Drug Diversion Toolkit

Buprenorphine—A Primer for Prescribers and Pharmacists

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

Content Summary

This booklet is intended to provide guidance to prescribers and pharmacists regarding buprenorphine regulatory requirements, prescribing and safety recommendations, and other information intended to improve decision-making and promote beneficial outcomes. Information on the history of opioid addiction and traditional treatments in comparison to buprenorphine is included. The booklet will detail the process of obtaining a Drug Addiction Treatment Act (DATA) waiver and will describe how to initiate and adjust buprenorphine therapy. Pharmacists will be informed on how to verify the DATA waiver status of a physician, how to validate a Drug Enforcement Administration registration number, how Federal privacy regulations pertain to opioid addiction treatment, and what key buprenorphine counseling parameters to consider. The use of buprenorphine as a viable alternative to traditional opioid treatment centers to address the unmet need for office-based treatment of opioid addiction is supported. This booklet will advocate the partnership of physicians and pharmacists in the effective administration and execution of a buprenorphine-based opioid addiction treatment plan.

Tar, smack, skag, mud, junk, H, Char, and Aunt Hazel are only a handful of the common street names for heroin. Felix Hoffman, a German chemist at pharmaceutical company Bayer, is best known for perfecting the synthesis of acetylating salicylic acid with acetic acid, which produced a chemically pure and stable compound that Bayer trademarked as aspirin in 1897. Less well known is the fact that soon after, Hoffman also perfected the synthesis of diacetylmorphine, which Bayer trademarked as heroin and initially marketed as a stimulant.[1] Likely, Bayer derived the name heroin from the German word heroisch, which means heroic and alludes to the feelings of grandeur the drug invokes.[2] Unfortunately, it became quickly apparent that Bayer's heroin cough syrup was highly addictive, and the product was pulled from the market in 1913.[3] Patients seeking treatment for addiction to heroin and other opium derivatives, including prescription opioids, turn to opiate substitutes that prevent withdrawal, such as methadone, levo-alpha-acetylmethadol (LAAM), or buprenorphine.

Mechanisms of Action

Unlike methadone and LAAM, which are full agonists, buprenorphine—a narcotic that appears in Schedule III of the Controlled Substances Act (CSA)—acts as a partial agonist at the mu-opioid receptor and acts as an antagonist at the kappa-opioid receptor.[4] As a mixed opiate agonist-antagonist, buprenorphine produces a therapeutic result similar to a full agonist, but allows addicts to be maintained at a less extreme level of physical dependence. In addition, the antagonist action offers the advantage of a ceiling effect that minimizes respiratory depression with overdose.[5] Extreme levels of physical dependence increase the likelihood of death due to overdose that may occur with full agonists like methadone. According to the Centers for Disease Control and Prevention, methadone is involved in more than 30 percent of prescription opioid deaths, even though only 2 percent of prescription opioids are written for methadone.[6] Buprenorphine also offers an advantage over full agonists: privacy. Physicians can initiate office-based treatment (outside of an opioid treatment program [OTP]), pharmacists can dispense buprenorphine at the local pharmacy, and patients can avoid the stigma associated with public appearances at an OTP facility, such as a methadone clinic.

Abuse and Adverse Drug Reactions

However, like other opiates and opioids, buprenorphine can be abused for its euphoric effects, especially in non-opioid tolerant patients. Prescribers and pharmacists should take appropriate precautions to protect buprenorphine from diversion. While minimized by the ceiling effect, buprenorphine can also cause adverse reactions such as headache, insomnia, moderate withdrawal upon discontinuation or taper, and nausea.[7] Serious adverse reactions, including respiratory depression and overdose may occur, especially when combined with other central nervous system depressants, such as alcohol or benzodiazepines.[8]

But as a Schedule III controlled substance, buprenorphine has less potential for abuse than methadone or LAAM (both of which appear on Schedule II)—even considering buprenorphine's high potential for psychological and low to moderate potential for physical dependence. The comparative milder adverse effect profile and decreased likelihood of abuse or dependence make buprenorphine a viable alternative to management of opioid addiction via specialized OTP clinics.

