BUPRENORPHINE FORMULATIONS
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**OVERVIEW**

Buprenorphine for treatment of opioid use disorder comes in several formulations and can be taken in several ways. The form you take will reflect your individual needs and, to the extent possible, your preferences. In this chapter, you will learn:

- The formulations in which buprenorphine is supplied
- How the buprenorphine formulations differ
- The routes of administration for buprenorphine
- The clinical situation in which each route of administration can be used
HOW BUPRENORPHINE IS SUPPLIED

A Medication Guide is available for each formulation of buprenorphine. Your provider can either give you a copy of the guide for the formulation you are prescribed or help you obtain it. The selection of which buprenorphine formulation is best for each individual involves consideration of a number of factors, which will be presented in this guide.

**Three Formulations of Buprenorphine:**

1. **Oral-via Sublingual Or Buccal Medication**
   Buprenorphine/naloxone tablets or film which are taken by mouth are the formulations that have been the most widely used to treat opioid use disorder.
   Patients dissolve the tablet or film slowly under the tongue or through the mucosa of the cheek, depending upon the product used. The medication is absorbed through the lining of the mouth and is not to be swallowed. Any medication that is swallowed does not enter your bloodstream very well. Swallowed buprenorphine also may produce gastrointestinal symptoms.
   **Buprenorphine Combination with Naloxone**
   Most buprenorphine medications taken by absorption through the lining of the mouth (mucosa) and are combined with a drug called naloxone (a mu opioid antagonist). The extra drug, naloxone, blocks euphoria if the medication is misused by injection. It has little effect on the action and effectiveness of buprenorphine when taken through the oral mucosa, as intended. If you are dependent on opioids, injecting buprenorphine with naloxone may cause unpleasant withdrawal symptoms. A sublingual formulation of the medication with just buprenorphine and no naloxone, called monotherapy, is also available. Monotherapy is used if there is a naloxone allergy and may be used for patients who are pregnant.

2. **Implants Under The Skin**
   A buprenorphine implant that is inserted under the skin is an option after you have a stabilized dose of the sublingual or buccal medication. They are currently only effective if your dose is moderate to low (8 mg generic buprenorphine or lower).

3. **Injection**
   A monthly injectable form is available for patients who have been stabilized for at least 7 days on sublingual or buccal buprenorphine.
ORAL BUPRENORPHINE/NALOXONE COMBINATION

The 4:1 combination of buprenorphine HCl with naloxone HCl dihydrate taken by mouth has been the most widely used form for opioid addiction for many years\(^1\).

Buprenorphine/naloxone that is taken orally is available in several forms (tablet, film). Formulations taken by oral mucosa also vary by where they are placed in the mouth (under the tongue or “sublingual” vs. on the mucosal lining of the cheek or “buccal”), dosage (small differences), time to dissolve and be absorbed through oral mucosa, and flavor.

Abuse Potential
Despite the use of naloxone, buprenorphine medications are misused and diverted, and so it is recommended that you keep your medication supply in a locked container and dispose of any unused medication carefully.

Dangers of Accidental Exposure
Children, pets, and anyone who is not used to taking opioids may experience overdose symptoms from exposure to even a small amount of buprenorphine. This is another reason to keep your medication supply in a locked container and to dispose of any unused medication carefully.

CAUTION TIPS

• Call 911 for exposure to buprenorphine tablets or film in anyone who is not used to taking opioids. Keep in mind that signs of an overdose, including problems breathing, may develop later.

• The packaging for some formulations of buprenorphine may not include child safety measures. You can transfer your medication to containers with safety cap bottles.

Oral Formulations:
Buprenorphine/naloxone combination medication for daily oral use is available in several brands/formulations: Generic tablets, sublingual Zubsolv® tablets, Suboxone® sublingual film, buccal Bunavail™. A slightly different dose may be needed when switching between formulations, and your provider would advise you of any change needed.
GENERIC TABLETS

Combination Buprenorphine/Naloxone Tablets
The generic combination buprenorphine/naloxone tablet is dissolved and allowed to absorb sublingually (not swallowed).

- These tablets are available in 2 mg and 8 mg strengths.
- Clinicians and patients have found that they can easily cut the tablets. With precision and care, a 2 mg tablet can yield 0.5 mg doses; the 8 mg tablet can be cut to yield 2 mg doses for precise dosing.
- The usual maintenance doses in the U.S. for sublingual buprenorphine average 10-16 mg, but providers may individualize the dose.

