Buprenorphine (Subutex®) sublingual tablets
Buprenorphine/naloxone (Suboxone®) sublingual film and sublingual tablets

Mechanism of Action
- Buprenorphine: partial mu-opioid receptor agonist and kappa-opioid receptor antagonist
- Naloxone: antagonist at the μ-opioid receptor, produces opioid withdrawal signs and symptoms when administered parenterally

Indications
- Treatment of opioid dependence

Pharmacokinetics
- Buprenorphine (Subutex®)
  - Absorption: Buprenorphine has rapid absorption following administration, with a bioavailability of 31%. There is wide inter-patient variability, with Cmax and AUC values increasing linearly with dose increased, although the increases are not directly proportional.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Analyte</th>
<th>Mean</th>
<th>Mean</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUCinf (h•ng/mL)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td>Buprenorphine</td>
<td>Mean</td>
<td>1.25</td>
<td>1.84</td>
<td>10.93</td>
<td>31.66</td>
<td>31.66</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.584</td>
<td>0.62</td>
<td>3.945</td>
<td></td>
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<td>12.66</td>
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<tr>
<td></td>
<td>Norbuprenorphine</td>
<td>Mean</td>
<td>0.301</td>
<td>2.36</td>
<td>12.39</td>
<td>39.28</td>
<td>20.85</td>
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<td></td>
<td>SD</td>
<td>0.127</td>
<td>2.75</td>
<td>4.526</td>
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<tr>
<td>8 mg</td>
<td>Buprenorphine</td>
<td>Mean</td>
<td>2.88 1.14</td>
<td>1.28 0.46</td>
<td>28.39</td>
<td>35.01</td>
<td>14.7</td>
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<tr>
<td></td>
<td>SD</td>
<td>1.38</td>
<td>1.75</td>
<td>10.22</td>
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</tr>
<tr>
<td></td>
<td>Norbuprenorphine</td>
<td>Mean</td>
<td>1.38 0.752</td>
<td>2.11</td>
<td>50.18</td>
<td>44.33</td>
<td>19.27</td>
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<tr>
<td></td>
<td>SD</td>
<td>0.752</td>
<td>2.11</td>
<td>22.61</td>
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<tr>
<td>16 mg</td>
<td>Buprenorphine</td>
<td>Mean</td>
<td>4.70 2.16</td>
<td>1.42 0.50</td>
<td>47.09</td>
<td>36.51</td>
<td>13.99</td>
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<tr>
<td></td>
<td>SD</td>
<td>4.70</td>
<td>1.42</td>
<td>20.03</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Norbuprenorphine</td>
<td>Mean</td>
<td>2.65 1.62</td>
<td>1.52 1.34</td>
<td>92.31</td>
<td>40.35</td>
<td>12.07</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>1.62</td>
<td>1.34</td>
<td>34.74</td>
<td></td>
<td></td>
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</tbody>
</table>
  - Distribution: The volume of distribution is 97 to 187 L in adults. It is 96% bound to alpha and beta globulin proteins.
  - Metabolism: Undergoes n-dealkylation via CYP3A4 to norbuprenorphine (active metabolite), as well as glucuronidation. Norbuprenorphine can go through further glucuronidation. Norbuprenorphine has been found to bind to opioid receptors in vitro, but it has not been studied clinically for opioid-like activity.
  - Elimination: Excreted 69% in the feces (33% unchanged) and 30% renally (1% unchanged), collected up to 11 days after dosing. In the urine, buprenorphine and norbuprenorphine were conjugated, in the feces, they were free. The mean elimination half-life is 31-35 hours.
• Buprenorphine/naloxone (Suboxone®), sublingual film
  o Absorption:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Analyte</th>
<th>Mean SD</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUCinf (h•ng/mL)</th>
<th>t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg/0.5 mg</td>
<td>Buprenorphine</td>
<td>Mean SD</td>
<td>0.947±0.374</td>
<td>1.72±0.60</td>
<td>8.65±2.85</td>
<td>33.4±13</td>
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<tr>
<td></td>
<td>Norbuprenorphine</td>
<td>Mean SD</td>
<td>0.312±0.140</td>
<td>2.26±2.03</td>
<td>14.5±5.77</td>
<td>56.0±31</td>
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<tr>
<td></td>
<td>Naloxone*</td>
<td>Mean SD</td>
<td>54.1±23.0</td>
<td>0.77±0.26</td>
<td>137.3±43.10</td>
<td>5.0±5.52</td>
</tr>
<tr>
<td>8 mg/2 mg</td>
<td>Buprenorphine</td>
<td>Mean SD</td>
<td>3.37±1.80</td>
<td>1.53±0.66</td>
<td>30.45±13.03</td>
<td>32.8±9.8</td>
</tr>
<tr>
<td></td>
<td>Norbuprenorphine</td>
<td>Mean SD</td>
<td>1.40±1.08</td>
<td>2.17±2.63</td>
<td>54.9±36.01</td>
<td>41.9±17.92</td>
</tr>
<tr>
<td></td>
<td>Naloxone*</td>
<td>Mean SD</td>
<td>193±91.2</td>
<td>0.81±0.19</td>
<td>480.8±201.0</td>
<td>6.25±3.14</td>
</tr>
</tbody>
</table>

