

Dosing Guide

For Optimal Management of Opioid Dependence

Suboxone[®]
(buprenorphine HCl/naloxone HCl dihydrate) © sublingual
tablet

KEY POINTS

The goal of induction is to safely suppress opioid withdrawal as rapidly as possible with adequate doses of Suboxone[®] (buprenorphine HCl/naloxone HCl dihydrate) or Subutex[®] (buprenorphine HCl) sublingual tablets. The same induction procedures described in this brochure are applicable for medical withdrawal (ie, detoxification) or initiating Suboxone[®] or Subutex[®] maintenance.

Because buprenorphine (the primary active ingredient of Suboxone[®] and Subutex[®]) is a partial mu-opioid agonist with a maximal effect less than that of a full mu-opioid agonist (eg, morphine, methadone, heroin), the induction regimen can be more aggressive. The risk of serious adverse effects such as an overdose or treatment dropout is greater if a patient is undertreated with buprenorphine and continues to self-medicate withdrawal symptoms with opioids, alcohol, or other sedative-hypnotics, in particular benzodiazepines.

The goal of maintenance is to prevent the emergence of opioid withdrawal symptoms, suppress the patient's craving for opioids, and greatly attenuate the effect of self-administered opioids in patients who continue to episodically use illicit opioids.

In short- and long-term medical withdrawal (ie, detoxification), the goal is to rapidly achieve control of withdrawal symptoms so patients can fully participate in treatment including medical, psychosocial, psychiatric, etc.* Suboxone[®] and Subutex[®] have been shown to be effective treatments in relieving withdrawal symptoms during medical withdrawal (ie, detoxification) from short-acting opioids and are generally comparable to, or superior to, other pharmacological treatment options.† Subutex[®] can be administered in a residential setting or physician's office since it will be administered under supervision. Suboxone[®] is the preferred medication for use at home.

- **Note: The preferred medication for a patient to use at home is Suboxone[®].**
- **Note: Throughout this guidance, the dosage refers to the buprenorphine content of the tablets. The ratio of buprenorphine to naloxone in Suboxone[®] is 4:1. Naloxone is present in Suboxone[®] to deter the abuse of buprenorphine by injection.**

* Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

† Strain E, Stitzer ML. Introduction and historical overview. In: *Methadone Treatment for Opioid Dependence*. Strain E, Stitzer ML, eds. Baltimore, Md: The Johns Hopkins University Press; 1999.

DOSING GUIDANCE FOR SUBOXONE® & SUBUTEX®

A. MAINTENANCE THERAPY

The goal of induction is to safely suppress opioid withdrawal as rapidly as possible with adequate doses of Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) or Subutex® (buprenorphine HCl) sublingual tablets.

The same induction procedures are applicable for medical withdrawal (ie, detoxification) or initiating Suboxone® or Subutex® maintenance.

Because buprenorphine (the primary active ingredient of Suboxone® and Subutex®) is a partial mu-opioid agonist with a maximal effect less than that of a full mu-opioid agonist (eg, morphine, methadone, heroin), the induction regimen can be more aggressive. The risk of serious adverse effects such as an overdose or treatment dropout is greater if a patient is undertreated with buprenorphine and continues to self-medicate withdrawal symptoms with opioids, alcohol, or other sedative-hypnotics, in particular benzodiazepines.

1. Induction from short-acting opioids (eg, morphine, oxycodone, hydrocodone, heroin)

- Instruct patient on how to take a sublingual tablet and provide the patient information about induction.
- Administer patient's first dose (4 mg) of Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) or Subutex® (buprenorphine HCl) sublingual tablets after moderate opioid withdrawal symptoms have developed. Consider the use of an opioid withdrawal scale for patient assessment (eg, Clinical Opiate Withdrawal Scale [COWS]). Remind patient that opioid withdrawal symptoms are usually alleviated in 20-40 minutes following the first dose of buprenorphine.

If possible, observe the patient for 1-2 hours. Dispense or prescribe a second dose of 4 mg of Suboxone® or Subutex® if no precipitated withdrawal is observed. The usual first day dose is 8 mg. Clinicians have reported prescribing a third dose (2-4 mg) to be taken later in the evening if needed for withdrawal symptoms.

