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Buprenorphine Implants (Probuphine) for Opioid Dependence

The FDA has approved subdermal implants of the partial opioid agonist buprenorphine (Probuphine – Titan) for maintenance treatment of opioid dependence in patients stabilized on low to moderate doses of transmucosal buprenorphine. Probuphine was designed to provide continuous low levels of buprenorphine for 6 months and to safeguard against illicit use of the drug.

PHARMACOKINETICS — Buprenorphine levels after insertion of 4 Probuphine implants (0.5-1 ng/mL) are comparable to those achieved with 8 mg/day of sublingual buprenorphine. In one unpublished pharmacokinetic study, summarized in the package insert, subjects were given sublingual buprenorphine 16 mg daily for a minimum of 5 consecutive days, followed by insertion of 4 buprenorphine implants. Peak plasma concentrations of buprenorphine were much lower after insertion of the implants than with daily sublingual tablets.

CLINICAL STUDIES — One unpublished trial found that buprenorphine implants were noninferior to sublingual buprenorphine/naloxone in maintaining clinical stability in opioid-dependent patients. A total of 177 patients treated with ≤8 mg/day of sublingual buprenorphine who met criteria for clinical stability (e.g., no reports of illicit opioid use, significant withdrawal symptoms, or hospitalization) were randomized to receive buprenorphine implants and placebo tablets or sublingual buprenorphine/naloxone tablets and placebo implants. During the 6-month

<table>
<thead>
<tr>
<th>Drug</th>
<th>Some Available Formulations</th>
<th>Target Maintenance Dosage</th>
<th>Cost 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>2, 8 mg sublingual tabs</td>
<td>16 mg once/day</td>
<td>$1671.80</td>
</tr>
<tr>
<td>Probuphine (Titan)</td>
<td>74.2 mg subdermal implant</td>
<td>4 implants for 6 months</td>
<td>4950.00</td>
</tr>
<tr>
<td>Buprenorphine/Naloxone</td>
<td>2/0.5 mg, 8/2 mg sublingual tabs</td>
<td>16/4 mg once/day</td>
<td>2813.90</td>
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<tr>
<td>Bunavail (BioDelivery Sciences)</td>
<td>2.1/0.3 mg, 4.2/0.7 mg, 6.3/1 mg buccal films</td>
<td>8.4/1.4 mg once/day</td>
<td>2660.40</td>
</tr>
<tr>
<td>Suboxone (Reckitt Benckiser)</td>
<td>2/0.5 mg, 4/1 mg, 8/2 mg, 12/3 mg sublingual films</td>
<td>16/4 mg once/day</td>
<td>2660.40</td>
</tr>
<tr>
<td>Zubzolv (Orexo)</td>
<td>1.4/0.36 mg, 5.7/1.4 mg sublingual tabs</td>
<td>11.4/2.8 mg once/day</td>
<td>2660.40</td>
</tr>
</tbody>
</table>

1. Approximate WAC for 6 months’ treatment at the target maintenance dosage. WAC = wholesaler acquisition cost, or manufacturer’s published price to wholesalers; WAC represents published catalogue or list prices and may not represent an actual transactional price. Source: AnalySource® Monthly. July 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.
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study period, 63% of patients in the buprenorphine implant group and 54% of those in the buprenorphine/naloxone group had no evidence of illicit opioid use. ADVERSE EFFECTS — Probuphine is only available through a restricted-access (REMS) program. The most common implant-site adverse effects have been pain, pruritus, and erythema, but insertion and removal of the implants are associated with serious risks such as implant migration, extrusion, and nerve injury. Healthcare providers must complete a live training session and become certified before they can prescribe, insert, or remove buprenorphine implants.

DRUG INTERACTIONS — Buprenorphine in any form may interfere with the analgesic efficacy of full opioid agonists. It is metabolized primarily by CYP3A4; plasma levels of buprenorphine should be monitored in patients who are taking a CYP3A4 inducer or inhibitor when switching to Probuphine or who begin taking one while on Probuphine treatment. As with any opioid, concomitant use of buprenorphine with selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, or other serotonergic drugs can result in serotonin syndrome.

DOSAGE AND ADMINISTRATION — Patients who are eligible for treatment with buprenorphine implants should be clinically stable and maintained on a stable transmucosal buprenorphine dose, such as ≤8 mg/day of sublingual buprenorphine or Suboxone, for ≥3 months. Each buprenorphine implant, measuring 26 mm in length and 2.5 mm in diameter, contains 74.2 mg of buprenorphine. A total of 4 buprenorphine implants are inserted subdermally in the inner upper arm. They should be removed after 6 months. Four new implants could then be placed in the opposite arm.

CONCLUSION — Buprenorphine implants (Probuphine) may provide more consistent dosing for opioid-dependent patients stabilized on low to moderate doses of transmucosal buprenorphine. The implants also provide an additional safeguard against illicit use of buprenorphine, but they are much more expensive than oral transmucosal buprenorphine, which is similarly effective.