Monotherapy Tablets
The buprenorphine monotherapy and buprenorphine/naloxone formulations have nearly identical effects when used as directed. Recommendations for the clinical use of one are also valid for the other unless specifically noted otherwise.

Almost all patients should be prescribed the buprenorphine/naloxone combination if not being maintained on the implant or receiving injections.

Monotherapy (buprenorphine without naloxone) is "a reasonable and recommended alternative to methadone for pregnant women". Evidence for the use of combination buprenorphine/naloxone in pregnancy was considered "insufficient." Although there is not much research available, monotherapy is also sometimes used during lactation.
COMBINATION FILM

Sublingual Film

- Suboxone® is a combination of buprenorphine and naloxone in the form of a thin film. This brand originally made a tablet form of the medication, but has discontinued it. In either form, this brand has had the most widely used formulation.
- The "film" is dissolved under the tongue and absorbed sublingually.
- The Suboxone film:
  - Is between the size of a nickel and a quarter
  - Comes in 2 mg, 4 mg, 8 mg, and 12 mg doses
  - Should not be cut, according to the medication guide (however, in practice, this is sometimes done to achieve a customized dose)
- Buprenorphine/naloxone sublingual tablet (Zubsolv®) has several differences in comparison with other formulations of combination buprenorphine/naloxone, including that they dissolve more rapidly and have greater bioavailability, which requires lower doses. For example, a 5.7 mg tablet of this formulation is the equivalent to an 8 mg tablet of Suboxone.

Buccal Film

A buccal buprenorphine/naloxone combination film formulation, (Bunavail™), is approved by the FDA. It is described as providing around twice the bioavailability of other available buprenorphine combination formulations, which may allow for lower doses. For example, a 4.2 mg film is equivalent to an 8 mg tablet of Suboxone. Product descriptions include a claim that fewer patients experience the side effect of constipation.

Switching Between Tablets And Film

The combination sublingual film is clinically interchangeable with combination sublingual tablets. However, a slight adjustment in dosage may be needed by some patients. Patients being switched between these two forms do NOT have to undergo an induction to change formulations.

However, the newer sublingual tablet (Zubsolv®) and buccal film (Bunavail™) may require dosage changes. Your provider will advise you about switching to these formulations from other formulations.
EXTENDED RELEASE IMPLANTS AND INJECTABLES

Two long-acting forms of buprenorphine are available that offer the advantage of not having to take them every day due to slow, extended release of the drug:

- An implant that is placed under the skin, lasting several months
- A monthly injection

Advantages of extended-release buprenorphine of implants and injectables include:

1. Ensure long-term compliance with taking medication
2. Provide steady levels of medication in the blood
3. Ensure a consistent dose, whereas absorption through oral mucosa is somewhat dependent on patient technique
4. Decreases loss of medication, theft, and diversion
5. Beneficial for patients who might have difficulty obtaining their buprenorphine, such as those who are incarcerated or travel extensively
6. Advantageous for patients who cannot use transmucosal buprenorphine – for example, due to sores in the mouth, lack of dexterity, such as after a stroke, or difficulty following the instructions to hold it in the mouth and let it slowly dissolve

Disadvantages:

1. These formulations cost more than transmucosal buprenorphine, especially the generic oral formulation – some pharma companies have offered various help to defray costs initially
2. Specific considerations, including side effects for each formulation, are discussed below.

Reduced Risk Of Accidental Exposure And Diversion

The buprenorphine implant and the injectable formulations reduce the risk of accidental exposure of others to the patient's medication supply. The injectable form may also help reduce diversion of the medication for recreational purposes by reducing the supply of single doses available for theft.
BUPRENORPHINE IMPLANTS

Implants
A subdermal buprenorphine implant, Probuphine®, was approved by the FDA in May, 2016. It releases a constant, low dose of buprenorphine into the bloodstream "for maintenance treatment of opioid dependence."

Implants: Basic Clinical Information:
- The implant only is appropriate for selected patients and in the maintenance phase only: Stable patients requiring a low/moderate dose of 8 mg per day or less. Clinical trials were in patients with ≥ 3 months of stability.
- The implants consist of small, inch long, solid rods made of a combination of ethylene-vinyl acetate and buprenorphine.
- Typically 4 implant rods are placed subdermally in a simple procedure by a physician, usually on the inside of the upper arm.
- The implants are placed surgically only by a healthcare provider who has completed specific training and certification, which including how to insert and remove the implant.
- Provider monitoring during the first week after implantation and no less than once monthly.
- Each implant placement is effective for 6 months and then must be replaced.
- Implants are for use as “part of a complete treatment program that includes counseling and psychosocial support.”