Prescribing Buprenorphine Products

Physicians may choose from several buprenorphine products, including Subutex®, Suboxone®, and Zubsolv®. Physicians should remember that injectable buprenorphine (Buprenex®) and transdermal buprenorphine (Butrans®) are not approved for the maintenance treatment of opioid dependence.[9, 10] Another important fact is that after Reckitt Benckiser Pharmaceuticals (RBP) introduced its new sublingual Suboxone® film, the pharmaceutical company ceased production of its brand name Subutex® tablets and brand name Suboxone® sublingual tablets.[11] RBP made this decision after unsuccessfully petitioning the FDA to require more stringent labeling and child-resistant packaging on all buprenorphine tablets, including newly approved generic products.[12] Generic versions of both tablet formulations remain available.[13]

Induction

Physicians should prescribe Subutex® (sublingual buprenorphine) for induction, at least four hours after the last opioid dose, in patients exhibiting symptoms of moderate opioid withdrawal.[14] Physicians should initiate the dose of Subutex® at 8 mg daily and increase in 2 to 4 mg increments as necessary over 2 to 4 days, based on the patient's prior opioid dose and degree of dependence. [15]

Maintenance

After induction is complete, patients should be converted to Suboxone® or Zubsolv® for maintenance, unless the patient is unable to tolerate naloxone. Suboxone® (buprenorphine and naloxone), originally approved in 2002, is dosed once daily, either as a sublingual film or tablet, with a maintenance dosage range between 4 mg buprenorphine/1 mg naloxone and 24 mg buprenorphine/6 mg naloxone.[16] Naloxone acts as a powerful antagonist at the mu-opioid receptor when administered parenterally, which helps discourage intravenous use of the product, as it would produce opioid withdrawal symptoms that are not seen when it is administered sublingually.[17] The Zubsolv® (buprenorphine and naloxone) formulation, approved in July 2013, contains the same active ingredients as Suboxone®, but has a higher bioavailability, which necessitates a lower dose—2.8 mg buprenorphine/0.72 mg naloxone to 17.1 mg buprenorphine/4.2 mg naloxone once daily.[18] Both products are designed for maintenance dosing only and are distributed in child-resistant packaging.

Buprenorphine Regulation

A 2010 national drug use survey found 359,000 people reported use of or addiction to heroin, while more than 5 times that number (1.92 million) reported use of or addiction to prescription analgesics.[19] To facilitate access for patients who seek treatment of opioid addiction, the Drug Addiction Treatment Act of 2000 (DATA) allows qualifying prescribers to obtain a waiver from the CSA special registration requirements that pertain to medications used to treat opioid addiction.[20] If methadone is prescribed for the treatment of pain, no special Drug Enforcement Administration (DEA) registration or Substance Abuse and Mental Health Services Administration (SAMHSA) certification is required. However, if a physician wishes to prescribe drugs to treat opioid addiction, he or she must first obtain a special certification from SAMHSA that officially states the physician meets the requirements of the CSA as they pertain to the distribution and administration of drugs for the purpose of opiate addiction treatment.[21] SAMHSA-certified physicians may only prescribe medications to treat addiction that are approved by the Food and Drug Administration (FDA) for the treatment of opioid addiction. These medications must be administered at an OTP facility, though an exception allows for take-home dosing for use on non-business days.[22] In contrast, a DATA-waived physician may prescribe any CSA Scheduled III, IV, or V medication approved by the FDA for the treatment of opioid addiction outside of an OTP facility. [23]

Drug Addiction Treatment Act Waiver Requirements

Physicians (Doctors of Medicine or Doctors of Osteopathic Medicine) interested in obtaining a DATA waiver must first contact SAMHSA through the Center for Substance Abuse Treatment (CSAT). To qualify for the DEA waiver, interested physicians must be licensed and agree to treat no more than 30 patients initially. However, the 30 patient maximum may be increased to 100 patients after 1 year, if requested by the physician and approved by CSAT.[24] In addition, to qualify for the waiver, a physician must have one of the following:

- American Board of Medical Specialties (ABMS) certification in addiction psychiatry;
- American Society of Addiction Medicine (ASAM) certification in addiction;
- American Osteopathic Association (AOA) certification in addiction medicine;
- Completion of 8 hours of addiction training provided by the ASAM, the American Academy of Addiction Psychiatry (AAAP), the American Medical Association, the American Osteopathic Academy of Addiction Medicine (AOAAM), the American Psychiatric Association (APA), or other approved organization;
- Investigator status, which leads to the approval of a CSA Scheduled III, IV, or V drug for the treatment of opioid addiction maintenance or detoxification; or
- Other training deemed by the State medical licensing authority or by the Secretary of Health and Human Services to demonstrate ability to manage opioid addiction maintenance or detoxification treatment.[25]

The Providers' Clinical Support System for Medication Assisted Treatment (PCSS-MAT) is an addiction training program that is a collaboration of the AAAP, AOAAM, and APA. The webinar is available online at http://pcssmat.org/education-training/waiver-eligibility-training/ on the program's website.[26] The online version of the DATA waiver form is available at http://buprenorphine.samhsa.gov/pls/bwns/waiver on SAMHSA's website. A physician who prescribes buprenorphine products should include the special "X" DEA registration number that identifies the prescriber as a DATA-waived physician on the face of any written prescription in addition to his or her regular DEA registration number. The prescriber should provide these registration numbers verbally if the prescription is phoned in to a pharmacy.

