IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
Abingdon Division

[UNDER SEAL],

Relator-Plaintiff,

v.

[UNDER SEAL]

Defendants.

SEALED

SECOND AMENDED COMPLAINT

CASE NO.: 1:13cv00036

FILED UNDER SEAL
31 U.S.C. Sec. 3730 (b)(2) & (3)

SEALED

Do Not Place in Press Box or Enter on Publicly Accessible System (PACER)

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF VIRGINIA
Abingdon Division

UNITED STATES OF AMERICA and the COMMONWEALTH OF VIRGINIA, the COMMONWEALTH OF MASSACHUSETTS, the States of CALIFORNIA, COLORADO, CONNECTICUT, DELAWARE, FLORIDA, GEORGIA, HAWAII, ILLINOIS, INDIANA, IOWA, LOUISIANA, MARYLAND, MICHIGAN, MINNESOTA, MONTANA, NEVADA, NEW HAMPSHIRE, NEW JERSEY, NEW MEXICO, NEW YORK, NORTH CAROLINA, OKLAHOMA, RHODE ISLAND, TENNESSEE, TEXAS, VERMONT, WASHINGTON, WISCONSIN, the DISTRICT OF COLUMBIA, the CITY of CHICAGO, the CITY of NEW YORK, the CALIFORNIA DEPARTMENT of INSURANCE and the ILLINOIS DEPARTMENT of INSURANCE

TO BE FILED IN CAMERA AND UNDER SEAL PURSUANT TO 31 U.S.C. §3730(b)(2)

CASE NO.: 1:13cv00036

Do Not Place in Press Box or Enter on Publicly Accessible System (PACER)

JURY TRIAL DEMANDED

***ex rel* ANN MARIE WILLIAMS**
3208 St. Stephens Way
Midlothian, VA 23113

Relator-Plaintiff,

v.

RECKITT BENCKISER, INC.
Morris Corporate Center IV
399 Interpace Parkway
Parsippany, New Jersey 07054

and

RECKITT BENCKISER, LLC
Morris Corporate Center IV
399 Interpace Parkway
Parsippany, New Jersey 07054

and

RECKITT BENCKISER PHARMACEUTICALS, INC.
10710 Midlothian Turnpike, Suite 430,
Richmond, Virginia 23235

and

RECKITT BENCKISER HEALTHCARE (UK) LTD.
Dansom Lane, Hull,
North Humberside
HU8 7DS, England

and

RECKITT BENCKISER GROUP, PLC,
103-105 Bath Road, Slough,
Berkshire, SL1 3UH, England

and

INDIVIOR, INC.
10710 Midlothian Turnpike, Suite 430
Richmond, Virginia 23235

and

INDIVIOR PLC,
103-105 Bath Road, Slough,
Berkshire, SL1 3UH, England

and

INDIVIOR UK LIMITED
103-105 Bath Road, Slough,
Berkshire, SL1 3UH, England

Defendants.

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SECOND AMENDED COMPLAINT

Ann Marie Williams, by counsel, states as follows for her Second Amended Complaint against Reckitt Benckiser, Inc., Reckitt Benckiser LLC, Reckitt Benckiser Pharmaceuticals, Inc., Reckitt Benckiser Healthcare (UK) LTD, Reckitt Benckiser Group, PLC, Indivior, Inc., Indivior PLC and Indivior UK Limited as follows:

I. INTRODUCTION

1. This Second Amended Complaint is filed *in camera* and under seal pursuant to 31 U.S.C. §3730(b)(2).

2. This is an action to recover treble damages and civil penalties on behalf of the United States of America, the Commonwealth Of Virginia, the Commonwealth Of Massachusetts, and the states of California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Louisiana, Maryland, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Rhode Island, Tennessee, Texas, Vermont, Washington, Wisconsin, the District Of Columbia, the City of Chicago, the City of New York, the California Department of Insurance and the Illinois Department of Insurance and private insurers in California and Illinois for false claims that were knowingly caused to be presented by the Defendants to certain agencies of the United States, the states and cities listed above, and private insurers in California and Illinois.

3. The false claims complained of herein arise from healthcare services provided under various United States government programs and under the Medicaid and other programs of the states listed in paragraph one, above. This action arises under the provisions of 31 U.S.C. §3729, et seq., commonly known as the False Claims Act (the "FCA") and the related provisions

of state law in effect at relevant times in the states listed in paragraph two and as cited in Counts 1 through 42, herein.

4. The false claims identified herein arise from the manufacture, sale and marketing by the Defendants of two pharmaceuticals, Suboxone and Subutex, which are used in the treatment of opioid addiction and paid for under the following governmental programs: 1) the United States government's Medicare, Medicaid, Railroad Retirement Medicare, CHAMPVA, CHAMPUS, F.A.M.I.S.[1], Tricare, State Legal Immigrant Assistance Grant, Indian Health Service and federal employee and veteran healthcare programs (these programs are sometimes referred to herein as "Federal Payors" or "Federal Payor Programs"); 2) the Medicaid, F.A.M.I.S. and state employee health insurance programs of several states and cities ("State Payors" or "State Payor Programs") including those of the Commonwealth of Virginia, the Commonwealth of Massachusetts and the states of California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Illinois, Indiana, Iowa, Louisiana, Maryland, Michigan, Minnesota, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Rhode Island, Tennessee, Texas, Vermont, Washington, Wisconsin, the District of Columbia, and the cities of Chicago and New York; and 3) programs paid for by private insurance companies in California and Illinois under the auspices and regulatory requirements of the California Department of Insurance and the Illinois Department of Insurance.

5. The Defendants actively marketed off-label dosages and uses of Suboxone and Subutex. They engaged in unlawful kickback schemes to promote the sales of these drugs and intentionally marketed them to physicians in violation of statutes intended to prevent over prescription and abuse. Perhaps most importantly, when faced with generic competition upon

[1] F.A.M.I.S. is an acronym for Family Access to Medical Insurance Security, a federal program to assist families with healthcare expenses not covered by Medicaid

losing "orphan drug" exclusivity status conferred pursuant to the Orphan Drug Act, Defendants knowingly and falsely marketed Suboxone film, under which they had patent protected rights, as being less vulnerable to diversion and safer than Suboxone tablets. They made these false claims in order to extinguish competition from generic Suboxone tablets.

6. Suboxone achieved sales volume placing it in the top 25 of the world's top 200 selling pharmaceuticals by dollar volume as of 2010. In 2013, Suboxone achieved approximately $1.4 billion in annual sales. Annual sales remain over $1 billion a year as of the filing of this Second Amended Complaint. The damages sustained by the Federal and State Payors as a result of the practices enumerated herein are extraordinarily significant.

II. JURISDICTION AND VENUE

7. The United States District Courts have exclusive jurisdiction over actions brought under the FCA pursuant to 31 U.S.C. §3732, and otherwise have jurisdiction under 28 U.S.C. §§1331 and 1345. This Court has subject matter jurisdiction over the claims brought under the respective state false claims acts identified herein and which are filed under seal pursuant to 31 U.S.C. §3730(b) and 31 U.S.C. §3732(b). This Court also has supplemental jurisdiction over the state and municipal claims pursuant to 28 U.S.C. §1367. At all times relevant hereto, the Defendants regularly conducted substantial business in the Commonwealth of Virginia and maintained and operated sales division offices and certain headquarters in the Commonwealth. Accordingly, the Defendants are subject to personal jurisdiction in the Commonwealth of Virginia. Venue is appropriate in the Western District of Virginia pursuant to 31 U.S.C. §3732(a) and 28 U.S.C. §1391(b)(1) and (2).

8. Section 3732(a) of the FCA provides that "any action under Section 3730 may be brought in any judicial district in which the defendant or, in the case of multiple defendants, any one defendant can be found, resides, transacts business, or in which any act proscribed by

Section 3729 occurred." The acts complained of herein occurred throughout the United States, the Commonwealth of Virginia and within the geographic area encompassed within the Abingdon Division of the United States District Court for the Western District of Virginia.

9. Under the FCA and the respective state false claims act statutes cited herein, this Complaint is to be filed and remain under seal until the Court orders otherwise.

III. DEFENDANTS

10. Reckitt Benckiser, Inc. ("RBI") is a Delaware corporation with its principal place of business located at Morris Corporate Center IV, 399 Interpace Parkway, Parsippany, New Jersey 07054. RBI manufactures and sells various products throughout the United States, including pharmaceuticals. RBI was duly authorized to conduct business within the Commonwealth of Virginia at all times relevant to this matter.

11. Reckitt Benckiser, LLC ("RBL") is a Delaware limited liability company and maintains its principal place of business at Morris Corporate Center IV, 399 Interpace Parkway, Parsippany, New Jersey 07054. RBL manufactures and sells various products, including pharmaceuticals. RBL was duly authorized to conduct business within the Commonwealth of Virginia at all times relevant to this matter.

12. Reckitt Benckiser Pharmaceuticals, Inc. ("RBP") is a Delaware corporation and maintains its principal place of business at 10710 Midlothian Turnpike, Suite 430, Richmond, Virginia 23235. RBP manufactures and sells, or at times relevant to this Second Amended Complaint manufactured and sold, various products throughout the United States, including pharmaceuticals. RBP was duly authorized to conduct business within the Commonwealth of Virginia at all times relevant to this matter.

13. Reckitt Benckiser Healthcare (UK) Ltd. ("RBH") is a British corporation incorporated under the laws of England and Wales and maintains its principal office at Dansom

Lane, Hull, North Humberside HU8 7DS, England. RBH manufactures and sells various products throughout the United States and the world, including pharmaceuticals. RBH or its subsidiaries were duly authorized to conduct business within the Commonwealth of Virginia at all times relevant to this matter.

14. Reckitt Benckiser Group, PLC ("RBG") is a British corporation incorporated under the laws of England and Wales and maintains its principal office at 103-105 Bath Road, Slough, Berkshire, SL1 3UH, England. RBG is a holding company and owns the other Reckitt entities identified herein. It had a market capitalization as of the filing of this Second Amended Complaint of $49.7 billion and total annual sales of more than $13 billion. RBG manufactures and sells various products throughout the United States and the world, including pharmaceuticals. RBG or its subsidiaries were duly authorized to conduct business within the Commonwealth of Virginia at all times relevant to this matter. RBG and its subsidiaries, including the other Reckitt entities named herein, manufacture and market branded products for household use, health and personal care, and sell a range of products through over 60 operating companies into nearly 200 countries. The company's geographical divisions include Europe, North America, Australia and developing markets.

15. RBI, RBL and RBP are operated by, and wholly owned subsidiaries of, RBH and RBG (the terms "Reckitt" and/or "Reckitt Defendant(s)" shall, unless otherwise indicated, include RBI, RBL, RBP, RBH and RBG). The Reckitt Defendants have common ownership, an integrated management structure and their operations and operational plans are intertwined. The managing officers of RBI, RBL and RBP ultimately reported and answered to executives of RBH and RBG at all times relevant to this Complaint.

16. Indivior Inc. is a Delaware corporation having a principal place of business at 10710 Midlothian Turnpike, Suite 430, Richmond, Virginia. Indivior purports to be a wholly owned subsidiary of Indivior PLC, a corporation organized under the laws of England and Wales. Indivior Inc. is a pharmaceutical company that has been engaged in the manufacture, marketing and sale of Suboxone and Subutex since approximately eight months after this suit was originally filed in May of 2013. Indivior, Inc. began operations in approximately January of 2014.