Implants: Efficacy And Safety Evidence For Implants
Research has shown that the implants are at least as effective as sublingual buprenorphine and even slightly better (96.4% responded vs. 87.6% for sublingual buprenorphine (p=0.034). The implant also produced superior rates of remaining free from illicit use of opioids (85.7% for implants vs. 71.9% for sublingual).

One study of patients who were stable on an appropriately low dose of sublingual buprenorphine found that a group switched to the implant had a lower relapse rate than the randomized control group that continued on sublingual buprenorphine (over 6 months: 85.7% vs. 71.9%).

Concerns regarding buprenorphine implants include:
- Some patients need to supplement their dose from the implant with sublingual buprenorphine.
BUPRENORPHINE INJECTABLE EXTENDED RELEASE

A subcutaneous injectable form of buprenorphine (Sublocade™) was approved by the FDA in late 2017 and became available for use in 2018. It is injected under the skin, that is, “subcutaneously”, by a health care provider as a once-monthly injection. It is only used in patients who have been stabilized at an effective dose of buprenorphine for at least one week on daily oral trans-mucosal buprenorphine. The medication is typically injected in the abdomen and forms a palpable depot subcutaneously from which the medication is slowly released over time. Injection by patients is not approved and is, in fact, dangerous because of the risk of intravenous injection.

Advantages of injectable over implants:
- Are available in higher doses than is available via implants
- Do not require a surgical procedure

Disadvantage of injectable over implant:
- Require monthly appointments
- Like implants, may need to be supplemented by daily oral mucosal medication if the dose given is too low

Patient Status Requirements
1. A stabilized dose of transmucosal buprenorphine for at least 7 days

Dose
- 300 mg is injected one per month for the first 2 months
- 100 mg are injected each month after that for maintenance; this may be increased to 300 mg for some patients not having enough therapeutic benefit from the lower dose
- Everyone gets the same dose, whether they had been on 8 or 16 mg in their daily dose
- Obtaining the medication: Providers may either prescribe it for the individual patient from a certified pharmacy. In this case, the patient must pick it up and bring it to the provider for the injection. Alternatively, some providers may be certified to supply the medication themselves.
- Storage: Store at 2-8 degrees Celsius (35.6-46.4 degrees Fahrenheit). May be stored in original package up to 7 days at room temperature before administration.
- Missed doses: Administer as soon as possible with the following dose no less than 26 days later.

Injectable Side Effects
- Some patients have reported withdrawal in week 2 or 3 of a monthly injection.
- Some patients have reported feeling like they are on too much medication.
- A visible lump is present under the skin of the abdomen and it is larger earlier in the month. It has been compared to the size of a silver dollar.

Injectable Risk:
Aside from the risks for any buprenorphine formulations:
- There is a risk of occlusion from an intravenous injection, and therefore it should only be injected subcutaneously and by a qualified health professional.
- If adverse reactions are requiring the medication be stopped before the end of the month, the depot must be surgically removed.
• A specific heart condition called a QT syndrome may be a contraindication.

Warning
The injectable formulation should only be injected by a qualified healthcare professional. Intravenous injection could result in serious harm.
BUPRENORPHINE FORMULATIONS COMPARISON

Products:

Suboxone® (Sublingual Film, Reckitt Benckiser)

- **How Supplied (Buprenorphine / Naloxone mg)**
  - 2 mg bup./0.5 mg nal.
  - 4 mg bup./1 mg nal.
  - 8 mg bup./2 mg nal.
  - 12 mg bup./3 mg nal.

- **Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
  - Increments/decrements of 2 mg bup./0.5 mg nal. or 4 mg bup./1 mg nal. up to 8 mg bup./2 mg nal.
  - Day 1 (in divided doses at around 2 hour intervals)
  - Day 2, administer up to 16 mg bup./4 mg nal. of sublingual film single daily dose.

- **Recommended Target Dose for Maintenance**
  - Target Dose: 16 mg bup./4 mg nal. single daily dose
  - (Range: 4 mg bup./1 mg nal. to 24 mg bup./6 mg nal. per day)

- **Instructions for Use**
  - Place film under the tongue, close to the base on the left or right side. Must be kept under tongue until completely dissolved.