- Assess patient's response to first day's dosing. If opioid withdrawal symptoms were fully suppressed and patient is feeling no withdrawal between doses, then keep dose at first day's total dose; otherwise increase the dose by 2 or 4 mg on day 2.
- Assess patient's response to second day's dosing. If opioid withdrawal symptoms are fully suppressed and patient is feeling no withdrawal between doses, then keep the dose at second day's dose; otherwise increase the dose by 2 or 4 mg Suboxone® on day 3.
- After 3 days, once the patient is stable, or after a target dose of 16 mg Suboxone® or greater is achieved, continue at that dose for 3-7 days until steady-state levels are achieved before increasing the dose further.
- Doses should be decreased by 2 mg at a time if the patient experiences intoxication (not withdrawal effects).
- **Note: The goal is to induce treatment smoothly and suppress withdrawal as completely and rapidly as possible. Failure to do so may cause the patient to use opioids, alcohol, benzodiazepines, or other medications to alleviate opioid withdrawal symptoms or may lead to early treatment dropout.**

2. Induction from long-acting opioids (eg, OxyContin^{®*}, MS Contin^{®*}, methadone)

It is generally not recommended that stable methadone patients transfer to Suboxone[®] (buprenorphine HCl/naloxone HCl dihydrate) or Subutex[®] (buprenorphine HCl) sublingual tablets. However, patients may request to transfer from methadone to Suboxone[®] or Subutex[®] for many different reasons.

For example, individual responses to methadone are variable, including the occurrence of side effects and drug interactions. Some patients are reluctant to be on effective methadone doses and may prefer to be maintained on Suboxone[®] in a private office setting. A limiting factor for many patients considering maintenance treatment is the problem of dependence on the maintenance opioid. The pharmacological properties of Suboxone[®] or Subutex[®], including slow dissociation from mu-opioid receptors, and apparent mild withdrawal syndrome, may be perceived as a benefit by the patient. It is recommended that the physician review the risks/benefits of transferring from methadone to Suboxone[®] or Subutex[®] with the patient well in advance of the transition and provide the patient with realistic expectations during the transition.

Step 1: Preparation

The care of patients being treated in a opioid treatment program should be coordinated with the program until the last day of methadone dosing at the program. Instruct the patient on how to take a sublingual tablet and provide the patient information about induction. Patients transferring from methadone or other long-acting opioids to Suboxone[®] or Subutex[®] may experience discomfort for several days and dysphoria for up to 2 weeks. It is critical that your patient is prepared for this.

Step 2: Long-acting opioid dose adjustments

As a practical matter, it may be very difficult for some patients maintained on methadone or who are dependent on other long-acting opioids to reduce their dose. Splitting the dose may be helpful.

Transfer from long-acting opioids to Suboxone[®] or Subutex[®] is best achieved if the patient's equivalent methadone dose is first reduced to ≤ 30 mg/day where possible (normal transfer).

Transfers are possible between a >30 - 60 mg/day of equivalent methadone dose (high-dose transfer), although dose reduction to ≤ 30 mg/day followed by a normal transfer is preferred.

Patients on a >60 mg/day methadone-equivalent dose should have their dose reduced to a ≤ 60 mg/day methadone-equivalent dose before attempting a high-dose transfer.

Transfers from a >60 mg/day methadone-equivalent dose to Suboxone[®] or Subutex[®] are **not generally recommended**. There have been anecdotal reports of patients being transferred from methadone or other long-acting opioids to a short-acting opioid and then transitioned to Suboxone[®]. However, this may be allowable for only 3 days given federal regulations (21 CFR 1306.07).

Step 3: Stop long-acting opioid dosing

- **Normal Transfer** (from methadone-equivalent dose ≤ 30 mg):
 - At least 24 hours should elapse after the last long-acting opioid dose. The initial dose of Suboxone[®] or Subutex[®] should be administered when moderate signs (see COWS) of withdrawal are evident.

* OxyContin and MS Contin are registered trademarks of Purdue Pharma, L.P.