17. Indivior PLC is a public limited company organized under the laws of England and Wales. It maintains its headquarters at 103-105 Bath Road, Slough, United Kingdom. It is a pharmaceutical company that has been engaged in the manufacture, marketing and sale of Suboxone and Subutex since 2014. It is the corporate successor to RBP and was demerged from RBP by actions of RBH and RBG in 2014. It is the corporate parent of Indivior, Inc. It had an initial capitalization of approximately $3 billion and has current total annual revenue of just over $1 billion. Indivior PLC's international headquarters shares the same address as the headquarters of RBH and RBG. Immediately after the demerger was effected, the entire RBP management team assumed roles in the service of Indivior identical to those they held at RBP. Relator asserts, upon information and belief, that the sole purpose or primary purpose of the demerger was for the Reckitt Defendants to shed or reduce liability associated with the conduct complained of herein. For this and other reasons, Relator asserts the Indivior entities are the alter ego of, and responsible for the actions of, RBP, and that the Reckitt Defendants remain responsible for the acts of Indivior, Inc., Indivior PLC and Indivior UK Limited.

18. Indivior UK Limited is a public limited company organized under the laws of England and Wales. It was formed in 2014. It maintains its headquarters at 103-105 Bath Road,

Slough, United Kingdom. Upon information and belief, Indivior UK Limited is a wholly owned subsidiary of RBH and/or RBG. Pursuant to the demerger agreement, RBH and Indivior UK Limited entered into a supply agreement executed December 23, 2014, but effective on April 1, 2015. Pursuant to the agreement, RBH manufactures the Suboxone product line exclusively for Indivior UK Limited. In turn, Indivior UK Limited is obligated under this agreement to purchase those products exclusively from RBH for a period of seven (7) years, until 2022, which is the year Suboxone film's patent protection expires. Upon information and belief, Indivior UK Limited is engaged in the distribution of Suboxone and Subutex worldwide.

19. The term "Indivior" shall, unless otherwise indicated herein, mean, jointly and severally, Indivior Inc., Indivior PLC, and Indivior UK Limited. The term "Defendants" shall, unless otherwise indicated, mean, jointly and severally, RBI, RBL, RBP, RBH, RBG, Indivior Inc., Indivior PLC and Indivior UK Limited.

20. The Defendants manufacture and market, or at times relevant hereto manufactured and marketed, various pharmaceuticals subject to approval of the United States Food and Drug Administration ("FDA") and were responsible for the conduct alleged herein.

IV. RELATOR-PLAINTIFF

21. Relator-Plaintiff Ann Marie Williams is a citizen of the United States and the Commonwealth of Virginia. She maintains her principal residence at 3208 St. Stephens Way, Midlothian, Virginia 23113. Williams began employment with RBP in the fall of 2009 in the position of State Government Manager and continued in that position as of the time this suit was originally filed. She has since left RBP. Areas under her supervision included the introduction of Reckitt pharmaceuticals into the various states and obtaining approval of these products from various state Medicaid offices. She has direct knowledge of the facts related herein and is the original source of same. While she is unaware of any of the Counts, fraud allegations and/or acts

described herein having been publicly disclosed as contemplated under 31 U.S.C. §3730(d)(4)(B), she has made voluntary disclosure of substantially all evidence and information in her possession to authorities responsible for investigating these allegations prior to filing her original Complaint. She has made further substantial disclosures to the United States of additional information that came into her possession after the filing of her original Complaint and of her tape recordings that include conversations of Reckitt executives, district managers, the compliance officer and others making important admissions.

V. FACTS

22. The Defendants knowingly and/or with deliberate indifference made or used false or fraudulent statements and schemes, or caused fraudulent statements to be made and unlawful schemes to be carried out, to obtain, or aid in obtaining, the payment and approval of false claims under Medicare, Medicaid, Railroad Retirement Medicare, CHAMPVA, CHAMPUS, Tricare, State Legal Immigrant Assistance Grant, Indian Health Service, F.A.M.I.S., state employee health insurance and federal employee and veteran health programs. As a result of these false and/or fraudulent statements and schemes, the Federal and State Payors identified herein paid very significant sums of money to the Defendants to which the Defendants were not entitled.

A. Background

23. Defendants manufacture and market or, at times relevant to this Second Amended Complaint manufactured and marketed, Suboxone and Subutex. They are both powerful prescription pharmaceuticals that are used to treat opioid addiction, primarily heroin, methadone, morphine and oxycodone addiction. More specifically, they were originally intended for use in attempting to wean opioid addicts off of these drugs and other opioids or in achieving lower maintenance doses for them. Suboxone is a unique composite drug product consisting of two active pharmacological ingredients, buprenorphine (four parts) and naloxone (one part). Subutex

contains only buprenorphine. A significant number of the patients who are prescribed Suboxone and Subutex are on Medicaid.

24. Buprenorphine provides a maintenance dose of a semi-synthetic opioid which is absorbed through the oral mucosa. Buprenorphine ostensibly has a well-documented "ceiling effect" when taken sublingually which is supposed to make it safer in overdose than other opioids. Defendants marketed these drugs as having a less euphoric effect, being less addictive, being less susceptible to diversion for improper uses, being safer, and having less of a potential for abuse compared to methadone, another drug used to treat opioid addiction. These characteristics ostensibly make it easier and safer to treat addicts and work toward lower doses with a goal of using the lowest optimal dose to avoid withdrawal and craving of opioids.

25. The naloxone contained within Suboxone ostensibly protects the patient from abusing the drug by blocking the action of the buprenorphine and thereby precipitating withdrawal symptoms when the buprenorphine is taken in any manner other than sublingually. According to the Defendants, the protective characteristics of the naloxone will only activate if it is subjected to the addicts' favored methods of abuse, i.e., dissolved in a solution and injected intravenously or snorted. The naloxone's blocking effect is ostensibly vitiated in Suboxone when taken sublingually, as directed, because naloxone is poorly absorbed through the oral mucosa. In theory, the combination of compounds in Suboxone allows a safer opioid to be substituted for heroin and the more dangerous opioids while blocking the primary abuse and more dangerous pathways of administration.

26. Naloxone was first approved by the FDA in the 1970's. Buprenorphine was first approved by the FDA in 1982 as an injectable analgesic. In the 1990's, Reckitt embarked upon exhaustive research to investigate buprenorphine's efficacy in the treatment of opioid

dependence. Substantial portions of this research were paid for by grants to Reckitt from the United States National Institutes of Health.

27. When Reckitt introduced Suboxone sublingual tablets in 2002, it was aware that neither Suboxone, its component compounds nor their application in opioid replacement therapy enjoyed patent protection.

28. Reckitt had significant concern about generic competition to Suboxone and engaged an aggressive strategy to prevent that competition. Reckitt sought and obtained from the FDA a seven year period of market exclusivity by having Suboxone categorized as an "orphan drug" under the Orphan Drug Act, 21 U.S.C. §360aa-dd. From the time of Suboxone's first approval by the FDA in October of 2002 until October of 2009, Reckitt marketed Suboxone tablets free from competition from generic buprenorphine /naloxone. This exclusivity resulted in U.S. sales of over $1 billion per year. The sales volume of Suboxone reached $1.4 billion in 2013 and remains over $1 billion.

29. Suboxone is an expensive drug for the consumer. The profit margins are extraordinarily large even by patent-protected pharmaceutical standards. Thirty tablets in the 8 mg dosage strength had an average wholesale price in early 2011 of $242.90, over $8.00 per tablet. The costs of manufacturing and delivering the drug to market does not exceed 10% of its wholesale cost. The patients who are prescribed Suboxone, almost exclusively drug addicts, are poor and often on Medicaid. A significant amount of the purchases are made by the Federal and State Payors identified herein. As a result, generic Suboxone was a particularly attractive market for generic manufacturers.

30. To put the size of this market in perspective, a list of the top 200 selling pharmaceuticals worldwide by dollar volume is attached as **Exhibit A.** Suboxone is number 25.

Suboxone generated more revenue than Viagra, Lunesta, Nasonex, Cialis, Avodart, Enbrel and other well-known and heavily marketed drugs.

31. The extraordinary volume and growth of Suboxone sales illuminate two critical facts: 1) Reckitt's representation in its successful application for "orphan drug exclusivity" that this protection was "necessary" for Reckitt to recover the cost associated with developing the drug for treatment of addicts (most of which studies were paid for by the National Institute of Health) was itself false; and 2) the volume of Suboxone being sold to and consumed by the public exceeds reasonable medical use and constitutes a "red flag" indicating an obvious and very significant level of diversion to improper uses, prescription in dosages which are far too high, and for uses which are inappropriate.

B. Development of Suboxone Film

32. On October 8, 2009, the period of orphan drug exclusivity was scheduled to expire for Suboxone tablets. Reckitt knew that its competitors in the generic market were preparing to manufacture a generic version of the drug.

33. The history of generic drugs in the United States clearly demonstrates that they can present significant, if not lethal, price competition to a brand-name manufacturer. Moreover, the effect of this competition is virtually immediate because of statutes and regulations which in many instances mandate substitution of generics for brand-name drugs. Reckitt was understandably concerned about the competitive market pressure that would be brought to bear when generic Suboxone entered the market.

34. Reckitt developed a plan to thwart competition from generic manufacturers. Approximately two years before the expiration of its orphan drug exclusivity, Reckitt announced to the FDA that it would submit application to manufacture and market a sublingual film version of Suboxone. The application was filed on October 21, 2008.

35. There is no medically-based therapeutic difference between the tablet and the film and there is only a slight difference in bioavailability. As a result, the recommended dosages as between Suboxone tablets and Suboxone film are equivalent. However, the delivery method is materially different. Reckitt knew that Suboxone tablets would not and could not be considered sufficiently similar to branded Suboxone film so as to justify the automatic substitution of less-expensive generic buprenorphine/naloxone tablets when pharmacists were presented with a prescription for the Suboxone film. This automatic substitution of cheaper generics is the regulatory means through which generic competition reduces drug prices for Federal and State Payors.

36. Under Reckitt's plan, if it could introduce its film version of Suboxone into the marketplace, it would cause the market for branded Suboxone tablets to collapse or completely vanish. Accordingly, if the film version of Suboxone became the common means by which patients used the drug then generic Suboxone tablet competition would be avoided and the substantial savings that would otherwise be realized for Suboxone users and the Federal and State Payors would disappear.

37. The FDA raised several objections to the film version of Suboxone. Among its chief concerns were improper diversion, safety and abuse of the film. The FDA had a specific concern regarding the film's safety in households with children. Reckitt specifically represented to the FDA and numerous state agencies and state legislatures that the film version raised no additional or unique safety, abuse or diversion concerns over the drug in the tablet form. In fact, Reckitt falsely represented to these agencies and organizations that the film was safer, less divertible and less vulnerable to abuse than the tablets.

38. Reckitt submitted a risk evaluation and mitigation strategy ("REMS") after a review of which the FDA approved the film version of Suboxone on August 30, 2010. Reckitt commenced marketing the Suboxone film about that time, although it does not manufacture the film. The film is manufactured for Reckitt by MonoSol Rx, LLC in Warren, New Jersey, which holds a patent on the film, thus rendering Suboxone safe from generic competition for the life of the patent. Introducing a third party manufacturer into its Suboxone production process highlights the lengths to which Reckitt sought to avoid generic tablet competition as the costs of the third party manufacturer reduced the Suboxone profit margin.

