BlueCross BlueShield of Alabama

Buprenorphine and Buprenorphine/Naloxone for Opioid Dependence Prior Authorization, Quantity Limit and Concomitant Use of Opioid Products Program Summary

This prior authorization program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

Subutex/buprenorphine tablets are subject to prior authorization, quantity limits, and concomitant use of opioid products prior authorization restrictions.
All other products are subject to quantity limits and concomitant use of opioid products prior authorization restrictions.

Buprenorphine for Opioid Dependence Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the Buprenorphine for Opioid Dependence Prior Authorization (PA) with Quantity Limit (QL) program is to ensure appropriate selection of patients for treatment of opioid dependence in appropriate quantities according to product labeling and/or clinical guidelines and/or clinical studies.
The product(s) will not be covered for the treatment of pain. Claims for opioids during buprenorphine therapy will only be covered with prior authorization and only in the event of acute pain/surgery not to exceed 5 day course of treatment (see separate criteria below "Concomitant Use of Opioid Products with Buprenorphine and Buprenorphine/Naloxone").

TARGET AGENT(S)
buprenorphine

PROGRAM QUANTITY LIMIT

Brand (generic)	GPI	Multisource Code	Quantity Limit per 90 Days
buprenorphine[ac]			
2 mg sublingual tablet	65200010100760	M, N, O, or Y	5 tablets/90 days
8 mg sublingual tablet	65200010100780	M, N, O, or Y	5 tablets/90 days

a - Available as a generic and included in the quantity limit program.
c – Brand Subutex no longer available.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation for Induction and Stabilization
Please provide clinical notes to support information below.
Buprenorphine will be approved when ALL of the following are met and supported by the medical record (e.g., chart notes, physician letter of attestation):

1. The patient has an active diagnosis of opioid dependence
   AND

2. The 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, indicating that he or she is a qualified physician under the DATA to prescribe buprenorphine, to be verified by the clinical review entity with SAMHSA upon submission
   AND
3. The patient is 16 years of age or older
   AND
4. ONE of the following:
   a. The patient is currently enrolled in an ongoing outpatient drug addiction treatment program/counseling (appointment dates if available)
      OR
   b. The patient has agreed to enroll in an ongoing outpatient drug addiction treatment program/counseling within the initial approval timeframe of 2 months

   AND
5. Evidence of an initial patient assessment and treatment plan which includes ALL of the following:
   a. Medication history review
      AND
   b. Performance of baseline urine drug screen (test results not required)
      AND
   c. Current informed consent or written agreement for treatment of substance abuse signed by the prescriber and the patient

   AND
6. ONE of the following:
   a. The patient is not currently taking an opioid agent, including tramadol and tapentadol, to be verified by absence of claims in patient claims history upon request submission
      OR
   b. Notation that the patient will discontinue use with the prescribed opioid agent(s) prior to/with the initiation of buprenorphine

   AND
7. ONE of the following:
   a. The patient is either not currently taking other non-prescription drugs of abuse or alcohol or there is notation that the patient will discontinue use of non-prescription drugs and/or alcohol with initiation of buprenorphine
      OR
   b. The patient is not currently taking other addictive prescription medications (e.g. muscle relaxants, benzodiazepines, sedative/hypnotics), to be verified by absence of claims in patient claims history upon request submission
      OR
   c. The prescriber has submitted documentation indicating benefits of treatment/use of the listed prescription agent(s) outweighs risk associated with concomitant buprenorphine product use (to be reviewed and verified by a pharmacist or physician)

   AND
8. Authorization will only be provided for one buprenorphine or buprenorphine/naloxone agent (including implantable and injectable buprenorphine) at a time
   AND
9. ONE of the following:
   a. The quantity requested is less than or equal to the program quantity limit
      OR
   b. The quantity (dose) requested is within FDA-approved labeling and the prescriber has submitted documentation in support of therapy stating the need

for a higher dose which has been reviewed and approved by the Clinical Review pharmacist