- **High-Dose Transfer** (from methadone-equivalent doses ranging from 30-60 mg):
 - No Suboxone[®] (buprenorphine HCl/naloxone HCl dihydrate) or Subutex[®] (buprenorphine HCl) sublingual tablets should be given after the last methadone or long-acting opioid dose **until the patient experiences maximal withdrawal discomfort (at least 48-96 hours after last dose). Earlier dosing with Suboxone[®] or Subutex[®] is highly likely to precipitate withdrawal.**
 - Be prepared to administer **limited amounts of withdrawal medication** (eg, clonidine, loperamide, sleep aid, NSAID, etc) for symptomatic relief.
 - High-dose transfer patients need careful monitoring and dose titration according to the response of the patient. If withdrawal symptoms have not worsened or have improved within 2-4 hours after the first dose of Suboxone[®] or Subutex[®], an additional 4-mg dose of Suboxone[®] or Subutex[®] is recommended. Clinicians have reported prescribing a third dose (2-4 mg) to be taken later in the evening if needed for withdrawal symptoms.

Step 4: Select initial Suboxone[®] or Subutex[®] dose

Note: The dosing of Suboxone[®] or Subutex[®] depends on the patient’s existing dose of long-acting opioid (labeled as the methadone-equivalent dose in the following table).

Last long-acting opioid dose	METHADONE-EQUIVALENT DOSE		
	≤10 mg	10–40 mg	40–60 mg
First day buprenorphine target dose	2-4 mg	4-8 mg	4-8 mg
Optional supplementary dose (2–4 hours after first dose)	Dose review not required	Dose review not required	Dose review required 2-4 mg additional if needed
Second day buprenorphine target dose	4 mg	8 mg (4-8 mg)	8 mg (6-10 mg)
Third day buprenorphine target dose	6 mg (6-8 mg)	12 mg (8-12 mg)	12 mg (10-16 mg)

See: National Clinical Guidelines on the Use of Buprenorphine in the Management of Heroin Dependence. Canberra: National Drug Strategy, Commonwealth of Australia. 2001. Lintzeris N, Clark NC, Muhleisen P, et al.

3. Dose adjustment/stabilization following induction

- You should aim to have reached a suitable maintenance dose of Suboxone[®] or Subutex[®] within 1-2 weeks.
- It takes from 3-7 days for steady-state blood levels to be achieved.
- After the patient is stabilized (2-3 days), once-a-day dosing should be possible.
- Doses should be titrated according to regular review of the following clinical signs/symptoms:
 - Intoxication, withdrawal, and cravings over the past 24 hours
 - Additional drug use and the patient’s reason for use of illicit street drugs or prescription opioids
 - Side effects or other adverse events
 - Adherence to dosing regimen
 - Patient’s expressed satisfaction

Adjustments to the Suboxone[®] (buprenorphine HCl/naloxone HCl dihydrate) or Subutex[®] (buprenorphine HCl) sublingual tablets dose should be made:

- At 3- to 7-day intervals
 - In 2- to 4-mg increases or 2-mg decreases if the patient experiences intoxication (not withdrawal effects)
- **It is believed that most patients can be stabilized on a dose between 12 mg and 16 mg; however, due to patient variability, each patient should be dosed to clinical effect. There is no maximum recommended dose; however, doses greater than 32 mg are not generally needed.**
 - **It is important to warn patients of the dangers of misusing benzodiazepines when taking Suboxone[®] or Subutex[®]. Overdose deaths have occurred when buprenorphine and benzodiazepines were concomitantly abused via the parenteral route.^{*†‡§} On at least one occasion, a buprenorphine overdose has been associated with oral benzodiazepine ingestion.[¶] Only two buprenorphine alone overdose deaths have been reported; in both cases, death was due to Mendelson's syndrome (ie, asphyxiation due to aspirating vomitus).[†]**
 - **As with all opiates, patients should be warned of the dangers of the self-administration of benzodiazepines when taking Suboxone[®] or Subutex[®].**

4. Maintenance dosing of Suboxone[®]

The goals of maintenance are to prevent the emergence of opioid withdrawal symptoms, suppress the patient's craving for opioids, and greatly attenuate the effect of self-administered opioids in patients who continue to episodically use illicit opioids.