Zubsolv® (Sublingual Tablet, Orexo)

- **How Supplied (Buprenorphine / Naloxone mg)**
  - 1.4 mg bup./0.36 mg nal.
  - 5.7 mg bup./1.4 mg nal.
  - Dissolves more rapidly, menthol flavor, and smaller tablet.

- **Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
  - Increments/decrements of 1.4 mg bup./0.36 mg nal. or 2.8 mg bup./0.72 mg nal.

- **Recommended Target Dose for Maintenance**
  - Target Dose: 11.4 mg bup./2.8 mg nal. single daily dose
  - (Range: 2.8 mg bup./0.72 mg nal. to 17.1 mg bup./4.2 mg nal. per day)

  - **Conversion Information**: One ZUBSOLV 5.7 mg bup./1.4 mg nal. sublingual tablet equivalent to one SUBOXONE 8 mg bup./2 mg nal. sublingual tablet

- **Instructions for Use**
  - Tablet should be placed under the tongue until dissolved.
  - Do not cut, chew, or swallow tablets.

Bunavail™ (Buccal Film, BioDelivery Sciences International)

- **How Supplied (Buprenorphine / Naloxone mg)**
Buprenorphine Formulations

- **2.1 mg bup./ 0.3 mg nal.**
- **4.2 mg bup./ 0.7 mg nal.**
- **6.3 mg bup./ 1 mg nal.**
  - Half a normal dose can achieve the same result as other products, due to twice the bioavailability.

**Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
- Increments/decrements of 2.1 mg bup./0.3 mg nal.

**Recommended Target Dose for Maintenance**
- Target Dose: 8.4 mg bup./1.4 mg nal. per day single daily dose
- (Range: 2.1 mg bup./0.3 mg nal. to 12.6 mg bup./2.1 mg nal. per day).
- Conversion information: BUNAVAIL 4.2 mg bup./0.7 mg nal. buccal film equivalent to a SUBOXONE 8 mg bup./2 mg nal. sublingual tablet

**Instructions for Use**
- Wet the inside of the cheek. Hold the film with the text (BN2, BN4, or BN6) facing up and place that side with the text against the inside of the cheek. Press and hold the film in place for 5 seconds.

**Generic Buprenorphine HCl & Naloxone HCl Dihydrate** (Sublingual Tablets, Actavis Elizabeth LLC)

- **How Supplied (Buprenorphine / Naloxone mg)**
  - 2 mg bup./0.5 mg nal.
  - 8 mg bup./2 mg nal.

- **Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
  - Increments/decrements of 2 mg bup./0.5 mg nal. or 4 mg bup./1 mg nal.

- **Recommended Target Dose for Maintenance**
  - Target Dose: 16 mg bup./4 mg nal. single daily dose
  - (Range: 4 mg bup./1 mg nal. to 24 mg bup./6 mg nal. per day).

- **Instructions for Use**
  - The tablet should be placed under the tongue until it is dissolved.

**Buprenorphine Without Naloxone** (HCl, Sublingual Tablet, Roxane Laboratories, Inc)

- **How Supplied (Buprenorphine / Naloxone mg)**
  - 2 mg bup.
  - 8 mg bup.

- **Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
  - Increment/decrements of 2 mg or 4 mg bup.
  - Up to 8 mg bup. on Day 1 and 16 mg bup. on Day 2.

- **Recommended Target Dose for Maintenance**
  - Target Dose: 16 mg bup. single daily dose
  - (Range: 4 mg bup. to 24 mg bup. per day).
• **Instructions for Use**
  ○ Put the tablet(s) under your tongue. Let them dissolve completely. While the tablets are dissolving, do not chew or swallow the tablet. Talking while the tablet is dissolving can also affect absorption.

**Probuphine®** (Subdermal Implant, Titan Pharmaceuticals, Braeburn Pharmaceuticals)

• **How Supplied (Buprenorphine / Naloxone mg)**
  ○ One inch long rods containing buprenorphine

• **Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
  ○ For use in patients already stable on a low to moderate dose of 8 mg buprenorphine or less per day. Placed surgically. Replaced at 6 months.

• **Recommended Target Dose for Maintenance**
  ○ Target dose is 8 mg or less per day

• **Instructions for Use**
  ○ The implant is typically placed inside the upper arm, under the skin, for 6 months. Requires specific REMS training and certification for the physician to insert and remove.

**Sublocade™** (Injectable, Invidior)

• **How Supplied (Buprenorphine / Naloxone mg)**
  ○ Comes pre-filled syringes with a 19 gauge 5/8-inch needle. In 100mg and 300 mg doses. Prescribe for the individual patient and have it sent from a certified pharmacy or become a REMS-certified clinic. Not dispensed to the patient.