OR

c. The patient is pregnant or has a documented intolerance, FDA labeled contraindication, or hypersensitivity to naloxone or naltrexone

Length of Approval: Allow for a single course of induction treatment within the quantity limit OR as requested and approved, based on submitted information up to 2 months OR duration of pregnancy if less than 2 months to term

Renewal Evaluation for Maintenance Therapy

Buprenorphine will be approved when ALL of the following are met and supported by the medical record (e.g., chart notes, physician letter of attestation):

1. The prescriber has verified the patient has been through induction and stabilization therapy and is **seeking approval for maintenance therapy**

   AND
2. The patient has an active diagnosis of opioid dependence (may be subject to verification upon submission or during authorization timeframe)

   AND
3. The 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, indicating that he or she is a qualified physician under the DATA to prescribe buprenorphine, to be verified with SAMHSA by the clinical review entity upon submission

   AND
4. ONE of the following:
   a. The patient is currently enrolled in an ongoing outpatient drug addiction treatment program/counseling (provider and appointment dates to be provided)

      OR

   b. The patient has completed 6 months or more of outpatient drug addiction treatment/counseling and the prescriber provides rationale as to why the patient no longer needs to continue (to be reviewed and verified by a pharmacist or physician)

   AND
5. The prescriber has submitted a current (within 30 days) patient assessment and treatment plan which includes **ALL** of the following:
   a. Medication history review

      AND

   b. Frequency of urine drug screening, including results of most recent drug screen indicating patient is free from illicit drug use or treatment plan has been adjusted based on the results of the drug screen

      AND

   c. Informed consent or written agreement for treatment of substance abuse signed by the prescriber and the patient

      AND

   d. Anticipated duration of therapy and plan for dose taper **OR documentation of barriers to drug taper** if patient is not a candidate for dose taper at this time

   AND
6. The patient is not currently taking an opioid agent, including tramadol and tapentadol, to be verified by absence of claims in patient claims history since last authorization (excluding short term use approved through the Concomitant Use of Opioid Products with Buprenorphine and Buprenorphine/Naloxone criteria below)

   AND

7. BOTH of the following:
    a. The patient is not currently taking other non-prescription drugs of abuse or alcohol
    AND
    b. ONE of the following:
        i. The patient is not currently taking other addictive prescription medications (e.g. muscle relaxants, benzodiazepines, sedative/hypnotics, non-prescription drugs of abuse or alcohol) to be verified by absence of claims in patient claims history upon request submission
        OR
        ii. The prescriber has submitted documentation indicating benefits of treatment/use of the listed prescription agent(s) outweighs risk associated with concomitant buprenorphine use (to be reviewed and verified by a pharmacist or physician)

AND

8. The patient continues to be compliant with all elements of the treatment plan <u>required at that time</u> (including but not limited to recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
AND
9. The prescriber has reviewed the patient's records in the state's prescription drug monitoring program (PDMP) as attestation that, to the best of the providers knowledge, the patient is not diverting the requested medication
AND
10. Authorization will only be provided for one buprenorphine or buprenorphine/naloxone agent (including implantable and injectable buprenorphine) at a time
AND
11. ONE of the following:
    a. The quantity requested is less than or equal to the program quantity limit
    OR
    b. The quantity (dose) requested is within FDA-approved labeling (e.g. Suboxone 24 mg, Zubsolv 17.2 mg, and Bunavail 12.6 mg) and the prescriber has submitted documentation in support of therapy stating a need for a higher dose which has been reviewed and approved by the Clinical Review pharmacist
    OR
    c. The patient is pregnant or has a documented intolerance, FDA labeled contraindication, or hypersensitivity to naloxone or naltrexone

Length of Approval: 6 months or duration of pregnancy if less than 6 months to term

Buprenorphine/Naloxone for Opioid Dependence Quantity Limit

OBJECTIVE
The intent of the Buprenorphine/Naloxone for Opioid Dependence Quantity Limit (QL) program is to ensure appropriate selection of patients for treatment of opioid dependence in appropriate quantities according to product labeling and/or clinical guidelines and/or clinical studies. These products will not be covered for the treatment of pain. Claims for opioids buprenorphine/naloxone therapy will only be covered with prior authorization and only in the event of acute pain/surgery not to exceed 5 day course of treatment (see separate criteria below "Concomitant Use of Opioid Products with Buprenorphine and Buprenorphine/Naloxone").