39. The new film formulation of Suboxone is actually inferior to Suboxone tablets, and known to Reckitt to be inferior, for many reasons:

i. The film is more susceptible to diversion because it is easy to conceal. Reckitt learned this itself before the film was approved by the FDA when nearly 6,000 strips (46% of those dispensed to study patients) went missing during the clinical studies Reckitt performed in the FDA process. This serves to illuminate the desperation of these patients, the extent of the diversion problem and helps to explain why this drug has a greater sales volume than drugs like Viagra, Nasonex and Enbrel.

ii. Compared to sublingual use of a Suboxone tablet, the film version increases naloxone bioavailability when taken sublingually (this difference in biovailability does not exist when the Suboxone is dissolved and injected). Accordingly, when used sublingually, the film risks unwanted precipitation of opioid withdrawal, this causes significant induction and stabilization problems at the inception of the patients' treatment.

iii. The film is much easier to dissolve and inject than the tablet formulation, thus increasing its abuse potential and reducing one of the main benefits Suboxone is supposed to provide.

iv. The film presents substantially increased danger to children because it dissolves rapidly and children who accidentally place Suboxone film in their mouths tend to absorb the buprenorphine it contains dangerously fast. It is difficult or impossible for a child to spit out or remove the film from their mouth because, upon putting it in their mouth, the film hydrates to a gel within approximately 30 seconds and dissolves completely over the course of approximately three minutes releasing all of the buprenorphine. In contrast, Suboxone tablets have a much longer oral residence time and children often spit them out. Moreover, when tablets are swallowed by children, the buprenorphine is absorbed to a far lesser extent compared with the film.

v. The packaging of the film also presents significant safety concerns for children. Each dose of the film is packaged in a child-resistant sleeve. Once the integrity of the sleeve is breached, it no longer offers protection. Reckitt knew that a significant portion of patients took their Suboxone in divided doses, yet supplied no child-resistant bottle or other container into which unused portions of the film could be stored. Suboxone tablets were supplied in a child-proof bottle.

C. Prescription Standards: Permitted "On Label" Uses & DATA 2000 Compliance

40. When Suboxone and Subutex were introduced in their original tablet form, the United States Food and Drug Administration Center for Drug Evaluation and Research reviewed Reckitt's new drug application ("NDA") for data and information from clinical trials for the purpose of ensuring that they were appropriate for the asserted uses, dosages and indications. Once Suboxone and Subutex were approved, the FDA worked with Reckitt on the final

publication of the package insert/prescribing information ("Package Insert") that was to be distributed with the medication. The Package Inserts for Suboxone and Subutex tablets are attached hereto as **Exhibit B.** The Package Insert later approved for Suboxone film is attached as **Exhibit C**.

41. Under the Food, Drug and Cosmetic Act of 1938, pharmaceutical manufacturers are prohibited from "misbranding" or marketing a drug for use in other than FDA approved indications and dosages as set forth in the Package Insert. *See, e.g.,* 29 U.S.C. §331.

42. Suboxone tablets are uncoated and intended for sublingual administration. Suboxone film is also intended for sublingual administration. Both the tablet and the film are available in two dosage strengths: 2 mg buprenorphine with .5 milligrams naloxone; and 8 mg buprenorphine with 2 mg naloxone.

43. Subutex tablets are uncoated and intended for sublingual administration. They are available in two dosage strengths, 2 mg buprenorphine and 8 mg buprenorphine. Subutex contains no naloxone.

44. The Package Insert approved for Suboxone and Subutex tablets by the FDA indicates that they are "indicated for the treatment of opioid dependence."

45. Under the "**Dosage and Administration**" section of the Package Insert for the tablets it is noted that "Subutex or Suboxone is administered sublingually as a single daily dose in the range of 12-16 mgs/day."

46. The following guidance is contained under the section of the tablet Package Insert captioned "**Adjusting the dose until the maintenance dose is achieved:**"

> The recommended target dose of Suboxone is 16 mg/day. Clinical studies have shown that 16 mg of Subutex or Suboxone is a clinically effective dose compared with placebo and indicate that doses as low as 12 mg may be effective in some patients. The

> dosage of Suboxone should be progressively adjusted in increments/decrements of 2 mg or 4 mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4 to 24 mg/day depending on the individual.

47. An addicts' treating physician must perform a form of diagnosis or assessment known as "induction" before maintenance treatment can begin. During the induction phase the physician determines the appropriate maintenance dosage. Reckitt performed no studies, and no studies were performed by any third parties, assessing Suboxone's efficacy for use in the induction/diagnosis phase of patient assessment. The Package Insert states as follows:

> In a one-month study of Suboxone tablets induction was conducted with Subutex tablets. Patients received 8 mg of Subutex on day 1 and 16 mg Subutex on day 2. From day 3 onward, patients received Suboxone tablets at the same buprenorphine dose as day 2. Induction in the studies of buprenorphine solution was accomplished over 3-4 days, depending on the target dose.

48. The tablet Package Insert does not state that Suboxone is appropriate for use during induction.

49. The Package Insert for Suboxone film resolves this issue by noting that "Suboxone film is indicated for the maintenance treatment of opioid dependence" thus making it clear that it is not indicated for induction.

50. The dosage information set forth in the Suboxone film Package Insert is identical to the tablet Package Insert.

51. The Suboxone tablet Package Insert contains a table of "adverse events" by body system and treatment group that were observed during a 16 week study. The study observed and evaluated adverse reactions at various daily dosage levels of Suboxone up to 16 mg. The various dosage levels studied were described as follows:

i. A 1 mg solution, which would be less than a tablet dose of 2 mg, was described as a "very low" dose;

ii. A 4 mg solution was noted as approximating a 6 mg tablet and described as a "low dose";

iii. An 8 mg solution was noted as approximating a 12 mg tablet and described as a "moderate dose";

iv. A 16 mg solution was noted as approximating a 24 mg tablet and was described as a "high dose".

52. No higher doses were studied for adverse events and, except as noted with a potential 24 mg dose in paragraph 46, *supra*, no higher doses were otherwise noted or contemplated in the Suboxone Package Inserts.

53. The Suboxone Package Inserts for both the film and the tablets note that the drug is indicated for "maintenance treatment of opioid dependence" (Suboxone film) and "treatment of opioid dependence" (Suboxone tablets) "as part of a complete plan to include counseling and psychosocial support." In order to ensure that physicians monitored the counseling and psychosocial support element of treatment and to stem other potential negative consequences of physicians running Suboxone "mills," the Drug Addiction and Treatment Act of 2000 ("DATA 2000") mandated that treating physicians be certified to treat addicts and have no more than 30 patients on Suboxone during their first year of qualification and no more than 100 patients under their supervision on Suboxone after their first year of qualification[2].

54. Suboxone and Subutex were never approved or indicated for use as a medication for induction, for use in dosages more than 24 mg for use during pregnancy or for treatment of pain by the FDA, and any such uses are off label uses.

[2] These limits were increased in 2016.

D. Defendants' Fraudulent Practices

55. Defendants' executives, sales representatives and paid physician "treatment advocates" ("TA's"), including but not limited to: Ana Farr (sales representative), Scott Daniel (sales representative), Jaime Neil (sales representative), Joe Hall (sales representative), Clint Gagnon (sales representative), Andie Hall (sales representative), Jessica Burke (sales representative), Mary Bashkar (sales representative), Teri Turconi (sales representative), Melanie Miller (sales representative), Mathew Holland (sales representative), Scott Norman (sales representative), Gina Reed (sales representative), Lori Davis (sales representative), Lori Eaton (sales representative), Stephanie Galicia (sales representative), Jeff Bodenburg (sales manager), Jason Boehmer (sales manager), Mike Himple (sales manager), Rosemarie Paulus (sales manager), Michael Bruno (sales manager), James Sharp (executive), Richard Powers (executive), Adrian Norton (executive), Brandy Duso (executive), Vickie Seeger (executive), David Byram (executive), Dr. Jane Ruby (executive), Dr. Mark Crause (TA), Dr. Tom Kosten (TA), Dr. Michael Frost (TA), Dr. Bryan Woods (TA), Dr. Stephen Lamb (TA), Dr. Robin Peavler (TA), Dr. Seth Ivins (TA), Dr. George Bright (TA), Dr. Carl Sullivan (TA) and/or Dr. Bernd A. Wollschlaeger (TA) under the supervision and direction of Shaun Thaxter, former United States CEO and now International CEO, knowingly, with reckless disregard and/or deliberate ignorance as to the truth, falsity and lawfulness of said practices committed the following unlawful acts and fraudulent practices as described in paragraphs 55 through 151, herein[3], which include the following:

i. Defendants' sales representatives actively and unlawfully marketed "off-label" dosages of Suboxone over 24 mg per day when the maximum daily dosage indicated in

[3] Some of Reckitt's sales representatives, including some of those listed in this paragraph, complained to their area managers that it was an "off label" practice to market Suboxone/Subutex in the manner described in this Complaint. When this would occur, representatives were dissuaded from taking any further action or faced disciplinary action.

the Package Insert and approved by the FDA, was 16-24 mg per day. Defendants' TA's and sales representatives supported this unlawful marketing by providing physicians written detail pieces and oral representations that dosing over 24 mg per day was effective and safe and/or by encouraging physicians that they could prescribe higher dosages by writing the prescriptions for pain (an off label use) rather than addiction.

ii. Defendants' sales representatives unlawfully promoted the off-label use of Suboxone for induction, in both the film and tablet form, when no studies had been performed to evaluate Suboxone's efficacy for induction and in spite of the fact that Suboxone was expressly indicated only for "maintenance treatment" (film) and "treatment" (tablet) for opioid dependence.

iii. Defendants' sales representatives unlawfully promoted the off-label use of Suboxone for use during pregnancy in both the film and tablet form, when no studies had been performed to evaluate Suboxone's efficacy for pregnancy.

iv. Defendants intentionally and unlawfully marketed Suboxone and Subutex to physicians in violation of the Drug Addiction Treatment Act of 2000, 21 U.S.C. §801, et seq. ("DATA 2000") by:

a) knowingly selling, marketing and promoting Suboxone and Subutex to physicians who were not certified and/or registered under DATA 2000;

b) knowingly selling, marketing and promoting Suboxone and Subutex to physicians who had been certified and/or registered under DATA 2000 for less than one year and were treating more than thirty patients in violation of 21 U.S.C. §823(g);

c) knowingly selling, marketing and promoting Suboxone and Subutex to physicians who had been certified and/or registered under DATA 2000 for more than one year and were treating more than 100 patients in violation of 21 U.S.C. §823(g);

d) knowingly selling, marketing and promoting Suboxone and Subutex to physicians to treat additional "addicted" patients over the Data 2000 patient limit; and

e) knowingly selling, marketing and promoting Suboxone and Subutex to physicians by encouraging and persuading them to prescribe higher than approved dosages by writing the prescriptions for pain (an off label use) rather than addiction.

v. Defendants obtained approval of Suboxone film by making false representations to the FDA, and then unlawfully marketing the product to the United States and to multiple states, by knowingly and falsely representing to physicians, State Payors, Federal Payors, state agencies and legislatures that Suboxone film was "safer" for the patients and children than Suboxone tablets;

vi. Defendants obtained approval of Suboxone film by making false representations to the FDA, and then unlawfully marketing the product to the United States and to multiple states, by knowingly and falsely representing to physicians, State Payors, Federal Payors, state agencies and legislatures that Suboxone film had less risk of diversion, misuse and abuse than Suboxone tablets;

vii. Defendants unlawfully paid physicians money ostensibly for providing some educational service to other physicians when, in fact, the physicians were simply being paid to write prescriptions, promote and market Suboxone "off label", and to falsely promote and market Suboxone film as safer and less divertible than tablets. More specifically, these physicians, many of whom were in Reckitt's TA program, were paid by Reckitt to market and

promote Suboxone in "off label" dosages (in excess of 24 mg per day) and uses (induction, during pregnancy and for pain) and to support Reckitt's false claims that Suboxone film was safer and less divertible. These ruses included: payments for "lunch and learns", mentorships, speaker programs, "teach the rep" programs, managed care presentations, and presentations to officials for state Medicaid agencies and state legislatures. Such conduct was in violation of the False Claims Act and the Anti-Kickback statute, 42 U.S.C. §1320a-7b.

