid dependence, as a type of substance dependence, is defined as follows:

A **maladaptive pattern of substance use**, leading to clinically significant impairment or distress, **as manifested by** three (or more) of the following, occurring at any time in the same 12-month period:

1) Tolerance, as defined by either of the following:
    a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect **or**
    b) markedly diminished effect with continued use of the same amount of the substance
2) Withdrawal, as manifested by either of the following:
    a) the characteristic withdrawal syndrome for the substance (refer to criteria A and B of the criteria sets for withdrawal from the specific substances) **or**
    b) the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
3) The substance is often taken in larger amounts or over a longer period than was intended
4) There is a persistent desire or unsuccessful efforts to cut down or control substance use
5) A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects

6) Important social, occupational, or recreational activities are given up or reduced because of substance use
7) The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g. current cocaine use despite recognition of cocaine-induced depression, or continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

Reference: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Text Revision, Fourth Edition

DIAGNOSTIC CRITERIA FOR "OPIOID DEPENDENCE" BASED ON ICD-10

≥ 3 of the following during the previous 12 months

- Strong desire or compulsion to take opioids
- Difficulty in controlling opioid-use behaviors, specifically onset, termination, or level of use
- Physiologic withdrawal state when opioid use ceased or reduced resulting in either
  - Characteristic opioid withdrawal syndrome
  - Use of opioids (or closely related substances) in order to relieve or avoid withdrawal symptoms
- Tolerance (increased doses required to achieve effects originally achieved with lower doses)
- Progressive neglect of alternative pleasures or interests or increased amounts of time spent on obtaining opioids or recovering from their effects
- Persistent use despite negative consequences, such as depressive mood states after periods of heavy use or impairment of cognitive function (effort should be made to determine whether user actually, or could be expected to be, aware of nature and extent of impairment)

Reference: World Health Organization (WHO). Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. WHO 2009 PDF Available at: http://www.who.int/substance_abuse/activities/treatment_opioid_dependence/en/

APPENDIX 3: Prescription Drug Monitoring Program (PDMP)

A PDMP is a ***statewide*** electronic database which collects designated data on substances dispensed in the state. The PDMP is housed by a specified statewide regulatory, administrative or law enforcement agency. The housing agency distributes data from the database to individuals who are authorized under state law to receive the information for purposes of their profession

Each state designates a state agency to oversee its PDMP, which may include health departments, pharmacy boards, or state law enforcement. The Alliance of States with Prescription Monitoring Programs (**www.nascsa.org/rxMonitoring.htm**) maintains a list of state contacts.

The National Alliance for Model State Drug Laws (**www.namsdl.org/prescription-monitoring-programs.cfm**) provides links to each state's statutes and regulations regarding PDMPs.

- According to the Alliance of States with Prescription Monitoring Programs, (www.pmpalliance.org) as of October 16, 2011, 37 states have operational PDMPs that have the capacity to receive and distribute controlled substance prescription information to authorized users. States with operational programs include: *Alabama, Arizona, California, Colorado, Connecticut, Florida, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Massachusetts, Michigan, Minnesota, Mississippi, Nevada, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, West Virginia, and Wyoming.*
- Eleven states (Alaska, Arkansas, Delaware, Georgia, Maryland, Montana, Nebraska, New Jersey, South Dakota, Washington, and Wisconsin) and one U.S. territory (Guam), have enacted legislation to establish a PDMP, but are not fully operational.
- The California PDMP, known as CURES (Controlled Substance Utilization Review and Evaluation System) encourages judicious prescribing including use of the CURES system before prescribing controlled substances. visit http://oag.ca.gov/cures or http://www.deadiversion.usdoj.gov/faq/rx_monitor.htm

APPENDIX 4

[8-31-2016] A U.S. Food and Drug Administration (FDA) review has found that the growing combined use of opioid medicines with benzodiazepines or other drugs that depress the central nervous system (CNS) has resulted in serious side effects, including slowed or difficult breathing and deaths. Opioids are used to treat pain and cough; benzodiazepines are used to treat anxiety, insomnia, and seizures. In an effort to decrease the use of opioids and benzodiazepines, or opioids and other CNS depressants, together, we are adding *Boxed Warnings*, our strongest warnings, to the drug labeling of prescription opioid pain and prescription opioid cough medicines, and benzodiazepines.

Reference: Food and Drug Administration Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. August 31, 2016. Available http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm Accessed January 2017.

OPIOID PAIN AND COUGH MEDICINES* **The following is not a comprehensive list.*	
Generic Name	**Found in Brand Name(s)**
alfentanil	Alfenta
buprenorphine	Belbuca, Buprenex, Butrans
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Soma Compound w/ codeine, Tylenol w/ codeine, Prometh VC w/ codeine (cough), Triacin-C (cough), Tuzistra-XR (cough)
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER, Flowtuss (cough), Hycofenix (cough), Obredon (cough), Rezira (cough), Tussicaps (cough), Tussigon (cough), Tussionex Pennkinetic (cough), Vituz (cough), Zutripro (cough)
hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER

BENZODIAZEPINES AND OTHER CNS DEPRESSANTS*

The following is not a comprehensive list.

Drug Interactions with Benzodiazepines and Other Sedatives: Concomitant use of benzodiazepines has been reported in the literature to be implicated in buprenorphine non-fatal overdose and overdose deaths (Reynoaud M., 1998). In many of these cases users crushed and intravenously injected the buprenorphine. For adults, fatal overdoses almost always involve co-ingestion of buprenorphine with sedative-hypnotic drugs, such as benzodiazepines or barbiturates, or with large quantities of alcohol (Ferrant, 2011; Lai 2006; Schifano 2005). Therefore, it is recommended that concurrent prescribing of buprenorphine with sedative-hypnotics be used only when absolutely required for treatment of psychiatric illness unresponsive to other medications, and that the administration be closely monitored. Another reason to avoid this combination of medications is because of the significant abuse potential of benzodiazepines, and the fact that this medication class should generally be avoided in patients with an addiction history of any kind. Other CNS depressants, such as alcohol, may have a similar effect, and patients should be warned about this.