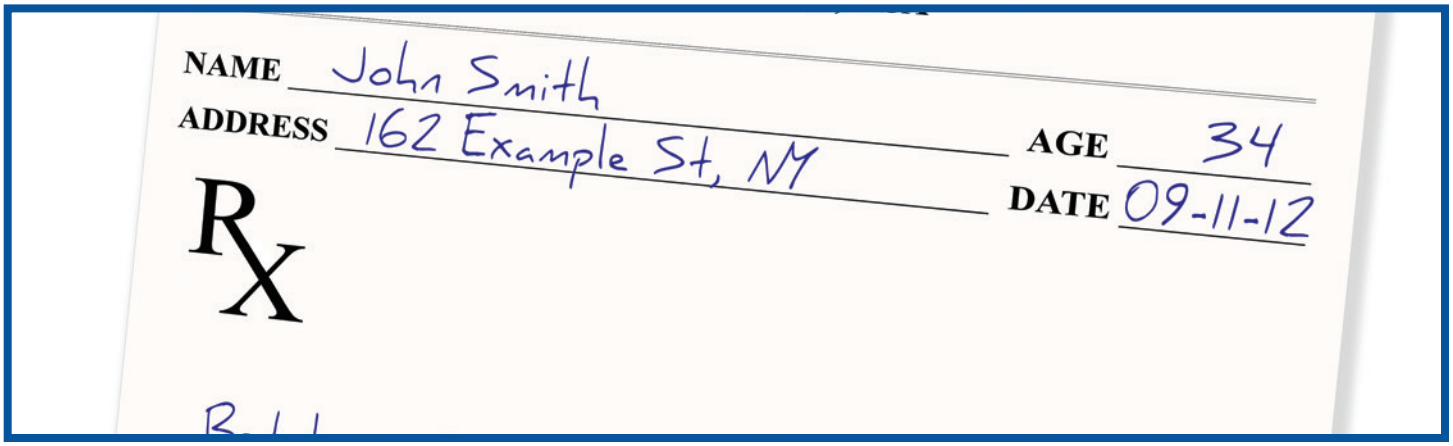
Filling Buprenorphine Prescriptions

When a patient presents a buprenorphine prescription to be filled at the pharmacy, pharmacists should verify that the prescribing physician is appropriately registered with the DEA and that the physician has received a SAMHSA-approved DATA waiver to prescribe buprenorphine outside of an OTP. Keep in mind that no mid-level practitioners, such as physician assistants or nurse practitioners, can obtain a DATA waiver, and therefore, no prescriptions written by mid-level practitioners should be accepted for buprenorphine products. If a physician has obtained the DATA waiver, the physician will be assigned an additional DEA registration number that begins with the letter X. Physicians prescribing buprenorphine products are required to include both the DEA number and the special X DEA registration number on any prescription for buprenorphine.[27] All other aspects of the DEA number remain the same. DEA registration numbers consist of two letters and seven numbers. Pharmacists can perform a simple calculation to determine if both DEA numbers presented meet construction composition standards. To perform this check, add the first, third, and fifth digits; then add double the sum of the second, fourth, and sixth digits. Combine the two calculated numbers. If the last digit of this sum is identical to the seventh digit of the DEA number, the DEA number conforms to the composition model.[28] Take, for example, DEA number AZ1234567, for a Dr. Zahara. The sum of the first, third, and fifth digits is 9. The sum of the second, fourth, and sixth digits is 12, which multiplied by 2 equals 24. When added together, 9 + 24 equals 33. If this were a valid DEA number, the last digit of this calculated value (3) would be identical to the last digit of the DEA number (7). In contrast, consider DEA number BA1424326 for a Dr. Abrahams. The sum of the first, third, and fifth digits is 6. The sum of the second, fourth, and sixth digits is 10, which multiplied by 2 equals 20. When added together, 6 + 20 equals 26. The last digit of this calculated value (6) is identical to the seventh digit of the DEA number, and therefore this DEA number "passed" the test.

Verification of DATA-Waived Prescriber Status

Pharmacists can verify the DATA-waived status of a physician using four different methods:

1. Check for the name of the physician on SAMHSA's Physician and Treatment Program Locator at http://buprenorphine.samhsa.gov/bwns_locator/index.html on the SAMHSA website;
2. Call SAMHSA directly at 866-287-2728;
3. Email SAMHSA at info@buprenorphine.samhsa.gov; or
4. Request a faxed copy of the physician's DATA waiver.[29]



Addiction Treatment and Patient Confidentiality

While verifying the DATA-waived status before filling a prescription for buprenorphine, pharmacists and prescribers should use discretion and pay careful attention to patient confidentiality. Confidentiality of patients' medication information has always been of utmost importance in the field of medicine. The Hippocratic Oath states, "Whatever I see or hear in the lives of my patients, whether in connection with my professional practice or not, which ought not to be spoken of outside, I will keep secret, as considering all such things to be private."[30]

Note that Federal regulations regarding privacy of patients being treated for substance abuse require a higher degree of discretion than what is required of prescribers and pharmacists under the security and privacy provisions of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Title 42—The Public Health and Welfare law and the associated regulations (Title 42, Part 2 of the Code of Federal Regulations) prohibit health care providers from revealing any identifying information of a patient being treated for substance abuse addiction, except in very specific circumstances. Even pharmacists communicating directly with the prescriber to verify a physician's DATA-waiver status when filling a buprenorphine prescription may not disclose the name of the patient.[31] Disclosure of specific patient identifying characteristics may be made only to qualified medical personnel in the event of an emergency or if authorized by an order of the court.[32]

Counseling

After the pharmacist has verified the DATA-waived status of the prescribing physician and has prepared the prescription for pickup, the last step in the process is to provide appropriate counseling to the patient. Pharmacist-provided counseling includes the following elements:

- Advise the patient of the prescribed once-daily dosing regimen, including dosing during induction and switching to a buprenorphine/naloxone combination product, if applicable;
- Instruct the patient to keep all naloxone-containing products away from children and advise the patient to seek immediate medical intervention if ingestion by a child is suspected;
- Inform the patient of the risk of breathing difficulties, especially when combined with benzodiazepines or alcohol and advise the patient to seek immediate medical intervention if breathing becomes shallow, slowed, or labored;
- Inform the patient that if injected, naloxone-containing products may cause immediate withdrawal symptoms including pain, vomiting/diarrhea, and dysphoria (Suboxone® and Zubsolv®);
- Remind the patient that Suboxone® films should not be chewed, cut, or swallowed;
- Advise the patient not to stop taking the buprenorphine product without consulting a physician because a gradual reduction in dose may be required;
- Remind the patient to take special precautions to protect the buprenorphine product from theft or loss; and
- Advise the patient that selling or giving away prescription medications is against the law.[33, 34, 35]

Referral for specialty addiction management may be required for some patients. However, office-based treatment of opioid dependence can offer a practical alternative to methadone or LAAM treatment programs. Through establishment of long-term patient relationships that promote continuity of care and enable meaningful patient–physician communication, primary care physicians can provide considerable addiction treatment services. Given the proper training, experience, and support, primary care physicians can collaborate with local pharmacists to augment specialized addiction care through screening and office-based treatment of opioid addiction with buprenorphine.