viii. Defendants' sales representatives and TA's routinely and unlawfully distributed physician pricing schedules, referrals and dispensed advice to physicians on how to start and grow Suboxone-based practices and provided other services of value to physicians in order to induce them to prescribe Suboxone and Subutex in violation of the False Claims Act and the Anti-Kickback statute, 42 U.S.C. §1320a-7b.

ix. Defendants unlawfully gave physicians services and things of value in return for their prescribing Suboxone and Subutex through its "Here to Help" program in violation of the False Claims Act and the Anti-Kickback statute, 42 U.S.C. §1320a-7b.

x. Defendants unlawfully paid kickbacks to state Medicaid officials in order to obtain exclusive status on state formularies and to destroy competition in violation of the following laws and regulations: the Anti-Kickback Statute, 42 U.S.C. §1320a-7b; the regulatory "safe harbor" guidance provided at 42 CFR §1001.952(h); and the OIG Compliance Program Guidance for Pharmaceutical Manufacturers, Federal Register Vol. 68, No. 86, pp. 23734-23735 (May 5, 2003) ("2003 OIG Guidance").

xi. Defendants conspired with TA's other physicians and other persons to achieve the unlawful purposes set forth herein.

1) Marketing "Off Label" Dosages and Uses of Suboxone and Subutex

56. From 2004 until at least through 2013, Defendants' executives, TA's and sales representatives actively and unlawfully marketed and promoted "off label" dosages of Suboxone/Subutex in excess of 24 mg per patient per day to physicians so that these physicians would, in turn, prescribe these dosages to their patients. The maximum daily dosage/use approved by the FDA and/or indicated by the Package Insert was at the time, and still is today, 24 mg per day. All extant studies indicate that because of buprenorphine's "ceiling effect," daily dosages above 16 mg per day generally have no additional therapeutic benefits or use for patients.

57. Relator has personal knowledge that RBP's Vice President of Sales, Adrian Norton[4], was aware of and sanctioned the aggressive marketing and promoting of Suboxone and Subutex in dosages in excess of 24 mg per patient per day. RBP's and now Indivior's Zone Directors, and in particular Richard Powers, directed and continue to direct the Area Sales Managers to aggressively market and promote Suboxone and Subutex in dosages in excess of 24 mg per patient per day and directed their sales representatives to do the same.

58. To support and encourage sales representatives to market dosages over 24 mg per day, Defendants presented PowerPoint training programs promoting daily Suboxone and Subutex dosages of over 24 mg. While it is unknown to the Relator exactly how many times this PowerPoint presentation had been presented nationally, it was used on several occasions in regions throughout the United States to persuade sales representatives to market, promote and encourage physicians to prescribe Suboxone and Subutex in dosages above 24 mg per day.

[4] It is unknown whether Adrian Norton is still employed by Indivior, however, at the time Indivior was spun off from RBG and RBH the entire executive team of RBP, including Norton, remained as Indivior's executives.

59. In addition, Defendants' TA's were instructed to promote doses of Suboxone and Subutex in excess of 24 mg per patient per day to other physicians, health care personnel and state agencies, and did, in fact, promote the use of both drugs in dosages over 24 mg per day throughout the United States.

60. Defendants' Zone Director and National Sales Director, Richard Powers, along with Area Business Directors and Area Business Managers, including but not limited to, Jeff Bodenburg, Jason Boehmer, Rosemarie Paulus, Michael Himple, Laurie Kyle and Michael Bruno, exhorted their sales representatives and TA's to increase volume on Suboxone and Subutex sales. These executives openly encouraged sales representatives to persuade physicians that dosages in excess of 24 mg per day were beneficial to many patients. Such promotion was done by utilizing information from misleading "detail pieces," such as their Product Monograph, and by verbally suggesting that dosing over 24 mg per day was effective. These executives further unlawfully marketed Suboxone and Subutex for the off label use of pain to circumvent the maximum allowed dosage, cover up the unlawful prescription dosage level and/or bypass the constrictions of DATA 2000. Some of the sales representatives personally known to the Relator as having made misleading representations are Ana Farr, Scott Daniel, Jaime Neil, Joe Hall, Clint Gagnon, Andie Hall, Mary Bashkar, Teri Turconi, Melanie Miller, Mathew Holland, Scott Norman, Gina Reed, Stephanie Galcia, Lori Davis, Lori Eaton and managed care specialists Paul Bragoli, Keith Lockwood, Juan Tripp and Sam Moffett.

61. The effort by Defendants' executives, sales representatives and TA's to market Suboxone and Subutex for use in dosages exceeding 24 mg per day was coordinated and well known to senior executives including those identified in the paragraphs above. In fact, in the

summer of 2013, while in her office, Brandi Duso, the Compliance Officer for RBP, admitted to Relator that evidence of the high dosage marketing practice was "overwhelming."

62. The State and Federal Payors paid significant sums because of prescriptions issued as a result of Defendants' unlawful efforts that otherwise would not have been paid. By 2010, state Medicaid programs, legislators and others began expressing concern about the high dosages (and the corresponding government payments for these higher dosages) as well as the diversion and misuse of the drug that was occurring. A few states began to limit the dosage levels for which Medicaid payment would be allowed. Defendants' employees nevertheless continued to market the drug at higher dosage levels which encouraged physicians, at times, to write two prescriptions, one paid for by Medicaid and another paid for in cash.

63. Defendants' employees knew that, as a consequence of prescribing higher dosages, many patients would divert the tablets or film for resale and misuse by the public. Such diversion and misuse by the public became pandemic and a root cause of further addiction and crime.

64. Some of Defendants' sales representatives complained to their Area Managers that it was an "off label" practice to market Suboxone and Subutex in the manner described in the preceding paragraphs. These representatives were dissuaded from taking any further action or were fired.

65. In June 2010, Relator was present at a Kentucky Pharmacy Association meeting in Louisville, Kentucky. Reckitt sales representative, Jamie Neal, was also there and was operating Defendants' promotion booth for Suboxone. She openly promoted Suboxone in dosages above 24 mg per day. When Neil was confronted by Relator about her marketing statements concerning the dosages, Neil stated, "You don't understand, I must keep my volume

up or my boss [Jeff Bodenburg] will fire me." Relator confirmed through other sources that Bodenburg instructed sales representatives to promote dosages above 24 mg.

66. In the summer of 2010, Dr. Thomas Badgett, Kentucky Medicaid Medical Director, convened a meeting to discuss serious concerns involving the high volume and dosages of Suboxone being paid by Medicaid. Other concerns involving public safety issues surrounding the misuse of the drug were discussed. Dr. Badgett, Van Ingram (Kentucky Office of Drug Policy), Michelle Flowers (Kentucky State Behavioral Health and Substance Abuse) and Relator were in attendance.

67. Dr. Badgett presented Relator with data showing an astounding number of high dosage prescriptions of Suboxone. These data included prescriptions over 24 mg and up to 108 mg per patient per day and also included physicians who were prescribing to more than the 100 patient limit allowed by Data 2000. While this was consistent with what Relator was hearing in other states, Kentucky was more severe. Dr. Badgett expressed great concern over the misuse and abuse of Suboxone. He questioned whether Suboxone was being used for treatment or whether it was just another opioid to be abused like OxyContin.

68. The evening after that meeting, Relator emailed her immediate boss, David Byram, along with Vickie Seeger, Richard Powers, and Adrian Norton about Dr. Badgett's concerns and her own concerns. She asserted that Defendants were intentionally marketing the large volumes and off label dosages of over 24 mgs per day per patient. She asserted that RBP was creating the environment for diversion and misuse. Relator cited specific examples of unlawful marketing and accused them of being fully knowledgeable of the ongoing abuse in the Appalachian area. She questioned how they could tout their concern for patient care with

Suboxone on one hand, yet still promote dosages in excess of 24 mgs per day per patient and support physicians who were over their Data 2000 limit.

69. The following morning Relator received a call from Byram and was told that her email was inappropriate and should not have been written. She was advised that Norton and Seeger were furious. When Relator asked what was untrue about the email, Byram admitted that it was all true but asserted that it should have been stated orally and not in writing.

70. Seeger also called Relator and assured her the Suboxone film was going to help with the diversion and pediatric exposure issues. Seeger admitted that she knew things were out of control and understood her concerns. Relator later learned that Seeger's representation of how the film would help curb the diversion problem was false and that Reckitt officials knew same was false. Dr. Ed Johnson, RBP's Medical Director, was privately stating that the film was not safer, was not less divertible, and not subject to less abuse as discussed *infra*.

71. Relator also received a response to her email from Norton. He directed her not to put anything in writing again concerning these matters. Relator's emails to Norton, Powers, Bodenburg, Seeger and Byram referencing these issues were removed by Defendants after her computer was turned over to RBP's IT department for a software update.

72. After Relator's email referenced in paragraph 68, above, Richard Powers set up a meeting in Indianapolis, Indiana, with Relator, Jeff Bodenburg, Jason Boehmer and a Reckitt Medical Associate. Powers started the meeting by suggesting that Relator was new to the company and did not understand the history of Reckitt and the marketplace of opioid addiction. Powers had Bodenburg and Boehmer attempt to indoctrinate Relator by explaining the history of Reckitt. She was advised that they knew about the diversion but diminished the concern by stating diversion was good as it led addicts to treatment. They also tried to convince Relator that

32 mg was an appropriate dosage. Relator challenged the appropriateness of the dosage. At times Bodenburg was angered and accused Relator of working against the team.

73. On September 16, 2010, a hearing of the Kentucky Medicaid Pharmacy and Therapeutics Committee was held in Frankfurt, Kentucky. Of major concern to the committee were the high dosages of Suboxone being prescribed. The committee was meeting, in part, to consider the necessity of a "pre-authorization" from Medicaid before Suboxone and Subutex could be prescribed. Dr. Badgett was present and reported that 33% of the Kentucky Medicaid population was on dosages of 32 mg per day per patient or more.

74. Two of Reckitt's TA's attended the meeting to argue against pre-authorization and supported dosages over 24 mgs. A committee member asked Dr. Stephen Lamb, one of the Reckitt TA's, if he had any interest in Reckitt, and Lamb responded that he attended the committee meeting on his own volition. Upon further questioning he admitted that he had been asked to attend the meeting by Jamie Neil, Defendants' sales representative. He did not disclose his status as a paid Reckitt TA. Relator questioned Dr. Lamb afterwards, and he again confirmed that he had been asked to attend by Neil.

75. Relator reported her concerns about Neil requesting that Lamb attend the meeting to David Byram and to Richard Powers. Relator was advised in an email from Byram to "leave it alone now."

76. Relator has personal knowledge of other sales representatives marketing off label dosages of Suboxone. One of the most successful was Joe Hall. His territory included Kentucky, Tennessee, and Southwest Virginia and his patient numbers using Suboxone were approximately 9000. When Relator asked him how he was so successful, he stated that you had to increase value to get bonuses at Reckitt. When a physician got to a hundred, he had to get them to write

dosages of over the 24 mg maximum dose. She asked him if this increased the rate of diversion, and he replied "absolutely". He further advised that his boss, Jeff Bodenburg, instructed him specifically to do what he was doing with respect to the excess dosaging.