TARGET AGENTS
buprenorphine/naloxone
Bunavail™ (buprenorphine/naloxone)
Suboxone® (buprenorphine/naloxone)
Zubsolv® (buprenorphine/naloxone)
PROGRAM QUANTITY LIMIT

Brand (generic)	GPI	Multisource Code	Quantity Limit per Day
Bunavail (buprenorphine/naloxone)			
2.1 mg/0.3 mg buccal film	65200010208260	M, N, O, or Y	3 film/day
4.2 mg/0.7 mg buccal film	65200010208270	M, N, O, or Y	2 film/day
6.3 mg/1 mg buccal film	65200010208280	M, N, O, or Y	1 film/day
Suboxone (buprenorphine/naloxone)			
2 mg/0.5 mg sublingual tablet[ab]	65200010200720	M, N, O, or Y	3 tablets/day
8 mg/2 mg sublingual tablet[ab]	65200010200740	M, N, O, or Y	2 tablets/day
2 mg/0.5 mg sublingual film	65200010208220	M, N, O, or Y	3 films/day
4 mg/1 mg sublingual film	65200010208230	M, N, O, or Y	1 film/day
8 mg/2 mg sublingual film	65200010208240	M, N, O, or Y	2 films/day
12 mg/3 mg sublingual film	65200010208250	M, N, O, or Y	1 film/day
Zubsolv (buprenorphine/naloxone)			
0.7 mg/0.18 mg sublingual tablet	65200010200710	M, N, O, or Y	1 tablet/day
1.4 mg/0.36 mg sublingual tablet	65200010200715	M, N, O, or Y	3 tablets/day
2.9 mg/0.71 mg sublingual tablet	65200010200725	M, N, O, or Y	1 tablet/day
5.7 mg/1.4 mg sublingual tablet	65200010200732	M, N, O, or Y	1 tablets/day
8.6 mg/2.1 mg sublingual tablet	65200010200745	M, N, O, or Y	1 tablets/day
11.4 mg/2.9 mg sublingual tablet	65200010200760	M, N, O, or Y	1 tablet/day

a - Available as a generic and included in the quantity limit program.
b – Brand Suboxone tablets discontinued by manufacturer but may still be available.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Evaluation
Please provide clinical notes to support information below.
Quantities above the program set limit for **Bunavail/Suboxone/Zubsolv (buprenorphine/naloxone)** will be approved when ALL of the following are met and supported by the medical record (e.g., chart notes, physician letter of attestation):

1. The patient has an active diagnosis of opioid dependence
   AND
2. The 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, indicating that he or she is a qualified physician under the DATA to prescribe Bunavail, Suboxone, buprenorphine/naloxone, or Zubsolv, to be verified by the clinical review entity with SAMHSA upon submission
   AND
3. The patient is 16 years of age or older
   AND
4. Authorization will only be provided for one buprenorphine or buprenorphine/naloxone agent (including implantable and injectable buprenorphine) at a time
   AND
5. ONE of the following:
   a. The quantity requested is less than or equal to the program quantity limit
      OR
   b. The quantity (dose) requested is within FDA-approved labeling (e.g. Suboxone 24 mg, Zubsolv 17.2 mg, and Bunavail 12.6 mg) and the prescriber has submitted documentation in support of therapy stating the need for a higher dose which has been reviewed and approved by the Clinical Review pharmacist

Length of Approval: 6 months

Concomitant Use of Opioid Products with Buprenorphine and Buprenorphine/Naloxone

Prior Authorization for Opioid Use During buprenorphine or Bunavail/Suboxone/Zubsolv (buprenorphine/naloxone) therapy will be approved when the following are met:

1. The prescriber has submitted documentation supporting concurrent use of an opioid and the requested buprenorphine product due to one of the following:
   a. Dental procedure with dates
   b. Surgery with dates
   c. Acute injury with dates

Length of Approval: 5 days

Acceptable rationale and supporting documentation for concurrent opioid and buprenorphine/buprenorphine-naloxone use include clinical notes indicating treatment of acute pain with surgery, acute injury or dental procedure dates. The patient must remain enrolled in ongoing outpatient drug addiction treatment program/counseling if appropriate as established in original treatment plan.

