

Buprenorphine for the Treatment of Pain

Background

Buprenorphine is a semi-synthetic thebaine derivative, categorized as a mixed partial agonist opioid receptor modulator (opioid agonist-antagonist). It binds to various opioid receptors, and acts as a partial agonist at mu-opioid receptors and as an antagonist at kappa receptors. This opioid is used to treat opioid addiction in higher doses and chronic pain in lower doses. There are two properties that distinguish buprenorphine from other opioids. First, a ceiling effect occurs as the dose is increased. This contributes greatly to its safety profile but may limit its usefulness for treatment of severe, escalating pain. In other words, at high doses, the respiratory depressive and analgesic effects level off. In overdose situations, however, respiratory depression can still occur and will be more difficult to treat with naloxone compared to overdoses with other opioids due to buprenorphine's very tight binding to opioid receptors (very high naloxone doses of 10-35mg may be required).

Secondly, it has a bell-shaped dose-response curve. At moderate to high doses, the euphoric effects also level off, thus lowering its potential for misuse and overdose. The abuse potential of buprenorphine, although low, is further reduced in a transdermal preparation because the plasma levels slowly rise to a therapeutic level, unlike the rapid peak level that occurs with other formulations.

Buprenorphine has poor oral bioavailability due to significant first pass metabolism and therefore is not offered as an oral formulation. Buprenorphine is highly lipophilic and well absorbed by the oral mucosa. As such, transdermal, sublingual, and buccal formulations are available in addition to an injectable (intravenous/intramuscular) formulation.

Buprenorphine is currently available in four types of single agent products:

1. Butrans transdermal patch
2. Belbuca buccal film
3. Subutex sublingual tablet
4. Buprenex injectable solution

Butrans and Belbuca are FDA indicated for the treatment of chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Subutex is **not** FDA indicated for treatment of acute or chronic pain and carries a manufacturer warning against use as an analgesic due to reported deaths of opioid naïve patients receiving a buprenorphine 2 mg sublingual dose. Sublingual buprenorphine has been successfully studied for postoperative pain control, although caution is warranted if using off label for this indication given the manufacturer warning of fatal overdose at 2 mg in opioid naïve patients (Johnson, Fudala, Payne, 2005). Buprenex is indicated for acute moderate to severe pain. Buprenex has a slow onset of analgesic effect (15 minutes to onset, 1-3 hours to peak effect) and therefore may not be considered an ideal analgesic choice for acute pain management in comparison to other injectable opioids. Parenteral buprenorphine is approximately 30 times more potent than parenteral morphine (buprenorphine 0.3 mg ~ morphine 10 mg). Please note that all buprenorphine formulations do still carry a black box warning due to the risk of severe, life-threatening respiratory depression

Buprenorphine is also available in combination with naloxone for the treatment of substance abuse disorder in products such as Bunavail, Suboxone, and Zubsolv. These medications when used for opioid dependence are limited for use by qualified prescribers.

Initial dosing of Butrans patch:

For Opioid naïve patients: initiate treatment with a 5mcg/hr patch, replaced weekly.

Conversion from Other Opioids to Butrans: Discontinue all other around-the-clock opioids when Butrans therapy is initiated to reduce potential of precipitated withdrawal. Initial Butrans dose:

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)	<30 mg	30-80 mg
	↓	↓
Recommended BUTRANS Starting Dose	5 mcg/hour patch	10 mcg/hour patch

BUTRANS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalent. Consider the use of an alternate analgesic. Limitations of Use: Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation. Use with caution when prescribing with other medications which increase the QTc interval.

Initial dosing of Belbuca buccal strips:

For Opioid naïve patients: initiate treatment with a 75 mcg film once daily or, if tolerated, every 12 hrs.

Conversion from Other Opioids to Belbuca: To reduce the risk of opioid withdrawal, taper patients to no more than 30mg oral morphine equivalent daily before beginning Belbuca. Initial Belbuca dose:

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent) before taper	<30 mg	30-89 mg	90-160 mg
	↓	↓	↓
Recommended BELBUCA Starting Dose	75mcg QD-BID	150mcg q12h	300mcg q12h

BELBUCA may not provide adequate analgesia for patients requiring greater than 160 mg oral morphine equivalent per day. Consider the use of an alternate analgesic. The maximum daily dose of Belbuca is 900mcg.

Initial dosing of Buprenex injectable (IV/IM) formulation:

The usual dosage for persons 13 years of age and over is 1 mL buprenorphine hydrochloride injection (0.3 mg buprenorphine) given by deep intramuscular or slow (over at least 2 minutes) intravenous injection at up to 6-hour intervals, as needed. Repeat once (up to 0.3 mg) if required, 30 to 60 minutes after initial dosage, giving consideration to previous dose pharmacokinetics, and thereafter only as needed.

In high-risk patients (e.g., elderly, debilitated, presence of respiratory disease, etc.) and/or in patients where other CNS depressants are present, such as in the immediate postoperative period, the dose should be reduced by approximately one-half. Extra caution should be exercised with the intravenous route of administration, particularly with the initial dose.

References

Buprenorphine Is a Weak Partial Agonist That Inhibits Opioid Receptor Desensitization
Virk M, Arttamanghul S, Birdsong W T , Williams J T. The Journal of Neuroscience, 3 June 2009, 29(22): 7341-7348.

Transdermal buprenorphine in the management of persistent pain – safety aspects
Likar R. Ther Clin Risk Manag. 2006 Mar; 2(1): 115–125.

Butrans – buprenorphine patch, extended release [package insert]. Stamford, CT: Purdue Pharma L.P.; Revised 6/2014.

Belbuca – buprenorphine hydrochloride film [package insert]. Malvern, PA: Endo Pharmaceuticals Inc.; Revised 12/2015.

Pasero C, McCaffery M. Pain Assessment and Pharmacologic Management.
St. Louis: Mosby Elsevier; c2011. Section IV, Opioid Analgesics, Characteristics of Selected Agonist-Antagonist Opioids; p. 356-358.

Buprenex- Buprenorphine hydrochloride injection [package insert]. Lake Forest, IL:Hospira.; Revised 2/2016.

Johnson RE¹, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. J Pain Symptom Manage. 2005 Mar;29(3):297-326.

Subutex- Buprenorphine hydrochloride sublingual film [package insert]. Hull, UT:Reckitt Benckiser; Revised 6/2016.