Generic	Brand Name(s)
alprazolam	Xanax, Xanax XR
chlordiazepoxide	Librium, Librax
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed
lorazepam	Ativan
oxazepam	No brand name currently marketed
quazepam	Doral
temazepam	Restoril
triazolam	Halcion
Other Sleep Drugs and Tranquilizers	
butabarbital sodium	Butisol
eszopiclone	Lunesta
pentobarbital	Nembutal
ramelteon	Rozerem
secobarbital sodium	Seconal sodium
suvorexant	Belsomra
zaleplon	Sonata
zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist
Muscle Relaxants	
baclofen	Gablofen, Lioresal
carisoprodol	Soma, Soma Compound, Soma Compound w/ codeine
chlorzoxazone	No brand name currently marketed
cyclobenzaprine	Amrix
dantrolene	Dantrium, Revonto, Ryanodex
metaxalone	Skelaxin
methocarbamol	Robaxin, Robaxin-750
orphenadrine	No brand name currently marketed
tizanidine	Zanaflex

ANTIPSYCHOTICS *Opioids (including methadone and buprenorphine) will exacerbate the sedative effects of antipsychotics, and some psychoactive medications, such as carbamazepine, will induce the metabolism of methadone and buprenorphine resulting in decreased plasma levels. There do not appear to be any interactions between naltrexone and antipsychotics.*	
aripiprazole	Abilify, Abilify Maintena, Aristada
asenapine	Saphris
cariprazine	Vraylar
chlorpromazine	No brand name currently marketed
clozapine	Clozaril, Fazaclo ODT, Versacloz
fluphenazine	No brand name currently marketed
haloperidol	Haldol
iloperidone	Fanapt
loxapine	Adasuve
lurasidone	Latuda
molindone	No brand name currently marketed
olanzapine	Symbyax, Zyprexa, Zyprexa Relprevv, Zyprexa Zydis
paliperidone	Invega, Invega Sustenna, Invega Trinza
perphenazine	No brand name currently marketed
pimavanserin	Nuplazid
quetiapine	Seroquel, Seroquel XR
risperidone	Risperdal, Risperdal Consta
thioridazine	No brand name currently marketed
thiothixene	Navane
trifluoperazine	No brand name currently marketed
ziprasidone	Geodon

APPENDIX 5: BUPRENORPHINE/NALOXONE PRODUCT AVAILABILITY

Table below is for reference only. Refer to FDA-approved labeling and manufacturer product information for updated information.

Product Name	Route	Dose form	Generic Name/Strengths		Market Status
			BUPRENORPHINE HYDROCHLORIDE	NALOXONE HYDROCHLORIDE	
buprenorphine	Sublingual	Tablet Sublingual	2 mg	--	Active
			8 mg	---	Active
buprenorphine HCl-naloxone HCl[2]	Sublingual	Tablet Sublingual	2 mg	0.5 mg	Active
			8 mg	2 mg	Active
Suboxone	Sublingual	Tablet Sublingual ***Discontinued***	2 mg	0.5 mg	Discontinued
			8 mg	2 mg	Discontinued
Suboxone	Sublingual	Film	2 mg	0.5 mg	Active
			4 mg	1 mg	Active
			8 mg	2 mg	Active
			12 mg	3 mg	Active
Bunavail	Buccal	Film	2.1 mg	0.3 mg	Active
			4.2 mg	0.7 mg	Active
			6.3 mg	1 mg	Active
Zubsolv	Sublingual	Tablet Sublingual	1.4 mg	0.36 mg	Active
			2.9 mg	0.71 mg	Active
			5.7 mg	1.4 mg	Active
			8.6 mg	2.1 mg	Active
			11.4 MG	2.9 MG	Active

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
NA	

HCPCS	Description
J0571	Buprenorphine, oral, 1 mg
J0572	Buprenorphine/naloxone, oral, less than or equal to 3 mg (Code Price is per 1 tab/film)
J0573	Buprenorphine/naloxone, oral, greater than 3 mg, but less than or equal to 6 mg (Code Price is per 1 tab/film)
J0574	Buprenorphine/naloxone, oral, greater than 6 mg, but less than or equal to 10 mg (Code Price is per 1 tab/film)
J0575	Buprenorphine/naloxone, oral, greater than 10 mg (Code Price is per 1 tab/film)

ICD-10	Description [For dates of service *on or after* 10/01/2015]
F11.20	Opioid dependence, uncomplicated
F11.22	Opioid dependence with intoxication
F11.23	Opioid dependence with withdrawal
F11.221	Opioid dependence with intoxication delirium
F11.222	Opioid dependence with intoxication with perceptual disturbances
F11.229	Opioid dependence with intoxication, unspecified
F11.24	Opioid dependence with opioid-induced mood disorder
F11.250	Opioid dependence with opioid-induced psychotic disorder with delusions
F11.251	Opioid dependence with opioid-induced psychotic disorder with hallucinations
F11.259	Opioid dependence with opioid-induced psychotic disorder, unspecified
F11.281	Opioid dependence with opioid-induced sexual dysfunction
F11.282	Opioid dependence with opioid-induced sleep disorder
F11.288	Opioid dependence with other opioid-induced disorder
F11.29	Opioid dependence with unspecified opioid-induced disorder

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