Prior Authorization for Opioid Use for Chronic Pain Management during authorization period for buprenophine or Bunavail/Suboxone/Zubsolv (buprenorphine/naloxone) therapy will be approved when the following are met:

1. The prescriber has submitted documentation supporting use of the opioid for chronic pain management
   AND

2. The prescriber has indicated that the patient will no longer be using buprenorphine or Bunavail/Suboxone/Zubsolv

Buprenorphine or Bunavail/Suboxone/Zubsolv prior authorization will terminated with an effective date of the request review. Prior authorization will no longer be required for the opioid once the buprenorphine or Bunavail/Suboxone/Zubsolv PA will no longer be active in the system.

FDA APPROVED INDICATIONS AND DOSAGE[1-3,15-17]

Agent	Treatment of opioid dependence and induction; should be used as part of a complete treatment plan to include counseling and psychosocial support.	Maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support
buprenorphine sublingual tablet[ac]	✓	
Bunavail™ (buprenorphine/naloxone buccal film)	✓	✓
Suboxone® (buprenorphine/naloxone sublingual tablet)[ab]		✓
Suboxone® (buprenorphine/naloxone sublingual film)	✓	✓
Zubsolv® (buprenorphine/naloxone sublingual tablet)	✓	✓

a – Generic available.
b –Brand Suboxone tablets discontinued by manufacturer but may still be available.
c – Brand Subutex no longer available.

Under the Drug Addiction Treatment Act of 2000 (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence.

Dosing[1-3,15-17]
For the prevention of undue symptoms of opiate agonist withdrawal during induction of opiate agonist dependence treatment
NOTE: For induction treatment, single-agent buprenorphine is preferred.
For patients dependent on short-acting opioid products who are in opioid withdrawal, single agent buprenorphine or Suboxone (buprenorphine/naloxone) may be used for induction. For patients dependent on methadone or long-acting opioid products, single-agent buprenorphine is recommended.

Single agent buprenorphine induction is initiated with 8 mg sublingually on day 1, buprenorphine 16 mg sublingually on day 2, and then the patient should begin maintenance treatment. Dosage titration over 2 days rather than 3—4 days appears to result in greater treatment success.

Single-agent buprenorphine should be limited to a maximum of 5 days, except in pregnant women and patients with a documented allergy to naloxone or naltrexone. These patients should be allowed treatment with single-agent buprenorphine beyond 5 days.[4]

When determining treatment initiation, consider the opioid's duration of action, time since last opioid use, and degree of opioid dependence. Administer first dose of buprenorphine at least 4 hours after the last used opioid or preferably when early signs of opioid withdrawal appear. Use of buprenorphine/naloxone during induction may result in more withdrawal symptoms than if single-agent buprenorphine is used.

Bunavail induction can be used with patients dependent on heroin or short-acting opioid products. On Day 1, an induction dosage of up to 4.2 mg/0.7 mg buprenorphine/naloxone buccal film is recommended. Clinicians should start with an initial dose of 2.1 mg/0.3 mg buprenorphine/naloxone and repeat at approximately 2-hours, under supervision, to a total dose of 4.2 mg/0.7 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms. On Day 2, a single daily dose of up to 8.4 mg/1.4 mg buprenorphine/naloxone buccal film is recommended.

