SUBSTANCE USE DISORDER AGENT | C-III

Buprenorphine-Naloxone

Suboxone, Zubsolv, Cassipa, Bunavail (discontinued)

Partial mu-agonist plus abuse-deterrent naloxone; first-line office-based maintenance treatment for opioid use disorder.

USUAL ADULT DOSE	HALF-LIFE	METABOLISM	ONSET
16 mg/4 mg SL daily	24-42 h (buprenorphine)	CYP3A4; UGT1A1/2B7	Withdrawal relief in 30-60 min

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for the treatment of opioid dependence as part of a complete plan that includes counseling and psychosocial support.
- First-line maintenance treatment for opioid use disorder, halving all-cause and overdose mortality compared with no medication treatment.
- The X-waiver was eliminated by the Consolidated Appropriations Act of 2023, so any DEA-registered clinician can prescribe it in ordinary office practice.
- Suitable for outpatient induction and maintenance without the daily-dispensing structure that federal rules impose on methadone.
- Used off-label for chronic pain in patients with opioid use disorder, though buprenorphine monoproducts are the labeled analgesic options.
- Adolescent use is supported by AAP and ASAM guidance even where the specific product label does not carry a pediatric indication.

DOSING & TITRATION

- Induce only when objective withdrawal is present, generally a COWS score of **8-12** or higher and 12-24 h after the last short-acting opioid.
- Day 1: give up to **8 mg/2 mg** in divided doses starting with 2 mg/0.5 mg to 4 mg/1 mg; Day 2 may be given as a single **16 mg/4 mg** dose.
- Maintenance is usually **16 mg/4 mg** daily with a labeled range of 4 mg/1 mg to 24 mg/6 mg; doses under 8 mg predict dropout and return to use.
- Low-dose or micro-dose cross-induction lets patients on fentanyl or methadone start without waiting for full withdrawal, an off-label but widely used approach.
- The film or tablet must dissolve fully under the tongue or against the cheek; it cannot be cut, chewed or swallowed, and no food or drink until dissolved.
- Taper gradually if stopping, but counsel that discontinuation sharply raises overdose risk and that indefinite maintenance is an acceptable outcome.

MECHANISM OF ACTION

- Buprenorphine is a partial mu-opioid agonist with a ceiling on respiratory depression, giving a wide safety margin relative to full agonists.
- Extremely high mu receptor affinity displaces full agonists, which relieves craving and blocks the effect of heroin, fentanyl and oxycodone.
- That same high affinity precipitates withdrawal if given while a full agonist still occupies receptors, which is why induction timing matters.
- Kappa receptor antagonism may contribute to improved mood and reduced dysphoria during early recovery on maintenance therapy.
- Naloxone has under **10%** sublingual bioavailability and is present only to deter injection, where it would precipitate withdrawal.

PHARMACOKINETICS

- Sublingual bioavailability of buprenorphine is roughly **30%**; swallowed drug is destroyed by first-pass metabolism and is clinically inert.
- Elimination half-life is **24-42 h**, which supports once-daily and even alternate-day dosing once a patient is stable on maintenance.
- Metabolized by CYP3A4 to the weakly active norbuprenorphine, then glucuronidated by UGT1A1 and UGT2B7 before mainly fecal excretion.
- CYP3A4 inhibitors such as ritonavir, ketoconazole and clarithromycin raise concentrations, while rifampin, carbamazepine and phenytoin can drop them into withdrawal.
- No renal dose adjustment is needed, but severe hepatic impairment raises exposure to both components and favors a buprenorphine monoproduct.

ADVERSE EFFECTS

- Constipation, headache, nausea, sweating, insomnia and oral mucosal irritation are the common complaints, each in roughly **10-15%** of patients.
- Dental caries, tooth loss and dental infections prompted an FDA safety communication in 2022; advise rinsing with water and delaying brushing.
- Precipitated withdrawal from premature induction is severe, prolonged and the main reason patients refuse to try buprenorphine again.
- Respiratory depression is uncommon alone but real when combined with benzodiazepines, alcohol, gabapentinoids or other sedatives.
- Transaminase elevation and rare hepatitis occur, particularly with hepatitis C coinfection or intravenous misuse of the formulation.
- Neonatal opioid withdrawal syndrome follows in utero exposure but tends to be milder and shorter than with methadone.

MONITORING

- Score withdrawal with COWS before the first dose and during induction, and document objective signs rather than patient report alone.
- Baseline liver function tests with periodic repeat, plus hepatitis B and C and HIV screening in anyone with injection drug use.
- Urine drug testing that distinguishes buprenorphine from norbuprenorphine helps confirm actual dosing rather than film tampering.
- Check the prescription drug monitoring program at initiation and periodically, and document counseling and psychosocial engagement.
- Ask about oral health at least yearly and refer for dental care given the caries signal with sublingual formulations.

INTERACTIONS & CAUTIONS

- Benzodiazepines and other CNS depressants raise respiratory depression risk, but the FDA specifically warns against withholding buprenorphine for that reason alone.
- CYP3A4 inhibitors including ritonavir, azole antifungals and macrolides increase exposure and may require a dose reduction.
- CYP3A4 inducers such as rifampin, carbamazepine, phenytoin and efavirenz can lower levels enough to cause withdrawal and craving.
- Naltrexone and other opioid antagonists are contraindicated, and full opioid agonists given for pain will be substantially blocked.
- Modest QT effects are far less than with methadone, but combine cautiously with other QT-prolonging drugs in patients with cardiac risk.

SPECIAL POPULATIONS

- Pregnancy: buprenorphine is a preferred medication for opioid use disorder; the combination product is increasingly considered acceptable, with monoproduct an alternative.
- Lactation: milk levels are low and breastfeeding is encouraged if the patient is stable and not using illicit drugs, with infant sedation monitoring.
- Pediatric labeling generally starts at age 16, but AAP and ASAM support treating younger adolescents with opioid use disorder off-label.
- Geriatric patients tolerate maintenance well; watch for sedation, constipation, falls and interactions with other CNS depressants.
- Hepatic: no change in mild disease, halve doses or avoid the combination product in moderate to severe impairment, and no renal adjustment is required.

PRESCRIBING PEARLS

- Wait for objective withdrawal, COWS **8-12** or higher, or you will precipitate a miserable withdrawal.
- No X-waiver since 2023: any DEA registrant can prescribe it in routine office practice.
- Aim for **16 mg/day**; under-dosing below 8 mg is the commonest cause of treatment dropout.

References

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NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.