*Naloxone Cmax expressed as pg/mL. Naloxone AUCinf expressed as h•pg/mL

  o Distribution: buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.
  o Metabolism: As above for buprenorphine. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo-group.
  o Elimination: As above for buprenorphine. Based on studies of film, buprenorphine has a half-life ranging from 24-42 hours and naloxone has an elimination half-life ranging from 2-12 hours.

• Buprenorphine/naloxone (Suboxone®), sublingual tablets
  o Absorption: There is a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects variability was low. Cmax and AUC increased in a linear fashion with increase in doses, but the increase was not directly proportional. Naloxone does not affect the pharmacokinetics of buprenorphine and levels were too low to assess dos-proportionality. At naloxone doses of 1mg, 2mg, and 4mg, levels above quantitation (0.05ng/mL) were not detected beyond 2 hours in seven of eight patients. There was overall a trend of increase in naloxone concentrations with increase in dose.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Suboxone® 4 mg</th>
<th>Suboxone® 8 mg</th>
<th>Suboxone® 16 mg</th>
<th>Subutex® 16 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, ng/mL</td>
<td>1.84 (39)</td>
<td>3.0 (51)</td>
<td>5.95 (38)</td>
<td>5.47 (23)</td>
</tr>
<tr>
<td>AUC0-48, hour. ng/mL</td>
<td>12.52 (35)</td>
<td>20.22 (43)</td>
<td>34.89 (33)</td>
<td>32.63 (25)</td>
</tr>
</tbody>
</table>

  o Distribution: as above for Suboxone® sublingual film.
  o Metabolism: as above for Suboxone® sublingual film.
  o Elimination: as above for Suboxone® sublingual film. Buprenorphine has a mean elimination half-life from plasma of 37 hours, naloxone has a mean elimination half-life from plasma of 1.1 hours.

Dosage
• Buprenorphine (Subutex®)
  o Induction: Initiate when objective signs of opioid withdrawal are evident, once daily. Individualize dose based on type and degree of opioid dependence and timing of last
dose. Titrate rapidly to effective dose. Buprenorphine plus naloxone typically replaced buprenorphine after 2 days.

- **Maintenance:** buprenorphine and naloxone preferred, but when patients cannot tolerate naloxone, solely buprenorphine can be used. Buprenorphine may be adjusted in increments/decrements of 2mg or 4mg to a level that hold the patient in treatment while suppressing opioid withdrawal signs and symptoms. Maintenance range is typically 4-24mg daily.

- **Dose Adjustments:**
  - Severe hepatic impairment: reduce initial and incremental dose during titration by one-half
  - Geriatric: start at low end of dosing range

- **Buprenorphine/naloxone (Suboxone®), sublingual film and tablets**
  - **Patients dependent on methadone or long-acting opioid products:**
    - Induction onto SL buprenorphine monotherapy recommended
  - **Maintenance:**
    - Adjust dose in 2mg/0.5mg or 4mg/1mg increments or decrements
    - Target dose is 16mg/4mg as single daily dose
    - Usual doses 4mg/1mg to 24mg/6mg
  - **Induction therapy for patients dependent on heroin or other short-acting opioids:**
    - Day 1: 2mg/0.5mg or 4mg/1mg SL film, may titrate up in 2-4mg increments of buprenorphine every 2 hours based on acute withdrawal symptoms to a target of 8mg/4mg
    - Day 2: administer up to 16mg/4mg SL film as a single daily dose

**Administration**

- **Sublingual tablets:** Should be placed under the tongue until dissolved. For doses requiring ≥ two tablets, patients should be advised to place all tablets at once or two tablets at once under the tongue. Swallowing the tablets reduces the bioavailability of the drug.
- **Sublingual film:** Place one film under the tongue, close to the base on the left or right side, allow to completely dissolve. May also do buccal administration, place one film on the inside of the left or right check and allow to completely dissolve. Do not cut, chew, or swallow film.