References

1 Klein, A. (n.d.). Felix Hoffmann. University of Cologne. Faculty of Mathematics and Natural Sciences. Department of Chemistry. Retrieved July 14, 2014, from http://www.chemie.uni-koeln.de/406.html?&L=1&tx_ttnews%5Btt_news%5D=186&cHash=f19758d73ae761ae60b561569ac6eb62

2 Collins English Dictionary–Complete & Unabridged 10th Edition. Definition of Heroin. Retrieved July 14, 2014, from http://www.collinsdictionary.com/dictionary/english/heroin

3 Borigini, M. (2012, January 11). Overcoming Pain. Psychology Today. Retrieved July 14, 2014, from http://www.psychologytoday.com/blog/overcoming-pain/201201/when-heroin-was-available-housewives-and-aspirin-was-bad-the-heart

4 National Institutes of Health. National Library of Medicine. (2012, January). DailyMed. Buprenorphine. Retrieved July 14, 2014, from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=601cc950-ee0f-4a57-8e79-7b4a012b1d11

5 Substance Abuse and Mental Health Services Administration. (n.d.). About Buprenorphine Therapy. Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/about.html

6 Centers for Disease Control and Prevention. (2012, July). Prescription Painkiller Overdoses. Retrieved July 14, 2014, from http://www.cdc.gov/vitalsigns/MethadoneOverdoses/index.html

7 National Institutes of Health. National Library of Medicine. (2012, January). DailyMed. Buprenorphine. Retrieved July 14, 2014, from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=601cc950-ee0f-4a57-8e79-7b4a012b1d11

8 National Institutes of Health. National Library of Medicine. (2012, January). DailyMed. Buprenorphine. Retrieved July 14, 2014, from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=601cc950-ee0f-4a57-8e79-7b4a012b1d11

9 National Institutes of Health. National Library of Medicine. (2012, March). DailyMed. Buprenex®. Retrieved July 14, 2014, from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b086772e-d15a-4d13-b1a2-38bfbde1f18c#nlm34067-9

10 National Institutes of Health. National Library of Medicine. (2013, February). DailyMed. Butrans®. Retrieved July 14, 2014, from http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b25457a9-6237-4ba9-84dd-847b81cbcdae#nlm34067-9

11 Substance Abuse and Mental Health Services Administration. Discontinuation of Sale and Distribution of Subutex® Tablets CIII. (2011, September 16). Reckitt Benckiser Pharmaceuticals, Inc. Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/SubutexDiscontinuation9-16-11.pdf

12 Reckitt Benckiser Pharmaceuticals Inc. Receives FDA Response to Citizen's Petition and Announcement of Generics Approval. (2013, February 25). Retrieved July 14, 2014, from http://www.rb.com/reckitt-benckiser-pharmaceuticals-inc-receives-fda-response-to-citizens-petition-and-announcement-of-generics-approval

13 U.S. Food and Drug Administration. (n.d.). Buprenorphine Hydrochloride. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Overview&DrugName=BUPRENORPHINE%20HYDROCHLORIDE

14 U.S. Food and Drug Administration. (2011, December). Subutex® Full Prescribing Information. Reckitt Benckiser Pharmaceuticals Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

15 U.S. Food and Drug Administration. (2011, December). Subutex® Full Prescribing Information. Reckitt Benckiser Pharmaceuticals Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

16 U.S. Food and Drug Administration. (2011, December). Subutex® Full Prescribing Information. Reckitt Benckiser Pharmaceuticals Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