Daily Dosing

- Clinical evidence suggests optimal daily doses will be between 12 mg and 16 mg. Higher doses have been utilized as needed.
- **Remember: As Suboxone[®] has less potential for intravenous abuse, ALL patients, except those who are sensitive to naloxone or who are pregnant, should be maintained on Suboxone[®] during maintenance to minimize diversion and misuse of the medication.**

Use in Pregnancy

- **There are no adequate and well-controlled studies of Suboxone[®] or Subutex[®] in pregnant women. Suboxone[®] or Subutex[®] should only be used during pregnancy if the potential benefit justifies the risk to the fetus. If a woman becomes pregnant (see attached full Prescribing Information: Use in Pregnancy) and, after weighing the risk/benefits, she decides to continue treatment with buprenorphine, Subutex[®] is the preferred medication.**

* Kintz P. Deaths involving buprenorphine: a compendium of French cases. *Forensic Sci Int.* 2001;121:65-69.

† Kintz P. Buprenorphine-related deaths. In: *Buprenorphine Therapy of Opiate Addiction*. Kintz P, Marquet P, eds. Totowa, NJ: Humana Press, 2002.

‡ Reynaud M, Tracqui A, Petit G, Potard D, Courty P. Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. *Am J Psychiatry.* 1998;155:448-449.

§ Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Annal Toxicol.* 1998;22:430-434.

|| Tracqui A, Tournoud C, Flesch F, et al. Buprenorphine poisoning in drug abusers on substitution therapy; 29 non-fatal and 20 fatal cases. *La Press Medicale.* 1998;27:557-561.

¶ Gaulier JM, Marquet P, Lacassie E, Dupuy JL, Lachatre G. Fatal intoxication following self-administration of a massive dose of buprenorphine. *J Forensic Sci.* 2000;45:226-228.

5. Dose reduction/medical withdrawal following maintenance

- Significant withdrawal symptoms are unusual during gradual Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) or Subutex® (buprenorphine HCl) sublingual tablets dose taper.
- The rate of dose reduction should be determined in collaboration with the patient.
- Prepare the patient for possible feelings of less energy, lower appetite, irritability, difficulty sleeping, etc. It is the duty of the physician to prepare patients for these effects in order to maximize their chance of a successful treatment outcome. However, these effects are transitory and should only last a few days.
- Realistic goals for reduction should be established.
- Generally, the more gradual the reduction, the better the outcome.
- Your patients should expect to experience some withdrawal discomfort once they reach low doses or stop taking Suboxone® or Subutex® completely.
- Slow down or stop the dose reductions if:
 - Your patient starts to reuse opioids
 - Your patient's physical, psychological, or social well-being begins to deteriorate
- Examples of dose reduction rates and schedules are shown below:

DOSE REDUCTION RATES	
<u>Daily buprenorphine maintenance dose</u>	<u>Dose reduction rate</u>
Above 16 mg of buprenorphine	4 mg every 1-2 weeks
8-16 mg of buprenorphine	2-4 mg every 1-2 weeks
Below 8 mg of buprenorphine	2 mg every 1-2 weeks

See: Buprenorphine: how to use it right. Johnson RE, Strain EC, Amass L. *Drug Alcohol Depend.* 2003;70:S59-S77.

DOSE REDUCTION SCHEDULES		
<u>Day</u>	<u>Equal reduction schedule</u>	<u>50% reduction schedule</u>
1-4	16 mg buprenorphine	16 mg buprenorphine
5-8	14 mg buprenorphine	8 mg buprenorphine
9-12	12 mg buprenorphine	4 mg buprenorphine
13-16	10 mg buprenorphine	2 mg buprenorphine
17-20	8 mg buprenorphine	0 mg buprenorphine
21-24	6 mg buprenorphine	
25-28	4 mg buprenorphine	
29-32	2 mg buprenorphine	
33-36	0 mg buprenorphine	

See: Buprenorphine: how to use it right. Johnson RE, Strain EC, Amass L. *Drug Alcohol Depend.* 2003;70:S59-S77.