• **Induction Dosage Increments** (until opioid withdrawal signs and symptoms are suppressed)
  ○ Not used for induction. For use after the patient is stabilized for at least one week on transmucosal buprenorphine.

• **Recommended Target Dose for Maintenance**
  ○ Target Dose: 300 mg monthly for two months, then 100 mg monthly but may be increased up to 300 mg if needed. See product information for details.

• **Instructions for Use**
  ○ Once monthly subcutaneous injection by a qualified health care provider after dose stabilized at least one week on submucosal buprenorphine. Forms a visible depot under the skin from which medication is slowly released over time.
**BUPRENORPHINE FOR PAIN**

The transdermal patch (Butrans®), injection (Buprenex®), and a newer buccal film (BELBUCA™) are the buprenorphine formulations that are FDA-approved for chronic pain control, but NOT opioid use disorder. A sublingual formula for pain is available in some other countries.

These formulations of buprenorphine are used to manage moderate to severe pain\(^{27-29}\). They are used for round-the-clock, long-term pain management rather than as-needed. They are used when alternative pain management options, such as non-opioid analgesics or immediate-release opioids, are inadequate.

Conversely, use of buprenorphine formulations for treating opioid use disorder to treat pain is considered off-label use. The formulation specifically for treating pain should be used to treat pain\(^{30}\).

**Like the formulations for treating opioid addiction, the formulations of buprenorphine for treating pain have the potential for physical dependence, drug interactions, abuse, and diversion.** See the specific product information of each formulation for details.
KEY POINTS

- Patient education regarding buprenorphine should include an understanding that you will be physically dependent on it, should not stop taking it abruptly, and will probably need to take it for a long time (years).
- Buprenorphine comes in a number of formulations that vary in route of delivery (absorption through the oral mucosa, implant, or injection) and, for oral delivery, rate of absorption.
- Provider selection of the best formulation for a patient is based on such factors as patient preference, cost and insurance coverage, availability at the pharmacy, dexterity, and the patient’s ability to understand and follow instructions.

Summary of Buprenorphine Formulations

Buprenorphine/naloxone tablets or film are the formulations that have been the most widely used to treat opioid use disorder. A buprenorphine subcutaneous implant is available for moderate to low dose maintenance (8 mg or lower). A monthly injectable form is available for patients having been stabilized for at least 7 days on submucosal buprenorphine. Monotherapy, buprenorphine without naloxone is "a reasonable and recommended alternative to methadone for pregnant women”\(^ {17}\). Evidence for the use of combination buprenorphine-naloxone in pregnancy was considered “insufficient.” However, many pregnant women have been treated successfully with buprenorphine.

Abuse Potential

- Buprenorphine has a risk for misuse, even in combination with naloxone.
- Buprenorphine should be kept in a locked cabinet to avoid risk of accidental poisoning, especially of children.
- Buprenorphine does have some addictive properties and is abused and so the precautions taken for any addictive substance to avoid abuse and diversion apply.
- Implants and injectable formulations may result in less diversion.

Drugs Characteristics And Additional Comments

**Buprenorphine/naloxone combination**

- Preferred formulation for most patients
- Buprenorphine/naloxone combination is the formulation preferred for most patients to treat opioid use disorder.

**Buprenorphine tablet (swallowed)**

- Formulation not available
- A swallowed formulation of buprenorphine is NOT available. Instead, it is allowed to dissolve slowly in the mouth and absorbed through the oral mucosa or slow release versions are implanted or injected.

**Naloxone**

- Abuse deterrent
- Naloxone is combined with buprenorphine as an abuse deterrent.

**Buprenorphine monotherapy**

- Formulation used in pregnancy
• In pregnancy, buprenorphine monotherapy without naloxone is recommended.

Buccal film
• Greater bioavailability than original buprenorphine formulas
• The buccal film has greater bioavailability than the original formula and some of the other formulations, so typically, a lower dose may be needed. Dosages vary by formula and so product information needs to be consulted.

Buprenorphine implant
• Reduces diversion and accidental exposure
• The buprenorphine implant is diversion resistant and reduces risk of accidental exposure.

Injectable buprenorphine
• Not used for induction
• Patients should be stabilized on submucosal buprenorphine for 7 days prior to being transferred to long-acting injectable buprenorphine.

Buprenorphine for Pain Control
• Patch
• Not to be used for the treatment of opioid addiction.
REFERENCES