Suboxone induction is initiated with a recommended dose of up to 8 mg /2 mg on day one. Clinicians should start with an initial dose of 2 mg/ 0.5 mg or 4 mg/1 mg buprenorphine/naloxone and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms. On day 2, a single daily dose of up to 16 mg/4 mg Suboxone sublingual film is recommended.

Zubsolv induction is initiated with a recommended dose of up to 5.7 mg/1.4 mg on day one. This is administered sublingually in divided doses under supervision. Clinicians should start with an initial dose of 1.4 mg/0.36 mg ZUBSOLV sublingual tablet. The remainder of the day 1 dose of up to 4.2 mg/1.08 mg should be divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals. Some patients (e.g., those with recent exposure to buprenorphine) may tolerate up to 3 x 1.4 mg/0.36 mg ZUBSOLV sublingual tablets as a single, second dose. On Day 2, a single daily dose of up to 11.4 mg/2.9 mg ZUBSOLV sublingual tablet is recommended. All doses should be based on clinical need to control acute withdrawal symptoms and administered under supervision.

Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long-or short-acting opioid products), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating an opioid withdrawal syndrome, the first dose of buprenorphine/naloxone should be started only when objective signs of moderate withdrawal appear.

For maintenance treatment of opiate agonist dependence
NOTE: Buprenorphine/naloxone is preferred over single-agent buprenorphine for maintenance treatment, especially when drug administration will not be supervised. Only use single-agent buprenorphine for unsupervised administration in those patients who cannot tolerate buprenorphine/naloxone.

A suggested target dose of buprenorphine for Suboxone sublingual film or tablets is 16 mg once daily; however, doses ranging from 4—24 mg/day buprenorphine for Suboxone film or tablets may be required. Titrate dosage in increments of 2—4 mg/day to a dose that holds the patient in treatment and suppresses opiate withdrawal symptoms. Higher dosages (12—16 mg/day) have been associated with reduced opiate craving and fewer opiate-positive urine tests.

A suggested target dose of buprenorphine for Zubsolv is 11.4 mg once daily; however, doses for Zubsolv SL tablets ranging from 2.8-17.1 mg/day may be required. The dosage of Zubsolv should be progressively adjusted in increments/decrements of 1.4 or 2.8 mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

A target dose of buprenorphine for Bunavail buccal film is 8.4 mg once daily is suggested. However, doses ranging from 2.1-12.6 mg/day buprenorphine for Bunavail may be required. Dosage should be titrated in increments of 2.1 mg buprenorphine per day to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.

Buprenorphine and buprenorphine/naloxone is indicated for daily administration; however, efficacy has been demonstrated when the same total weekly dose is divided and given in 3 doses (i.e., dosing 3 times/week). Duration of treatment and the best method for drug discontinuation have not been determined; both abrupt discontinuation and dose tapering have been used. Withdrawal symptoms may occur upon discontinuation of buprenorphine/naloxone.

Switching Between Products[1-3,15-17]

Buprenorphine and buprenorphine/naloxone (Suboxone) sublingual tablets

Buprenorphine dosing for buprenorphine tablets and Suboxone is considered interchangeable

8 mg buprenorphine in buprenorphine tablets is equivalent to 5.7 mg buprenorphine (1.4 mg naloxone) dose within Zubsolv

Switching between buprenorphine/naloxone (Suboxone) sublingual tablets and buprenorphine/ naloxone (Suboxone) sublingual film

Start on same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Because of the potentially greater relative bioavailability of sublingual film compared to sublingual tablet, patients switching from sublingual tablet to sublingual film should be monitored for over-medication. Patients switching from sublingual film to sublingual tablet should be monitored for withdrawal or other indications of under-dosing.

Switching between Suboxone sublingual tablets and Zubsolv sublingual tablets

Suboxone Sublingual Tablet Dose	Corresponding Zubsolv Sublingual Tablet Dose
2 mg/0.5 mg buprenorphine/naloxone	1.4 mg/0.36 mg buprenorphine/naloxone
8 mg/2 mg buprenorphine/naloxone	5.7 mg/1.4 mg buprenorphine/naloxone
12 mg/3 mg buprenorphine/naloxone	8.6 mg/2.1 mg buprenorphine/naloxone
16 mg/4 mg buprenorphine/naloxone	11.4 mg/2.9 mg buprenorphine/naloxone

Switching between Suboxone sublingual tablets or film and Bunavail buccal film.