77. As stated previously, the off label dosages were not only promoted by the sales representatives but also by Defendants' Treatment Advocates. One such TA was Dr. Bryan Wood. Dr. Wood and other TA's were paid by Defendants to go to other physicians' offices and promote the use of Suboxone for "off label" purposes. Dr. Wood discussed his practice's liberal use of dosages above 24 mg per day at the "lunch and learns" and similar forums where Defendants promoted and endorsed this practice as well as others.

78. On December 8, 2010, Dr. Wood reported in an email to Defendants' executives and sales representatives Derrick Hawkins, Terry Ragland, James Durham, Jaime Neil and the Relator that 40% of patient dosages at a large practice in Kentucky and Tennessee known as SelfRefind Physicians exceeded 24 mg per day in November of 2010. In this practice, 18.03% of their patients were taking 28 mg per day, 21.21% were taking 32 mg per day, and 1% were taking more than 32 mg per day. Dr. Wood stated to the Reckitt sales representatives and executives in the email, "[W]e will use it [the dosage data related above] as we move forward educating our physicians about appropriate dosing strategies, tapering strategies and comparisons among like providers (other SR physicians.) Thought you would want to know."

79. In addition to the above, Relator also has direct knowledge of Defendants maintaining a sales representative bonus structure known as the Sales Incentive Program ("SIP") pursuant to which sales representatives were paid on volume of Suboxone and Subutex prescribed thus encouraging and supporting the unlawful marketing. Defendants have maintained this program or a variation of it for many years.

80. Sales bonus volumes were not capped at individual prescription volumes of 24 mg per day but were paid on volumes exceeding the 24 mg limit as well. This provided an incentive to the sales representatives to market Suboxone and Subutex at higher levels so their sales volumes were high and, correspondingly, their bonuses were high.

81. In April 2013, at the Reckitt National Sales meeting in Florida, Brad Ashby, the manager of the SIP program, admitted to Relator that he knew that the marketing and sales of Suboxone at dosages over 24 mg per day was endemic from "New Orleans up the Appalachian Trail" and further admitted that he knew the SIP program was paying bonuses to the sales representatives which included volumes of the drug sold for prescription dosages over 24 mg per day. While at the meeting, Gay Green Cardin, a sales representative, also admitted to Relator that Area Business Manager Boehmer had instructed sales representatives to try and persuade physicians to dose at 32 mg and above per day per patient.

82. The use of Defendants' SIP program was a fundamentally different and more egregious bonus or incentive practice than those employed by other pharmaceutical companies. In the case of Defendants, Suboxone and Subutex were not indicated for dosages over 24 mg per day. Reckitt had the ability to easily determine if Suboxone was being prescribed by physicians in dosages higher than 24 mg per day, and in fact, maintained statistics on same. Despite being able to easily determine whether doctors were prescribing Suboxone off-label and restricting the SIP program bonuses only to those individual patient sales volumes at or below 24 mg per day, Defendants intentionally ignored this information and paid bonuses for sales volumes that included individual patient dosages higher than 24 mg per day. By the very nature of the SIP program, Defendants intentionally and knowingly encouraged and permitted the illegal dosage scheme and paid their employees bonuses for their success. This incentivizing system was one of

the engines that drove up the alarming dosage levels seen by state legislators and the state Medicaid agencies.

83. Defendants knowingly and unlawfully marketed and promoted the off label use of Suboxone in dosages greater than 24 mg per day to hundreds of physicians across the United States, including, but not limited to, those listed below:

PHYSICIANS	PRACTICE LOCATION
Herbert G.	Pennsylvania
Frank S.	Pennsylvania
William C.	Pennsylvania
David S.	Pennsylvania
Philip L.	Pennsylvania
Arthur D.	Pennsylvania
Mariano P.	Pennsylvania
Adid B.	Pennsylvania
Leo F.	Pennsylvania
Rallie M.	Kentucky
Piotr Z.	Kentucky
William F.	Kentucky
Clifford D.	Tennessee
Richard P.	Tennessee
Clary F.	Tennessee
Michael M.	Tennessee
Daniel P.	Tennessee
Arthur B.	Tennessee
MacK H.	Tennessee
Melvin L.	Tennessee
Timothy C.	Virginia
Joshua W.	Virginia
Tomas V	West Virginia

The full names and practice locations of the above physicians, as well as others, have been provided in Relator's disclosure of evidence.

84. In addition to the off label use described above, Defendants' executives, sales representatives and TA's, including many of those identified in paragraph 55 above, knowingly

and unlawfully promoted off label use of Suboxone tablets and film for use in induction, treatment of pain and during pregnancy when no such uses were indicated in the Package Insert.

85. Throughout her tenure with RBP, Relator attended numerous roundtables and other meetings where Defendants' TA's promoted off label uses of Suboxone and Subutex as to dosage, pain treatment, use during pregnancy and for induction to other physicians. These roundtables and meetings were also attended by sales representatives who did nothing to restrain the TA's when they presented to the physicians.

86. In 2013, Defendants' TA's and managed care representatives were given a national training presentation sponsored by Defendants which encouraged and sanctioned the prescription of Suboxone, in both tablet and film form, in dosages greater than 24 mg per day and for use in induction. The Relator has personally observed these training materials, is in possession of some of them and has disclosed same to the United States and the states identified herein. Dr. Jane Ruby, RBP's Medical Affairs Director and other Reckitt officials drafted these training materials.

87. An example of said training materials are attached hereto as **Exhibit D** and incorporated herein by this reference. A consultant drafted the training materials contained within **Exhibit D** for Defendants. The consultant was paid to draft these materials and then market Suboxone in accordance with the presentation contained therein.

88. Even as late as the summer of 2013, just before Relator left her employment with Defendants, she witnessed Dr. Bernd A. Wollschlaeger, one of Defendants' TA's, give a presentation to Virginia Premier, a managed Medicaid organization, in which he openly promoted Suboxone for treatment of pain, use during pregnancy and dosing over 24 mgs.

89. Such practice has continued even after Relator's departure as she witnessed Dr. Carl Sullivan, another TA, promote off label use of dosages over 24 mg per day, for use in treatment of pain, during pregnancy and for induction while at the West Virginia Medical Association meeting in September 2013.

90. Promotion of the use of Suboxone film and tablets for use in induction, pain management, during pregnancy and in doses well above those contemplated in the Package Inserts occurred throughout the United States.

91. Admissions related to certain of the above facts were audio-recorded and said recordings have been disclosed to the United States.

92. From approximately 2003 or 2004, Defendants' sales representatives promoted off-label uses of Suboxone tablets by encouraging physicians to review materials and information provided by an ostensibly independent patient advocacy organization known as The National Alliance of Advocates for Buprenorphine Treatment ("NAABT").

93. NAABT, through its website and other means, openly and aggressively promoted and continues to promote, the safety and efficacy of off-label uses of Suboxone and Subutex.

94. NAABT is not independent. The Defendants or certain of the Defendants have been the primary source of NAABT's funding for many years.

95. NAABT has maintained a *quid pro quo* arrangement with the Defendants where, in return for financial support provided by the Defendants, NAABT regularly and systematically published material on its website that openly advocated off-label marketing of Suboxone and Subutex.

96. Defendants used NAABT's appearance as an independent, non-profit entity in order to propagate materially false and misleading information about the Suboxone/Subutex

product line, was fundamentally inconsistent with the drug's FDA-approved package labeling and which directly contradicted the FDA's October 8, 2002 mandate that Defendants disseminate accurate educational material that complies with all manufacturers' labeling information.

97. NAABT's active concealment of its financial dependence upon the Defendants greatly improved their ability to market and promote Suboxone and Subutex. In reality, NAABT is nothing more than a *de facto* marketing arm of Defendants which operates to serve Defendants' unlawful marketing and promotional agenda.

98. The close relationship between NAABT and the Defendants has existed since the inception of NAABT in 2004. Some of the same addiction treatment advocates and clinical researchers who founded NAABT were intimately involved with RBP's securing of FDA approval for Suboxone tablets in 2002.

99. One specific example of the off-label promotion NAABT undertook is an article feature in NAABT's February, 2007, newsletter, Volume 3, No. 2, written by Richard Gracer, MD, and entitled "The Buprenorphine Effect on Depression." As its title suggests, this article advocates the use of Suboxone's primary ingredient, buprenorphine, as a safe, effective and appropriate treatment for depression.

100. Another article accessible on NAABT's website, "Challenges in Using Opioids to Treat Pain in Persons with Substance Use Disorders," written by Drs. Savage, Kirsh and Passik and published in the June, 2008 issue of *Addiction Science in Clinical Practice*, advocates using buprenorphine for pain management.

101. It is in the manner of the examples cited in the two preceding paragraphs that NAABT used its appearance of independence to engage in off-label marketing efforts on behalf of the Defendants that so plainly violate the False Claims Act and the state statutes cited herein.

2) **Unlawful Kickback Schemes to Promote Sales of Suboxone/Subutex**

a. The Anti-Kickback Statute

102. The Anti-Kickback Statute prohibits any payment, inducement or reward being conveyed to, or received from, any person for referring, recommending or arranging for the purchase of any pharmaceutical, medical service or medical device for which payment may be made under a federally funded healthcare program. 42 U.S.C. §1320a-7b(b).

103. Under the Anti-Kickback Statute, drug companies may not provide any services or remuneration, in cash or in kind, directly or indirectly, to induce the purchase, order or recommendation of drugs that are paid for by a federal healthcare program. *2003 OIG Guidance,* p. 23734. In addition to prohibiting outright bribes and rebate schemes, the statute also prohibits any provision of services, payments, or things of value any one purpose of which is to induce a physician to write additional prescriptions for a particular product, service or pharmaceutical. *Id.* Even if the provision of such value is also intended to compensate the recipient for legitimate professional services, if any one purpose of the emolument is to induce a prescription or sale of a drug, it is unlawful. *Id.*

104. The Patient Protection and Affordable Care Act, 42 U.S.C. §18001, was signed into law on March 23, 2010. The Affordable Care Act changed the language of the Anti-Kickback Statute to provide that claims submitted in violation of the Anti-Kickback Statute automatically constitute violations of the False Claims Act. 42 U.S.C. §1320a-7b(g). Further, the amended language of the Anti-Kickback Statute provides that to be found in violation of the statute "a person need not have actual knowledge . . . or specific intent to commit a violation".

105. Violation of the Anti-Kickback Statute subjects the violator to exclusion from participation in federal healthcare programs, treble damages, civil monetary penalties and imprisonment of up to five years per violation. 42 U.S.C. §§1320a-7(b)(7), 1320a-7a(a)(7).

106. The 2003 OIG Guidance warns manufacturers that the provision of any service or any thing of value to a physician who might prescribe the manufacturer's products requires the manufacturer to evaluate whether it is providing a valuable, tangible benefit to the physician with any one purpose or intent (even if there are other legitimate purposes or intentions) to induce or reward referrals. More specifically, the 2003 OIG Guidance mandates the following:

a) That the manufacturer determine whether the provision of a service or a payment has the potential to interfere with, or skew, a physician's clinical decision-making process;

b) That the manufacturer determine whether the provision of a service or payment has the potential to undermine the clinical integrity of a formulary process;

c) That the manufacturer ensure that information provided to prescribers, decision-makers and/or patients is complete, accurate and not misleading;

d) That the manufacturer determine whether the provision of a service or payment has the potential to increase cost to federal health care programs, beneficiaries or enrollees;

e) That the manufacturer determine whether the arrangement or practice has the potential to be a disguised discount to circumvent the Medicaid Drug Rebate program best price calculation;

f) That the manufacturer determine whether the provision of the service or payment has the potential to increase the risk of over-utilization or inappropriate utilization of a product; and

g) That the manufacturer determine whether provision of the service or payment raises patient safety or quality of care concerns.