6. Induction onto naltrexone

- To avoid precipitated withdrawal, it is generally recommended that naltrexone be initiated 3-5 days after the last dose of Suboxone[®] (buprenorphine HCl/naloxone HCl dihydrate) or Subutex[®] (buprenorphine HCl) sublingual tablets following dose taper.
- Prior to administering the initial dose of naltrexone, patients should receive a naloxone challenge (although not referenced in the literature, current best practice is that the initial dose of naloxone should be 1.0 mg followed every 15 minutes with an additional 1-mg dose until a cumulative dose of 4 mg naloxone is administered within 1 hour or until withdrawal signs and symptoms are observed) similar to that recommended following cessation of a full mu-opioid agonist if they have been maintained on a chronic dose of Suboxone[®] or Subutex[®] for a period greater than 7 days.*

7. Transfer to methadone

In a number of clinical trials, study participants were transferred to methadone at the completion of the trial or during the trial if the subject was not controlled by buprenorphine. There were no reported difficulties in transferring subjects directly from Suboxone[®] or Subutex[®] to methadone. The patient should be transferred to 30-40 mg of methadone and the dose titrated to clinical effect. The first daily dose can be split to assess the patient's response and then adjust the daily dose according to their response.

(See: National Clinical Guidelines on the Use of Buprenorphine in the Management of Heroin Dependence: Canberra: National Drug Strategy, Commonwealth of Australia. 2001. Lintzeris N, Clark NC, Muhleisen P, et al.)

* Johnson, R.E. Buprenorphine: clinical use from maintenance to special populations. In: New options in Australia: Buprenorphine – a gateway treatment for opioid dependence. *Research and Clinical Forums*. 2001; 23(1):25-41.

DOSING GUIDANCE FOR SUBOXONE® & SUBUTEX®

B. SHORT- AND LONG-TERM MEDICAL WITHDRAWAL (ie, detoxification) — INPATIENT AND OUTPATIENT

The goal of medical withdrawal is to rapidly achieve control of withdrawal symptoms so patients can fully participate in treatment, including medical, psychosocial, psychiatric, etc. Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) or Subutex® (buprenorphine HCl) sublingual tablets have been shown to be effective treatments in relieving withdrawal symptoms during medical withdrawal (ie, detoxification) from short-acting opioids and are comparable to, or superior to, other pharmacological treatment options.* Subutex® can be administered in a residential setting or physician's office since it will be administered under supervision. Suboxone® is the preferred medication for use at home.

The following procedure is recommended:

- Instruct the patient on how to take a sublingual tablet and provide the patient with information about induction.
- To avoid the risk of precipitated withdrawal, the first Suboxone® or Subutex® dose should be administered:
 - When moderate [see Clinical Opiate Withdrawal Scale (COWS)] signs of opioid withdrawal are observed
 - At a dose of 4-8 mg
- Daily dispensing of Suboxone® or Subutex® and review of the patient's status are preferred.
- Doses should be titrated upward according to the patient's:
 - Withdrawal severity
 - Cravings
 - Side effects
 - Other drug use
- Administer the patient's first dose (4 mg of Suboxone® or Subutex®) after moderate opiate withdrawal symptoms have developed. Consider the use of an opioid withdrawal scale for patient assessment (eg, COWS). Remind the patient that opioid withdrawal symptoms are usually alleviated in 20-40 minutes following the first dose of buprenorphine.
- Other withdrawal medications are not routinely required; however, in the event of sleep disturbances, **limited amounts of benzodiazepines (eg, 5-10 mg zolpidem, 10-20 mg temazepam) or antidepressants (eg, trazadone 50-100 mg as sleep aid for 2 nights)** may be prescribed. If benzodiazepines are prescribed: **instruct the patient that severe, potentially lethal, reactions may result from misuse of Suboxone® or Subutex® with benzodiazepines, especially when the two are misused together by injection.**

* Gowing L, Ali R, White J. Buprenorphine for the management of opioid withdrawal (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

Outpatient or inpatient dosing regimen

1. Outpatient dosing regimen

- A short-term flexible 5-8 day and fixed 20-36 day Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) or Subutex® (buprenorphine HCl) sublingual tablets-managed medical withdrawal (ie, detoxification) are shown.