**Warnings/Precautions**

- **Warnings**
  - **Life-threatening respiratory depression**
    - Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route
    - A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly
    - Deaths also reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids
    - Suboxone® and Subutrex® should be used with caution in patients with compromised respiratory function
  - **CNS Depression**
    - Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression
When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered

- **Dependence**
  - Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper
  - Withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset

- **Addiction, abuse, and misuse**
  - Risk of opioid addiction, abuse, and misuse, which can lead to overdose and death
  - Assess each patient’s risk prior to prescribing and monitor all patients regularly for the development of these behaviors or conditions

- **Hepatitis, hepatic events**
  - Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports
  - Spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy

- **Use in ambulatory patients**
  - Suboxone® and Subutex® may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment
  - Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities
  - Like other opioids, buprenorphine may produce orthostatic hypotension in ambulatory patients

- **Head injury and increased intracranial pressure**
  - Like other potent opioids, buprenorphine may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased

- **Opioid withdrawal**
  - Because it contains naloxone, Suboxone® is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone
  - Because of the partial agonist properties of buprenorphine, Suboxone® and Subutex® may precipitate opioid withdrawal signs and symptoms in such persons if administered before the agonist effects of the opioid have subsided

**Precautions**

- **General**
  - Buprenorphine should be administered with caution in elderly or debilitated patients and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis
  - Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract
As with other mu-opioid receptor agonists, the administration of Suboxone® or Subutex® may obscure the diagnosis or clinical course of patients with acute abdominal conditions

- **Pregnancy**
  - Category C
  - Buprenorphine was not teratogenic in rats or rabbits
  - Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after sc administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), but were not observed at oral doses up to 160 mg/kg/day
  - Buprenorphine HCl sublingual tablets should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus
  - Neonatal withdrawal has been reported in the infants of women treated with buprenorphine HCl sublingual tablets during pregnancy

- **Lactation**
  - Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk; breast-feeding is therefore not advised in mothers treated with buprenorphine HCl sublingual tablets

- **Contraindications**
  - Contraindicated in patients who have shown to be hypersensitive to buprenorphine

### Adverse Reactions

- Safety of Suboxone® has been evaluated in 497 opioid-dependent subjects
- The prospective evaluation of Suboxone® was supported by clinical trials using Subutex® and other trials using buprenorphine sublingual solutions
- In total, safety data are available from 3,214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction
- In a comparative study, adverse event profiles were similar for subjects treated with 16 mg Suboxone® or 16 mg Subutex®

<table>
<thead>
<tr>
<th>Body System / Adverse Event (COSTART Terminology)</th>
<th>N(%) Buprenorphine and naloxone sublingual tablets 16 mg/day N=107</th>
<th>N(%) Buprenorphine HCl sublingual tablets 16 mg/day N=103</th>
<th>N(%) Placebo N=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Asthenia</td>
<td>7 (6.5%)</td>
<td>5 (4.9%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Chills</td>
<td>8 (7.5%)</td>
<td>8 (7.8%)</td>
<td>8 (7.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>39 (36.4%)</td>
<td>30 (29.1%)</td>
<td>24 (22.4%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6 (5.6%)</td>
<td>12 (11.7%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Pain</td>
<td>24 (22.4%)</td>
<td>19 (18.4%)</td>
<td>20 (18.7%)</td>
</tr>
<tr>
<td>Pain Abdomen</td>
<td>12 (11.2%)</td>
<td>12 (11.7%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Pain Back</td>
<td>4 (3.7%)</td>
<td>8 (7.8%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td>Withdrawal Syndrome</td>
<td>27 (25.2%)</td>
<td>19 (18.4%)</td>
<td>40 (37.4%)</td>
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<tr>
<td>Cardiovascular System</td>
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<tr>
<td>Vasodilation</td>
<td>10 (9.3%)</td>
<td>4 (3.9%)</td>
<td>7 (6.5%)</td>
</tr>
<tr>
<td>Digestive System</td>
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<tr>
<td>Constipation</td>
<td>13 (12.1%)</td>
<td>8 (7.8%)</td>
<td>3 (2.8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3.7%)</td>
<td>5 (4.9%)</td>
<td>16 (15.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (15.0%)</td>
<td>14 (13.6%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (7.5%)</td>
<td>8 (7.8%)</td>
<td>5 (4.7%)</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insomnia</td>
<td>15 (14.0%)</td>
<td>22 (21.4%)</td>
<td>17 (15.9%)</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>5 (4.7%)</td>
<td>10 (9.7%)</td>
<td>14 (13.1%)</td>
</tr>
<tr>
<td>Skin and Appendages</td>
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<tr>
<td>Sweating</td>
<td>15 (14.0%)</td>
<td>13 (12.6%)</td>
<td>11 (10.3%)</td>
</tr>
</tbody>
</table>