1) The Provision of Rebates Under the Anti-Kickback Statute

107. Most state Medicaid programs maintain formularies or preferred medication lists for the treatment of various conditions. It is extremely important for a drug manufacturer to be included on the formulary or preferred provider list for their products to be competitive and eligible for Medicaid prescription payments.

108. It is not uncommon for drug manufacturers to offer state Medicaid programs discounts or rebates to enhance their product's value and competitiveness within the market.

109. While the Anti-Kickback Statute allows for the provision of manufacturer discounts and rebates, they are only permitted under a specific exception or "safe harbor" to the statute. 42 U.S.C. §1320a-7b(b)(3)(A); 42 CFR §1001.952(h). In order to qualify for the safe harbor, any discount or rebate must be in the form of, or arise from, a reduction in the price of the good or service "based on an arm's length transaction." *Id.*

110. The *sine qua non* for manufacturer discount and rebate programs provided to drug purchasers under the Anti-Kickback Statute is "open and legitimate price competition in healthcare." 2003 OIG Guidance, p. 23735.

111. In addition, the discount or rebate must be given at the time of sale or, in certain cases, set at the time of sale, even if finally determined subsequent to the time of sale. Conditions for obtaining a rebate cannot be presented to a customer after the fact or on a *post hoc* basis.

2) OIG Opinions Providing Guidance on the Anti-Kickback Statute

112. In a special fraud alert issued in May of 1992, the OIG responded to an inquiry about whether a hospital offering free training for a physician's office staff in CPT coding or laboratory techniques violated the Anti-Kickback Statute. The OIG held that it did.

113. In an advisory opinion issued in October of 2006, the OIG responded to an inquiry regarding the propriety of a seller of durable medical equipment offering free reimbursement consulting services to some of its customers. The referenced "reimbursement consulting services" included: (1) general claims submission information, such as advice on how to code products; (2) how to review claims; (3) information on assistance in appealing denied claims; and (4) providing assistance related to medical justification for receiving particular products. *See* OIG-HHS, Adv. Op. No. 06-16 (issued October 3, 2006). The OIG found that these services constituted remuneration and violated the Anti-Kickback Statute.

114. The OIG further determined that the reimbursement consulting services at issue "would neither be limited in nature, nor free-standing," noting that the free services "would potentially confer substantial independent value upon the DME supplier." *Id.* at 5. The OIG also stated that any assistance "securing Federal reimbursement for individual beneficiaries to receive particular products could cause beneficiaries to receive greater quantities of, or more expensive" product than they actually required. *Id.* In addition, such reimbursement services would tend to provide a financial incentive to steer customers to purchase the supplier's products, "even if products from other manufacturers were less expensive or more appropriate."

115. In an additional advisory opinion, the OIG determined that any services, including pre-authorization services, that save a physician's office time, result in a realization of savings, or which were designed to refer or induce the purchase of a manufacturer's products could constitute unlawful remuneration and thus implicate the Anti-Kickback Statute. *See* OIG-HHS, Ad. Op. No. 10-04 (issued April 30, 2010).

b. Payment to TA's to Market Suboxone/Subutex Off Label

116. From 2006 until at least through 2013, Defendants knowingly, with reckless disregard and/or with deliberate ignorance of the truth violated the False Claims Act and Anti-

Kickback Statute, and caused false claims to be submitted to the Federal and State Payors identified herein, by designing and operating a program of paying their TA's to unlawfully promote Suboxone and Subutex. For most of the relevant time period between 2006 and the present date, Defendants retained far more TA's than it employed sales representatives. This intensive and unlawful use of TA's to market Suboxone and/or Subutex has played a critical role in achieving phenomenal sales volume.

117. The TA's were given cash payments to market Suboxone and Subutex to other physicians, state Medicaid agencies and government officials. The conduct of Drs. Wood, Lamb, Wollschlaeger and Sullivan, and others, as set forth in paragraphs above, provide examples of the fraudulent and unlawful purposes to which Defendants put TA's in the marketing of these drugs.

118. Defendants' TA's and sales representatives were given national training presentations and/or other documents by Reckitt that encouraged and sanctioned the prescription of Suboxone in dosages greater than 24 mg per day and/or for use in induction, during pregnancy and for treating pain. The Relator has personally observed some of these training materials, is in possession of some of them and has disclosed same to the United States and the states identified herein.

119. Defendants were well aware that the use of the TA's in this manner violated Federal regulations. Relator is in possession of a tape recording where Brandy Duso reported at Reckitt's National Meeting in April of 2013 that Richard Simpkin, President of Reckitt Benckiser Pharmaceuticals, acknowledged Defendants were out of compliance with the use of TA's. Defendants chose not to correct it until January 2014.

c. Unlawful Referrals from the "Here To Help" Program

120. From 2009 until at least through 2013, Defendants knowingly, with reckless disregard and/or with deliberate ignorance of the truth violated the False Claims Act and Anti-Kickback Statute, and caused false claims to be submitted to the Federal and State Payors identified herein, by designing and operating a program entitled "Here to Help" by which Defendants referred and continue to refer patients to physicians and provide valuable office assistance to physicians in exchange for the physicians prescribing Suboxone and Subutex.

121. The "Here to Help" program was fully funded and staffed by Defendants ostensibly to provide support to Suboxone and Subutex patients as part of a complete treatment plan that also included counseling but in actuality was implemented to increase Defendants' sales of Suboxone in light of the challenge from generics and branded products recently brought to market.

122. Defendants marketed the program to the physicians as a benefit to their practice. Defendants paid sales representative a separate bonus for the number of physicians that they successfully enrolled in the program.

123. Physicians would then be encouraged to enroll their patients in the program to receive counseling and encouragement to continue to use Suboxone and Subutex. In reality little counseling was achieved as the primary purpose of the program was to sell prescriptions.

124. Defendants marketed the program to physicians in such a manner as to highlight the benefits of the program to the physician's practice, to include : (1) receiving direct patient referrals from Defendants' program, (2) reducing their office staffing needs, and (3) improving profitability/efficiency for prescribing physicians by creating processes, policies and documents to alleviate their office workloads and overhead.

125. Documents supporting these allegations are attached hereto and incorporated herein as **Exhibit E** (Patient Focus Quality Care) and **Exhibit F** (Here to Help slide presentation to physicians). In one of the promotional slide presentations in **Exhibit F**, Dr. Gregory Dobash touted the benefits of the program and how he received a referral of a patient that was two hours away. Another physician relates how a care coordinator of the program "called in with the patient, stayed on the line to introduce the patient, then left the line." The patient subsequently made an appointment with the physician the following week.

126. Defendants knowingly, with reckless disregard and/or deliberate ignorance of the truth designed and marketed the program whereby in exchange for the physicians prescribing Suboxone and Subutex, the physicians would receive direct patient referrals, valuable benefits and office assistance. Such conduct violates the Anti-Kickback Statute and the False Claims Act and resulted in false and fraudulent claims being submitted to and paid by Federal and State Payors.

d. Unlawful Assistance in Promoting Suboxone/Subutex

127. From 2006 to present, Defendants' executives, sales representatives and TA's have knowingly, with deliberate indifference and/or deliberate ignorance of the truth violated the False Claims Act and Anti-Kickback Statute by designing and operating an unlawful marketing program to promote and assist physicians in starting their own Suboxone/Subutex clinics. Defendants unlawfully provided services, support and things of value to prescribing physicians in order to induce them to prescribe Suboxone and Subutex to their patients.

128. These kickbacks and things of value included advice, proprietary information, business information, consulting services, suggestions and support in establishing and growing Suboxone/Subutex based practices.

129. Defendants maintained NAABT as a surrogate marketing arm disguised as a not-for-profit patient advocacy group. NAABT provided valuable marketing services for the Defendants, including off-label marketing and providing unlawful referrals, all in violation of the False Claims Act and the parallel state statutes cited herein.

130. It was common for Defendants' employees to provide things of value to physicians in order to induce them to prescribe Suboxone and Subutex. Defendants' employees assisted physicians in setting up Suboxone and Subutex practices in order that they could be more profitable and efficient. This Relator was aware of the routine nature of this unlawful practice from conversations with TA's, sales representatives and executives and from documents instructing sales representatives to assist in this regard. In the winter of 2011, she personally witnessed one sales representative, Ana Farr, hand out documents to a physician with specific pricing, competitive and proprietary information in order to convince him to set up such a practice. Relator witnessed Farr taking information to prospective Suboxone physicians which showed that other physicians charged $150 cash for each visit. She showed these physicians how to do the cash office visit charges to make additional money and told them about other physicians who were also doing the same. Farr instructed the physician and office staff how to use Suboxone and how to induct with it. When questioned about what she had done, Farr told Relator that everyone in Reckitt was doing the same thing she was doing.

131. In 2013, Defendants' sales representatives were under pressure and required to sign up 16-18 physicians a year in order to receive the portion of the bonus related to increasing physician providers. Relator was also aware of other sales representatives marketing the cash pay model with Suboxone and Subutex in order to meet their 16-18 new physician quota. In West Virginia, sales representative Kathy McClain promoted Suboxone and Subutex by showing the

prospective Suboxone/Subutex physicians how much other physicians were making from patients paying in cash. She told the prospective physicians that other physicians were making between $300 to $500 per patient in cash a month for office visits, drug screens and higher dosage prescriptions. In Virginia, sales representative Dalphine Atkins was promoting the cash pay model by having prospective Suboxone/Subutex physicians shadow another established physician who already employed that system.

e. Unlawful Payments for State Formulary Exclusivity

132. Under the safe harbors found at 42 CFR §1001.952(h), a rebate provided by a drug manufacturer to a purchaser is lawful only if it is the result of open competition. 2003 OIG Guidance, p. 23735. In addition to the 2003 OIG Guidance, the safe harbor provision establishes a predicate requirement that the arrangement be the product of an "arms-length transaction." 42 CFR §1001.952(h)(5).

133. Beginning in early 2013, competitive products were placed on state formularies as alternatives to Suboxone film. Shortly after this occurred, Defendants restructured their bids to foreclose and prevent any competition with Suboxone film. They did this by threatening state Medicaid agencies with the elimination of rebates that the state agencies had enjoyed since the film went on formulary in September of 2010.

134. In July of 2015, Defendants informed officials of West Virginia Medicaid, including Brian Thompson, a drug utilization and review manager, that if Bunavail, a drug competitive to Suboxone, was placed on the West Virginia formulary, West Virginia would no longer receive the "supplemental rebate" that it had previously and routinely received from Defendants. Because of this threat, West Virginia Medicaid officials reversed an earlier decision made in April of 2015 to place Bunavail on their state formulary and left Suboxone as the only listed drug. Upon information and belief the same threats have been made and acceded to in

Virginia, Massachusetts, California, Connecticut, Delaware, Florida, Georgia, Hawaii, Maryland, Michigan, Minnesota, Missouri, Montana, Nevada, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Oregon, Tennessee, Texas, Utah, Washington, Wisconsin and the District of Columbia.