Outpatient Dosing Regimen for Opioid Medical Withdrawal

a) Flexible Dosing Schedule:

Day	Recommended upper and lower limits	Recommended buprenorphine dose
1	4 to 8 mg buprenorphine	6 mg buprenorphine
2	4 to 12 mg buprenorphine	8 mg buprenorphine
3	4 to 16 mg buprenorphine	10 mg buprenorphine
4	2 to 12 mg buprenorphine	8 mg buprenorphine
5	0 to 8 mg buprenorphine	4 mg buprenorphine
6	0 to 4 mg buprenorphine	–
7	0 to 2 mg buprenorphine	–
8	0 mg buprenorphine	–

See: National Clinical Guidelines on the Use of Buprenorphine in the Management of Heroin Dependence. Canberra: National Drug Strategy, Commonwealth of Australia. 2001. Lintzeris N, Clark NC, Muhleisen P, et al.

b) Fixed Dosing Schedule:

- The same long-term fixed equal dose or percent dose reduction schedule for medical withdrawal can be used in outpatients who have or have not been previously maintained. See **Dose Reduction Schedules**.
- If the patient continues using opioids during an outpatient withdrawal episode, helpful options are:
 - Extension of the above regimens over several weeks
 - Transfer of the patient to inpatient withdrawal services (see examples of inpatient reduction schedules)
 - Transfer of the patient to long-term maintenance should be considered

2. Inpatient dosing regimen

- Inpatient regimens can be adapted according to the degree of monitoring and supervision available.
- Flexible or fixed dosing schedules can be used.
- Flexible and fixed dosing schedule with Suboxone® or Subutex® as shown on page 11.

Inpatient Dosing Regimen for Opioid Medical Withdrawal

a) Flexible Dosing Schedule:

Day	Recommended buprenorphine dose	Total daily dose
1	4 mg at onset of withdrawal, & additional 2 to 4 mg evening dose prn	4 to 8 mg
2	4 mg morning, with additional 2 to 4 mg evening dose prn	4 to 8 mg
3	4 mg morning, with additional 2 mg evening dose prn	4 to 6 mg
4	2 mg morning prn; 2 mg evening prn	0 to 4 mg
5	2 mg prn	0 to 2 mg
6	no dose	
7	no dose	

See: Buprenorphine dosing regime for inpatient heroin withdrawal: a symptom-triggered dose titration study. Lintzeris N, Bammer G, Rushworth L, Jolley DJ, Wheliam G. *Drug Alcohol Depend.* 2003;70:287-294.

b) Fixed Dosing Schedule:

Day	Buprenorphine dose		
	10-day	7-day	3-day
1	8 mg buprenorphine	8 mg buprenorphine	12 mg buprenorphine
2	6 mg buprenorphine	6 mg buprenorphine	8 mg buprenorphine
3	4 mg buprenorphine	4 mg buprenorphine	8 mg buprenorphine
4	4 mg buprenorphine	4 mg buprenorphine	
5	4 mg buprenorphine	2 mg buprenorphine	
6	2 mg buprenorphine	2 mg buprenorphine	
7	2 mg buprenorphine	0 mg buprenorphine	
8	2 mg buprenorphine		
9	2 mg buprenorphine		
10	0 mg buprenorphine		

See: Buprenorphine: how to use it right. Johnson RE, Strain EC, Amass L. *Drug Alcohol Depend.* 2003;70:S59-S77.

After the withdrawal episode

Having successfully become abstinent, patients should be encouraged to consider further treatment options to help them stay away from opioids. The options should be discussed as early as possible, including the possibility for ongoing psychosocial support and counseling, maintenance therapy, naltrexone treatment, self-help groups, or residential rehabilitation programs. Occasionally patients may, following medical withdrawal, request to be maintained on Suboxone® (buprenorphine HCl/naloxone HCl dihydrate) sublingual tablets (see induction protocol in these guidelines).