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms
Monitoring
- Periodic monitoring of liver function tests during treatment is recommended
- Respiratory and cardiac status periodically monitored especially during dose increase
- Monitor patients regularly for development of abuse and misuse

Interactions
- Buprenorphine (Subutex®)
  - CYP3A4 inhibitors and inducers
  - Antiretrovirals
  - Benzodiazepines, CNS depressants
  - Serotonergic drugs
- Buprenorphine/naloxone (Suboxone®)
  - As above

Product availability
- Buprenorphine (Subutex®)
  - Sublingual tablet: 2 mg, 8 mg
- Buprenorphine/naloxone (Suboxone®)
  - Sublingual film: 2.0/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg
  - Sublingual tablet: 2.0/0.5 mg, 8/2 mg

Efficacy
- Clinical data on the safety and efficacy of Suboxone® and Subutex® are derived from studies of buprenorphine sublingual tablet formulations, with and without naloxone, and from studies of sublingual administration of a more bioavailable ethanolic solution of buprenorphine

Cochrane Meta-analyses:
- Buprenorphine versus placebo or methadone maintenance for opioid dependence
  - Included 31 trials (5430 participants (n))
  - Buprenorphine vs. placebo
    - Buprenorphine superior to placebo in retention of participants in treatment
      - Low (2-6 mg) doses (5 studies, n=1131): risk ratio (RR) 1.5, 95% confidence interval (CI) 1.19-1.88
      - Medium (7-15 mg) doses (4 studies, n=887): RR 1.74, 95% CI 1.06-2.87
      - High (≥16 mg) doses (5 studies, n=1001): RR 1.82, 95% CI 1.15-2.9
    - Buprenorphine superior to placebo in suppressing opioid use measured by urinalysis
      - High doses (3 studies, n=729): standardized mean difference (SMD) -1.17, 95% CI -1.85 to -0.49
      - Medium and low doses did not suppress illicit opioid use better than placebo
  - Buprenorphine vs. methadone
    - Buprenorphine was less effective than methadone in retaining participants
      - Flexible dosing (5 studies, n=788): RR 0.83, 95% CI 0.72-0.95
      - Low dose (3 studies, n=253): RR 0.67, 95% CI 0.52-0.87
    - No difference observed in retention of participants
      - Medium dose (7 studies, n=780): RR 0.87, 95% CI 0.69-1.1
      - High dose (1 study, n=134): RR 0.79, 95% CI 0.2 to 3.16
    - No difference observed in suppression of opioid use as measured by urinalysis
• Flexible dosing (8 studies, n=1027): SMD -0.11, 95% CI -0.23 to 0.02
• Medium dose (4 studies, n=476): SMD 0.25, 95% CI -0.08 to 0.58
  ▪ No difference observed in suppression of opioid use as measured by self-report
• Flexible dosing (4 studies, n=501): SMD -0.11, 95% CI -0.28 to 0.07
• Medium dose (2 studies, n=174): SMD -0.82, 95% -1.83 to 0.19
• High dose (1 study, n=134): SMD -0.73, 95% CI -1.08 to -0.37

• **Buprenorphine for the management of opioid withdrawal**
  o Included 27 studies (3048 participants)
  o **Buprenorphine vs. methadone**
    ▪ Meta-analysis not possible for intensity of withdrawal or adverse effects
    ▪ Individual studies suggested similar capacity to ameliorate opioid withdrawal, without clinically significant adverse effects
    ▪ No difference in average treatment duration (2 studies, n=82): mean difference (MD) 1.3 days, 95% CI -8.11 to 10.72
    ▪ No difference in treatment completion rates (5 studies, n=457): RR 1.04, 95% 0.91-1.2
  o **Buprenorphine vs. alpha2-adrenergic agonists (clonidine or lofexidine)**
    ▪ Buprenorphine associated with lower average withdrawal score (7 studies, n=902): SMD -0.43, 95% CI -0.58 to -0.28
    ▪ Buprenorphine group stayed in treatment for longer (5 studies, n=558): SMD 0.92, 95% CI 0.57 to 1.27
    ▪ Buprenorphine group more likely to complete withdrawal treatment (12 studies, n=1264): RR 1.59, 95% 1.23-2.06
    ▪ No significant difference in adverse effects (3 studies, n=134): RR 0.2, 95% 0.04-1.15
    ▪ The difference in treatment completion rates translates to a number needed to treat for an additional beneficial outcome of 4 (95% CI 3 to 6), indicating that for every four people treated with buprenorphine, we can expect that one additional person will complete treatment than with clonidine or lofexidine

**Other Considerations**
• Under the Drug Addiction Treatment Act (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 who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription

**Recommendations**
• Add to formulary
References


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