135. Upon information and belief, Defendants have provided very significant and unlawful payments to gain exclusive positions on state Medicaid formularies in addition to West Virginia's. They have done so by communicating an express and open requirement to these states that in order for their Medicaid agencies to continue to receive substantial rebates, no other provider of similar or generic naloxone/buprenorphine pharmaceuticals may be placed on their respective formularies. Like West Virginia, states have acceded to Defendants' demand of exclusivity on state formularies because of Defendants' threat to end their rebate program.

136. By threatening to discontinue rebate programs in several states in the manner described above, Defendants have created a market environment in which open competition and arms-length transactions cannot occur. Their actions are antithetical to the goals of the Anti-Kickback Statute, the 2003 OIG Guidance, and 42 CFR §1001.952 to enhance and support free and open competition in an efficient and fair market. *See*, 2003 OIG Guidance, p. 23735; 42 CFR §1001.952(h)(5).

3) Marketing of Suboxone/ Subutex in Violation of DATA 2000

137. From 2004 until at least through 2013, in an effort to increase sales of Suboxone and Subutex, Defendants' executives, sales representatives and TA's knowingly, with deliberate indifference to and/or deliberate ignorance of the truth actively promoted and marketed Suboxone and Subutex in such a way as to encourage physicians to exceed the number of opioid addicted patients allowed under DATA 2000 and, more specifically, 21 U.S.C. §823(g).

138. Defendants maintained data on those physicians who prescribed to patients in excess of that allowed by Data 2000 and purposely continued to actively and unlawfully promote and market Suboxone and Subutex to those physicians. At times, sales representatives marketed Suboxone off label for pain in order to help support the physicians to circumvent the DATA 2000 patient limits. In Winter of 2013, Ray McIntyre, pharmacist for TennCare, reported to Relator the practice of physicians writing one prescription for the 8 mg limits and a second prescription for higher doses for pain.

139. In order to support the sales representatives' efforts to promote, target and encourage these physicians to exceed their 30 or 100 patient level, Defendants' employees were incentivized through the payment, based on volume, of SIP bonuses as previously discussed. Until 2011, sales bonus volumes were not capped at sales generated from those physicians who prescribed up to the lawfully permitted number of patients per physician, but allowed for, and paid on, patient volumes over and above the number of patients allowed to be treated under DATA 2000. When Relator complained about the SIP incentives, however, Defendants ceased the payment of bonuses for approximately a six month period on volumes over 100 patients. After subsequent complaints from the sales representatives, Defendants reinstated the bonus program. Since 2011, bonuses have been paid on the highest volume of a physician's patients up to 100 patients (not necessarily the first 100 allowed) plus a percentage of the total volume of all sales on the physician's patients.

140. As previously set forth, Defendants had the ability easily to determine if Suboxone/Subutex was being prescribed by physicians who had more than 100 patients and, in fact, Defendants maintained statistics on same. Despite being able to determine which physicians had a patient load greater than 100 patients and easily being able to exclude that

patient base and sales volume from the SIP bonus, Defendants intentionally ignored this information and included payment of bonuses based on sales volumes that were generated in violation of DATA 2000. These bonus systems generated substantial income to the sales representatives and substantial profits to Defendants. It is critical to note that virtually all bonuses paid to executives, directors and down to office staff employees of RBP and later Indivior were based on volume.

141. Defendants' executives, sales representatives, and TA's actively marketed Suboxone and Subutex to the following physicians, as well as many others, who were treating a number of opioid addicted patients in excess of the number permitted under 21 U.S.C. §823(g), and said marketing was done with knowledge of those facts:

PHYSICIANS	PRACTICE LOCATION
Herbert G.	Pennsylvania
Frank S.	Pennsylvania
William C.	Pennsylvania
David S.	Pennsylvania
Philip L.	Pennsylvania
Arthur D.	Pennsylvania
Mariano P.	Pennsylvania
Adid B.	Pennsylvania
Leo F.	Pennsylvania
Brian W.	Kentucky
Robin P.	Kentucky
Jerome D.	Kentucky
Robin P.	Kentucky
William C.	Kentucky
Christopher D.	Kentucky
William W.	Kentucky
Gary S.	Kentucky
Riley S.	Tennessee
Peter S.	Tennessee
Richard N.	Tennessee
John M.	Tennessee
Edgar O.	Tennessee
Robert G.	Tennessee
Micheal P.	Tennessee

Maria E.	Virginia

The full names and practice locations of the above physicians, as well as others, have been provided in Relator's disclosure of evidence.

4) Claims of False Superiority: Defendants Knowingly and Falsely Marketed Suboxone Film as Being Less Vulnerable to Diversion and Safer Than Suboxone Tablets

142. From the inception of the launch of Suboxone film until at least through 2013, Reckitt executives, sales representatives and TA's knowingly, with deliberate indifference and/or deliberate ignorance of the truth falsely promoted and marketed Suboxone film to Federal and State Payor officials and physicians as being less vulnerable to diversion and safer than Suboxone tablets. Many of these executives, sales representatives and TA's are identified in the paragraphs above. These false statements were made by Defendants' employees and TA's through oral and written communications as well as through handout marketing pieces.

143. Defendants' executives, sales representatives and TA's made numerous and material representations to state Medicaid officials that Suboxone film was less vulnerable to diversion, misuse and abuse than the tablets. Defendants' officials knew these representations were false when they were made. One example of these types of representations occurred shortly after Pierce Whites, a Kentucky Medicaid official, sent an email to James Sharp and Jessica Burke, both RBP executives, on April 18, 2013 and inquired as follows:

> As I understand it, you are making a public safety argument for the film based on diversion elimination and child proofing. We would like to see an argument showing that the short term savings on tablets is outweighed by the long term benefits of film. The argument against you is numbers based: the response should be too, at least in part. Diversion and child poisonings have costs, can you try to quantify those? Copy Senate staff as well, they seem receptive to your public safety argument and that is obviously critical.

144. Sharp responded to Whites' email as follows:

> Pierce,
>
> I can't thank you enough for the considerable time you shared with Karen, Patrick, Juan and I this morning and your willingness to find a way to encourage CoventryCare Managed Medicaid Plan to no longer pursue their current plan to force patients from the Suboxone Sublingual Film to the generic tablet. (A copy of CoventryCare's letter attached)
>
> . . . .
>
> To recap some of the key points I wrote down from today's meeting;
>
> • I wanted to start with the key advocates you thought we will need to work with going forward. In particular, we need to engage and develop best practices for MAT with PROP/Physicians for Responsible Opioid Prescribing, Kentucky ASAM and The Kentucky Board of Medical Licensure/KBML. ***We have a number of phenomenal clinical resources to contribute within our company and with Treatment Advocates/TA's who make up the best of the best local treatment providers that are role models for quality patient care.*** Each will be made available to these groups and to your offices as you require them. One of our company's guiding principles is to "Seek the Wisdom of the Team" and we look forward to our partnership with you and with them.
>
> . . . .
>
> • You also wanted to tap into any resource that would enable Kentucky to provide education on appropriate treatment and expand capacity to quality care. The first attachment is the Reckitt Benckiser Educational Grant Application. I was impressed by how much the state has already done to expand treatment capacity and would encourage you to work with the appropriate state association to apply for support for programming that will educate providers on the disease of opioid dependence and appropriate treatment with Suboxone Sublingual Film. Please have the interested association send their request to educationalgrants@rb.com. I believe that a full day summit can be developed as it has in Ohio to address this health and safety issue at the highest level and provide education to every key constituent that is engaged in providing a solution.

. . . .

- ***The subject of the use of Suboxone in pregnancy came up and as discussed this is an off label use for our product, so I recommended that you email me a request for this information from our Managed Care Medical Affairs Manager, Dr. Jane Ruby. Dr. Ruby can address any off label questions that you may have. Further, if you wish to have a more in depth perspective provided on the data we shared on unintentional pediatric exposures and the dire consequences attributed to the tablet version of our product, or the data supporting that there is clearly more diversion with the tablet versus our Suboxone Sublingual Film, don't hesitate to make that request as well as Jane is truly an expert on both topics.***

Finally and most importantly, you recommended that if the reasoning was sound, that a letter could be generated to the President of CoventryCares requesting that they reconsider their current plan to move patients in treatment with the ***safer Suboxone Sublingual Film to the generic tablets that can be crushed and inhaled and pose an increased risk of unintended pediatric exposure.***

Here are the salient points that should establish why this letter should be written as soon as possible and perhaps as you recommended that it gain appropriate media attention:

1. CoventryCares will be requiring KY Medicaid plan recipients to use a ***more divertible*** drug when they are already being treated with the ***safest product*** for them against their wishes. This is a disparity of treatment.

2. ***Moving patients to the generic increases the risk of diversion as the tablet can be crushed and inhaled,*** counter to what Congressman Rogers is fighting so passionately to eliminate with generics on Federal basis and which could increase the risk of relapse for many of those patients.

3. ***Tablets pose a measurably increased risk of unintentional pediatric exposure as loose tablets have shown to be attributed to all deaths of children to date[5] and over half of Medicaid recipients have children under the age of 6 which is the age group at greatest risk.*** A purely financial decision should not supersede the safety of even one child.

[5] As of this date, the experience with Suboxone was overwhelmingly with the pill form. The film had only recently been introduced.

I thank you again for your time, considerable attention and guidance today and look forward to working closely with your office in any way that I may be of service.

Regards,

James Sharp
State Government Manager-Midwest
Phone: (616) 974-9580
Reckitt Benckiser Pharmaceuticals, Inc.
10710 Midlothian Parkway, Suite 430
Richmond, VA 23235
www.suboxone.com

(Emphasis added).

145. Sharp then wrote an email to Dr. Jane Ruby, Reckitt's Medical Affairs Director. In this email, which was sent on April 18, 2013, Sharp states as follows:

Jane,

I know you are off tomorrow, but here's the response I received from Pierce Whites, the gentleman who is general counsel to speaker of the house Stumbo.

. . . .

We need costs savings long term showing that the short term savings on tablets is outweighed by the long term benefits of film. Pierce is pretty specific in terms of far reaching costs like ER visits, neonatal costs associated with unintentional drug poisoning cost, etc. This big picture cost data will compel him to generate the letter to CoventryCare's president.[6]

. . . .

146. These same claims of the false superiority of the film, and materially similar representations, were made by other of Defendants' sales representatives, executives and TA's. Defendants distributed **Exhibit G** to its TA's and prescribing physicians and asked them to send said correspondence to state Medicaid agencies. Many of them acceded in these requests. These

[6] CoventryCare is a contractor that provides support, advice and services to Kentucky Medicaid and Kentucky Medicaid patients.

letters falsely assert that Suboxone film is safer and less vulnerable to diversion than the Suboxone tablets. Defendants intentionally orchestrated this false and misleading campaign to achieve the unlawful objectives identified herein and to destroy competition and potential competition for the Suboxone brand. The false and misleading statements were material to the Federal Payors, State Payors and private insurers, all of whom relied on the veracity of the representations to their detriment. This caused a substantial delay in the market availability of generic Suboxone. This delay caused the Federal Payors, State Payors and private insurers significant damages.

147. When Relator questioned Defendants' practice of representing Suboxone film as less susceptible to pediatric exposure and injury, Jane Ruby sent her an email confirming that the U.S. Product Safety Commission had given the packaging of the tablet and film the same safety rating, effectively demonstrating the falsity of Sharp's representation to Kentucky Medicaid.