The difference in bioavailability of Bunavail compared to Suboxone sublingual tablet requires a different dosage strength to be administered to the patient. Patients should be started on the following corresponding dosage as defined below:

Suboxone Sublingual Tablet Dosage Strength	Corresponding Bunavail Buccal Film Strength
4/1 mg buprenorphine/naloxone	2.1/0.3 mg buprenorphine/naloxone
8/2 mg buprenorphine/naloxone	4.2/0.7 mg buprenorphine/naloxone
12/3 mg buprenorphine/naloxone	6.3/1 mg buprenorphine/naloxone

Maximum Dosage Limit[1-3,15-17]

For buprenorphine tablets and Suboxone or buprenorphine/naloxone tablets: 24 mg/day sublingually of the buprenorphine component.

For Zubsolv: 17.1 mg/day sublingually of the buprenorphine component.
Dosages higher than these have not been demonstrated to provide any clinical advantage.

For Bunavail: 12.6 mg/day buccal of the buprenorphine component.
Dosages higher than this have not been demonstrated to provide any clinical advantage.

CLINICAL RATIONALE
In October 2000, treatment of opioid dependence was transformed by Congressional approval of the Drug Addiction Treatment Act (DATA 2000). Under DATA 2000, qualified physicians may obtain a waiver allowing them to prescribe and/or dispense approved Schedule III-V medications for the treatment of opioid dependence. Previously, this type of treatment was available only in federally approved Opioid Treatment Programs (methadone clinics). Suboxone and Subutex (buprenorphine tablets) were the first narcotic drugs available under the Drug Abuse Treatment Act (DATA) of 2000 for treatment of opiate dependence that can be prescribed in a doctor's office. Only qualified doctors with the necessary DEA (Drug Enforcement Agency) identification number are able to start in-office treatment and provide prescriptions for ongoing medication.[1-3,5]

Efficacy
Buprenorphine is a semisynthetic mixed opiate agonist-antagonist. As a partial mu-receptor agonist, buprenorphine exhibits a ceiling to its pharmacological effects; thus, the danger of overdose, abuse liability, and toxicity from buprenorphine may be less than with full opioid agonists. Naloxone is a full opiate antagonist.[1,2] Since buprenorphine may be given outside of an opiate-treatment clinic, a formulation with naloxone (Suboxone, at a ratio of 4:1 buprenorphine: naloxone) was developed in an effort to dissuade patients from grinding up the Suboxone tablet and using as part of a combination of opiates that the user would inject. In this formulation, the naloxone component produces no clinical effect when administered sublingually; however, when dissolved in water and injected, the full opiate antagonist effect of naloxone occurs. As a result, the buprenorphine with naloxone combination product is preferred for maintenance therapy in patients with unsupervised drug administration.[1,2]

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.[1-3] In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone (Suboxone) tablets produced opioid agonist effects which reached a maximum between doses of 8/2 mg and 16/4 mg buprenorphine/naloxone (Suboxone). Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects.[1-3]

According to the Substance Abuse and Mental Health Services Administration (SAMHSA),[5] dosing can vary between 2mg/0.5mg (buprenorphine/naloxone) to 8mg/2mg (Suboxone) on the first and second day of induction, and up to 32mg/8mg during maintenance period. Dosing depends on the stabilization of withdrawal symptoms.[5] An observational retrospective chart-review study in 77 patients suggests that flexible dosing up to 32 mg buprenorphine (as Suboxone) per day has a potential benefit compared to lower doses.[14] However, it is important to note limitations of the study including but not limited to lack of randomization, a male-dominant population, and a small sample size which reduce generalizability and validity.[14]