17 U.S. Food and Drug Administration. (2011, December). Subutex® Full Prescribing Information. Reckitt Benckiser Pharmaceuticals Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

18 U.S. Food and Drug Administration. (2013, July). Zubsolv® Full Prescribing Information. Orexo US, Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204242s000lbl.pdf

19 Substance Abuse and Mental Health Services Administration. (2012, Winter). An Introduction to Extended-Release Injectable Naltrexone for the Treatment of People With Opioid Dependence. Retrieved July 14, 2014, from http://store.samhsa.gov/shin/content//SMA12-4682/SMA12-4682.pdf

20 Substance Abuse and Mental Health Services Administration. (n.d.). Buprenorphine Physician Waiver Qualifications. Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/waiver_qualifications.html

21 Certification of Opioid Treatment Programs, 42 C.F.R. § 8.11. Retrieved July 14, 2014, from http://www.gpo.gov/fdsys/pkg/CFR-2002-title42-vol1/pdf/CFR-2002-title42-vol1-part8.pdf

22 Certification of Opioid Treatment Programs, 42 C.F.R. § 8.12(i). Retrieved July 14, 2014, from http://www.gpo.gov/fdsys/pkg/CFR-2002-title42-vol1/pdf/CFR-2002-title42-vol1-part8.pdf

23 Substance Abuse and Mental Health Services Administration. (n.d.). Buprenorphine Physician Waiver Qualifications. Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/waiver_qualifications.html

24 Substance Abuse and Mental Health Services Administration. (n.d.). Buprenorphine. Drug Addiction Treatment Act of 2000. Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/titlexxxv.html

25 Drug Addiction Treatment Act of 2000, Pub. L. No. 106-310, 114 Stat. 1222. (2000, October 17). Retrieved July 14, 2014, from http://www.gpo.gov/fdsys/pkg/PLAW-106publ310/pdf/PLAW-106publ310.pdf

26 PCSS-MAT Training. (n.d.). Providers' Clinical Support System–Waiver Eligibility Training. Retrieved July 14, 2014, from http://pcssmat.org/education-training/waiver-eligibility-training/

27 Substance Abuse and Mental Health Services Administration. (n.d.). Frequently Asked Questions About Buprenorphine and the Drug Addiction Treatment Act of 2000 (DATA 2000). Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/bwns/faq.html#A20

28 Michigan Pharmacists Association. (2013, September 26). What's Your Number? Validating DEA and NPI Numbers. Retrieved July 14, 2014, from http://www.michiganpharmacists.org/news/article.php?x=3429

29 Substance Abuse and Mental Health Services Administration. (n.d.). Frequently Asked Questions About Buprenorphine and the Drug Addiction Treatment Act of 2000 (DATA 2000). Retrieved July 14, 2014, from http://buprenorphine.samhsa.gov/bwns/faq.html#A20

30 National Institutes of Health. National Library of Medicine. History of Medicine Division. (2002). Greek Medicine. Retrieved July 14, 2014, from: http://www.nlm.nih.gov/hmd/greek/greek_oath.html

31 Public Health Service, 42 C.F.R. § 2.12 (a)(1)(i). (1995, May 5). Retrieved July 14, 2014, from http://www.gpo.gov/fdsys/pkg/CFR-2010-title42-vol1/pdf/CFR-2010-title42-vol1-sec2-12.pdf

32 The Public Health and Welfare, 42 C.F.R. § 290dd-2(b)(2). (1992, October 1). Retrieved July 14, 2014, from http://www.gpo.gov/fdsys/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapIII-A-partD-sec290dd-2.pdf

33 U.S. Food and Drug Administration. (2011, December). Subutex® Full Prescribing Information. Reckitt Benckiser Pharmaceuticals Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

34 U.S. Food and Drug Administration. (2011, December). Subutex® Full Prescribing Information. Reckitt Benckiser Pharmaceuticals Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020732s006s007lbl.pdf

35 U.S. Food and Drug Administration. (2013, July). Zubsolv® Full Prescribing Information. Orexo US, Inc. Retrieved July 14, 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204242s000lbl.pdf

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