Current prescribing information states the recommended target dose during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24mg/6mg have not been demonstrated to provide a clinical advantage.[1] Evidence used to gain the FDA approval demonstrated efficacy in doses up to 16 mg/4 mg per day through clinical trial data

with safety being supported in open label extensions in doses up to 24 mg/6 mg per day of the tablets. Justification for approval of the 24 mg/6 mg dose is based on data extrapolations comparing the pharmacokinetic profiles of the tablet and sublingual solutions.[19]

Buprenorphine is indicated for daily administration; however, administering the total weekly dose over three days (roughly every other day) may be effective in decreasing opioid dependence.[1,2] In one study, comparable reductions in illicit opioid usage were found with three treatments for opioid dependence: buprenorphine, methadone, and levomethadyl acetate. The dosages were individually optimized within a range of 16—48 mg three times a week for buprenorphine, 60—100 mg daily for methadone, and 75—161 mg three times a week for levomethadyl acetate.[6]

Buprenorphine and buprenorphine/naloxone placebo controlled randomized trials have demonstrated that buprenorphine/naloxone is safe and reduces the use of opiates and the craving for opiates among opiate-addicted persons who receive these medications in an office-based setting.[6,7] There is limited evidence comparing buprenorphine with methadone, but completion of withdrawal appears to be more likely with buprenorphine and withdrawal symptoms may resolve more quickly with buprenorphine.[7] In pivotal trials, buprenorphine and buprenorphine/naloxone was used in combination with psychosocial counseling.[1]

The US National Institute on Drug Abuse considers buprenorphine and buprenorphine/naloxone as a first line option for office based management of opiate dependency.[9]

The Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction issued by the US Dept of Health and Human Services recommends the following:

> "The consensus panel recommends that the buprenorphine/naloxone combination be used for induction treatment (and for stabilization and maintenance) for most patients. However, pregnant women who are determined to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy. In addition, patients who desire to change from long-acting opioids (e.g., methadone) to buprenorphine should be inducted using buprenorphine monotherapy."[5]
>
> "Patients and their physicians together need to reach agreement on the goals of treatment and develop a treatment plan based on the patient's particular problems and needs. During the stabilization phase, patients receiving maintenance treatment should be seen on at least a weekly basis. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, the physician may determine that less frequent visits (biweekly or longer, up to 30 days) are acceptable. During opioid addiction treatment with buprenorphine, toxicology tests for relevant illicit drugs should be administered at least monthly."[5]

The American Society of Addiction Medicine National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use recommends the following:[18]

- Buprenorphine mono-product is a reasonable and recommended alternative to methadone for pregnant women.
- Methadone is recommended for patients who may benefit from daily dosing and supervision in an opioid treatment program (OTP), or for patients for whom buprenorphine for the treatment of opioid use disorder has been used unsuccessfully in an OTP or office based opioid treatment (OBOT) setting.

Safety

A review of the safety profile of the combined buprenorphine/naloxone product was conducted for the US National Institute on Drug Abuse. The Institute supported the use of buprenorphine, alone or together with naloxone, as the first-line option for office-based management of opiate dependence. This support was based on three observations:[9]

- reduced likelihood of diversion of the combination product for diversion to illicit parenteral misuse
- established utility of the mono product for the treatment of opiate dependence
- preferable safety profile of a partial mu-opiate receptor agonist such as buprenorphine compared with that of a full mu-opiate receptor agonist

Although methadone has been used as the standard of care for the treatment and maintenance of opioid dependence, the association with QT interval elongation with methadone has caused concern. Neither buprenorphine or buprenorphine/naloxone appear to be associated with QT interval prolongation.[10] A meta-analysis of 13 randomized controlled trials concluded buprenorphine is an effective intervention for use in the maintenance treatment of heroin dependence, and is as effective as methadone at adequate dosages.[11]

Despite measures to prevent abuse with buprenorphine, diversion and abuse of buprenorphine/naloxone have steadily increased from 2005 through 2009.[12,13] The number of emergency department visits due to abuse/misuse with buprenorphine as one of the drugs listed increased monotonically from 5025 in 2006 to 17,546 in 2009 (R^2 = .98, an additional 4403 visits per year, p = .01).[12]

Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:[1,3,5,15-17]

1. Absence of medication toxicity
2. Absence of medical or behavioral adverse effects
3. Responsible handling of medications by the patient
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities)
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use)

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.[3]

REFERENCES

1. Buprenorphine prescribing information. Roxane Laboratories, Inc. September 2012.
2. Clinical Pharmacology. http://www.clinicalpharmacology-ip.com/Default.aspx Accessed on December 6, 2017.
3. Suboxone sublingual film prescribing information. Reckitt Benckiser Pharmaceuticals, Inc. February 2016.
4. Appropriate use recommendations for Suboxone® sublingual film, Suboxone® sublingual tablet and Subutex® sublingual tablet. Reckitt Benckiser Pharmaceuticals, Inc. September 2010.
5. Center for Substance Abuse Treatment. Clinical guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Treatment Improvement Protocol (TIP) series 40. DHHS Publication No. (SMA) 04-3939. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2004. Available at: http://www.naabt.org/documents/TIP40.pdf. Accessed June 2012.
6. Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343:1290-1297.
7. Fudala PJ, Bridge T, Herbert S, et al. Office-Based Treatment of Opiate Addiction with a Sublingual-Tablet Formulation of Buprenorphine and Naloxone. *N Engl J Med.* 2003;349(10):949-958.
8. Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal. *Cochrane Database of Syst Rev* 2009;July 8;(3)CD002025.

9. Bridge, TP, Fudala PJ, et al. Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence. *Drug Alcohol Depend*. 2003;70(2 Suppl):S79-85.
10. Orman JS, Keating GM. Buprenorphine/Naloxone - a review in the treatment of opioid dependence. *Drugs* 2009;69(5):577-607.
11. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database of Syst Rev.* 2008 Apr 16;(2):CD002207.
12. Johanson CE, Arfken CL, di Menza S, Schuster CR. Diversion and abuse of buprenorphine: Findings from national surveys of treatment patients and physicians. *Drug Alcohol Depend*. 2012 Jan 1;120(1-3):190-195. Epub 2011 Aug 20.
13. Dasgupta N, Bailey EJ, Cicero T, et al. Post-marketing surveillance of methadone and buprenorphine in the United States*. Pain Med*. 2010 Jul;11(7):1078-1091.
14. Fareed et al. Treatment Outcome for Flexible Dosing Buprenorphine during Maintenance Treatment. *Am. J. Drug Alcohol Abuse*. 2012 Mar;38(2):155-160.
15. Zubsolv prescribing information. Orexo US, Inc. September 2017.
16. Suboxone sublingual tablets prescribing information. Reckitt Benckiser Pharmaceuticals, Inc. June 2016.
17. Bunavail buccal film prescribing information. BioDelivery Sciences International. April 2017.
18. ASAM Guideline http://www.asam.org/practice-support/guidelines-and-consensus-documents/npg/supplement. June 2015.
19. Application Number: 022410Orig1s000. Center For Drug Evaluation And Research. Medical Review(s).

Additional Information

Client states that have a fully operational prescription drug monitoring program (PDMP) as of October 2012 are Alabama, Florida, Illinois, Kansas, Minnesota, New Jersey, New Mexico, North Carolina, North Dakota, Oklahoma, Texas and Wyoming. Montana and Nebraska have enacted PDMP legislation, but program is not yet operational (as of October 2012). Please visit http://www.deadiversion.usdoj.gov/faq/rx_monitor.htm or http://www.pmpalliance.org/pdf/pmp_status_map_2012.pdf for the most up to date information.

1. Alliance of States with Prescription Monitoring Programs, *Status of Prescription Drug Monitoring Programs (PDMPs)*, October 2012, http://www.pmpalliance.org/pdf/pmp_status_table_2012.pdf.
For a map, see http://www.pmpalliance.org/pdf/pmp_status_map_2012.pdf.