148. While Defendants were stating that the film was less divertible, they knew same was untrue at the time they developed the product. Dr. Edward Johnson, RBP's and later Indivior's V.P of Clinical, Scientific and Regulatory Compliance admitted to Relator privately, and to others in meetings, that the film was as easily divertible. Moreover, he knew and admitted to Relator in April 2012, at Reckitt's National meeting in California, that all that anyone needed to do to achieve the same high available in tablet form was to put the film on a spoon in water, heat the spoon, place the contents in a spray bottle or syringe, and then inhale it or inject it.

149. Defendants intentionally marketed the film as being less divertible and subject to abuse and represented to Federal and State Payors that they would have a system in which they would track prescriptions to help prevent abuse. In fact, Dr. Johnson advised Relator that the tracking program was never intended to be instituted. It never was instituted.

150. While Defendants stated that the film was safer, they knew this to be untrue at the time of marketing same. Dr. Johnson stated to Relator that the F2 packaging rating that Reckitt was touting as safer was the same as a child resistant prescription bottle of the type that Suboxone tablets and other tablets and pills were sold in.

151. The Defendants, in taking the actions set forth above, acted in concert with their TA's and other physicians to effect the false claims identified herein. The Defendants' collusion with its TA's and others caused much of the off-label marketing identified herein. The actions of Drs. Wood, Lamb, Wollschlaeger and Sullivan, identified above, among others, were the result of this of this collusion. In addition, Defendants colluded with NAABT to promote Suboxone as set forth above. Defendants further colluded with their TA's and other physicians by sending them letters, drafted by RBP (**Exhibit G**), to send to government officials, and which were, in fact, sent to government officials, falsely representing that Suboxone film was less divertible and safer than Suboxone or generic Suboxone in tablet form. All of these actions, and others identified in this Second Amended Complaint, constitute unlawful conspiracies in violation of the False Claims Act and the state statutes cited herein.

152. In committing the fraudulent acts and practices set forth in all preceding paragraphs herein, the Defendants:

1) knowingly presented, or caused to be presented, to an officer or employee of the United States government and the state and municipal governments identified herein false and fraudulent claims for payment and/or approval;

2) knowingly made, used or caused to be made or used, false records and/or statements to get a false or fraudulent claim paid or approved by the Federal and State Payors and agencies identified herein ;

3) conspired to defraud the Federal and State Payors by getting false or fraudulent claims allowed or paid; and

4) knowingly made, used or caused to be made or used, false records or statements to conceal, avoid or decrease an obligation to pay or transmit money or property to the United States government or state governments identified herein.

153. The vast majority of false claims related in this Second Amended Complaint were, in fact, paid by the Federal and State Payors identified herein. In paying the unlawful "kickbacks" and/or providing the things of value described herein to induce physicians and others to prescribe or purchase Suboxone and Subutex, the Defendants violated the respective Anti-Kickback statutes and False Claims Acts, or comparable statutes, of the federal government and the states identified herein.

154. In taking the actions set forth herein, the Defendants violated the Federal and State False Claims Acts identified herein, including 31 U.S.C. §3729, et seq.

COUNT 1

Violation of the Federal False Claims Act

"Off Label" Marketing Of Higher Suboxone and Subutex Dosages Than Those Lawfully Permitted By The FDA's Approved Packaging Insert

155. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

156. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth marketed, advertised for and encouraged physicians to prescribe Suboxone and Subutex in dosages not indicated or not otherwise approved for use by the FDA. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false and

fraudulent claims for the improper approval and payment of prescriptions for Suboxone and Subutex and used false and fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

157. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal and State Payors identified herein.

COUNT 2

Violation of the Federal False Claims Act

Marketing Suboxone and Subutex for the Off Label Uses of Induction and During Pregnancy

158. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

159. Defendants' sales representatives and TA's knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth promoted the "off label" use of Suboxone and Subutex for induction and during pregnancy, in both the film and tablet form, when no such indications were permitted within the Package Insert and no studies had been performed evaluating their efficacy for induction or use during pregnancy. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and Subutex and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

160. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal and State Payors identified herein.

COUNT 3

Violation of the Federal False Claims Act and Anti-Kickback Statute

Making Unlawful Kickback Payments to Treatment Advocates

161. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

162. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth violated the False Claims Act and Anti-Kickback Statute by designing and operating a program of paying their TA physicians to unlawfully prescribe Suboxone and Subutex, promote the writing of prescriptions of Suboxone and Subutex by other physicians, to assist in setting up other physicians' addiction practices and to market the drugs off label to those physicians. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and Subutex and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

163. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal and State Payors identified herein.

COUNT 4

Violation of the Federal False Claims Act and Anti-Kickback Statute

Providing Things and Services of Value to Physicians Through Defendants' Business Assistance Program and Through Their "Here to Help" Program

164. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

165. Defendants' sales representatives and TA's routinely distributed and provided physician pricing schedules, proprietary information, business information, consulting services, suggestions, support and free advice to physicians on how to start and grow Suboxone and Subutex practices. They knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth committed these acts in order to have the targeted physicians prescribe Suboxone and Subutex in large volume to their patients.

166. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth marketed, advertised for and encouraged physicians to prescribe Suboxone and Subutex by unlawfully providing referrals and other services and things of value through its "Here to Help" program to those physicians who prescribed Suboxone and Subutex.

167. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and Subutex and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

168. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal and State Payor programs identified herein.

COUNT 5

Violation of the Federal False Claims Act and Anti-Kickback Statute

Paying Kickbacks to State Medicaid Agencies to Obtain Exclusive Position on State Formularies

169. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

170. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth paid unlawful kickbacks to state Medicaid agencies the sole purpose of which was to destroy competition and to obtain exclusive positions on state formularies. This had the practical effect of eliminating or significantly reducing competition for Suboxone. These kickbacks violated the Anti-Kickback Statute, 42 U.S.C. §1320a-7b(b).

171. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

172. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal Payor and State Payor Programs identified herein.

COUNT 6

Violation of the Federal False Claims Act

Unlawful Marketing of Suboxone and Subutex to Physicians In Violation of DATA 2000 and for the "Off Label" Use of Pain Treatment

173. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

174. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth unlawfully marketed, advertised for and encouraged physicians to prescribe Suboxone and Subutex even when physicians were treating in excess of 30 patients in their first year of qualification under DATA 2000 and when they were treating in excess of 100 patients after their first year of qualification under DATA 2000.

175. In addition, Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth unlawfully marketed, advertised for and encouraged physicians to prescribe Suboxone and Subutex for the off label use of pain treatment in order to encourage and persuade physicians to circumvent the 30 and 100 patient limits set by DATA 2000 and to otherwise achieve larger sales volumes of Suboxone and Subutex.

176. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and Subutex and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

177. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal and State Payors identified herein.

COUNT 7

Violation of the Federal False Claims Act

Claims of False Superiority:
Unlawful Marketing to Physicians and Making False Statements to Federal and State Agencies Regarding Diversion and Safety to Promote Orders and Payment for Suboxone Film

178. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

179. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth, marketed, advertised for and encouraged physicians to prescribe, large volumes of Suboxone film by knowingly and falsely representing to these physicians that Suboxone film was less divertible than, and safer for patients, children and the public at large than, the tablet form of the drug. In doing so, Defendants knowingly caused to be presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

180. Defendants knowingly, with reckless disregard of the truth and/or deliberate ignorance of the truth marketed, advertised for and encouraged federal and state agencies to pay claims for Suboxone film submitted to them by knowingly and falsely representing to these agencies that Suboxone film was less divertible than, and safer for patients, children and the public at large than, the tablet form of the drug. In doing so, Defendants knowingly caused to be

presented to Federal and State Payors false or fraudulent claims for the improper approval and payment of prescriptions for Suboxone and used false or fraudulent records and documents to accomplish this purpose. The Federal and State Payors identified herein, unaware of the falsity and/or fraudulent nature of the claims caused to be presented by Defendants' conduct, paid for claims that otherwise would not have been allowed.

181. Defendants engaged in this conduct, knowing it to be unlawful, in an effort to destroy competition and potential competition for the Suboxone brand.

182. Defendants' conduct was the proximate and actual cause of more than $300 million in actual loss and damages to the Federal and State Payors identified herein.

COUNT 8

Violation of the Virginia Fraud Against Taxpayers Act

Va. Code Ann. §§ 8.01-216.1 to 8.01-219

183. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

184. This is a claim for treble damages and penalties under the Virginia Fraud Against Taxpayers Act.

185. The Defendants violated the Virginia Fraud Against Taxpayers Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in

violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

186. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the Commonwealth of Virginia for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

187. In addition, Defendants conspired with each other and with others to defraud Virginia by inducing its agencies to pay or approve false or fraudulent claims.

188. Virginia and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

189. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the Commonwealth of Virginia.

190. The Commonwealth of Virginia is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 9

Violation of the Massachusetts False Claims Act

Mass. Ann. Laws ch. 12, §§ 5(A)–(O)

191. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

192. This is a claim for treble damages and penalties under the Massachusetts False Claims Act.

193. The Defendants violated the Massachusetts False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

194. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the Commonwealth of Massachusetts for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

195. In addition, Defendants conspired with each other and with others to defraud Massachusetts by inducing its agencies to pay or approve false or fraudulent claims.

196. Massachusetts and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

197. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the Commonwealth of Massachusetts.

198. The Commonwealth of Massachusetts is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 10

Violation of the California False Claims Act

Cal. Gov't Code §§ 12651 – 12656

199. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

200. This is a claim for treble damages and penalties under the California False Claims Act.

201. The Defendants violated the California False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e)

paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

202. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of California for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

203. In addition, Defendants conspired with each other and with others to defraud California by inducing its agencies to pay or approve false or fraudulent claims.

204. California and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

205. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of California.

206. The State of California is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 11

Violation of the Colorado Medicaid False Claims Act

Colo. Rev. Stat. §§ 25.5-4-303.5 to 25.5-4-310

207. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

208. This is a claim for treble damages and penalties under the Colorado Medicaid False Claims Act.

209. The Defendants violated the Colorado Medicaid False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

210. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Colorado for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

211. In addition, Defendants conspired with each other and with others to defraud Colorado by inducing its agencies to pay or approve false or fraudulent claims.

212. Colorado and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

213. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Colorado.

214. The State of Colorado is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 12

Violation of the Connecticut Medicaid False Claims Act

Chapter 319v Sec. §17b – 301b, et al

215. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

216. This is a claim for treble damages and penalties under the Connecticut Medicaid False Claims Act.

217. The Defendants violated the Connecticut Medicaid False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing

physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

218. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Connecticut for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

219. In addition, Defendants conspired with each other and with others to defraud Connecticut by inducing its agencies to pay or approve false or fraudulent claims.

220. Connecticut and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

221. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Connecticut.

222. The State of Connecticut is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 13

Violation of the Delaware False Claims and Reporting Act

Del. Code Ann. tit. 6, §§ 1201– 11

223. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

224. This is a claim for treble damages and penalties under the Delaware False Claims and Reporting Act.

225. The Defendants violated the Delaware False Claims and Reporting Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

226. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Delaware for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

227. In addition, Defendants conspired with each other and with others to defraud Delaware by inducing its agencies to pay or approve false or fraudulent claims.

228. Delaware and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

229. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Delaware.

230. The State of Delaware is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 14

Violation of the Florida False Claims Act

Fla. Stat. Ann. §§ 68.081–68.09

231. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

232. This is a claim for treble damages and penalties under the Florida False Claims Act.

233. The Defendants violated the Florida False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e)

paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

234. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Florida for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

235. In addition, Defendants conspired with each other and with others to defraud Florida by inducing its agencies to pay or approve false or fraudulent claims.

236. Florida and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

237. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Florida.

238. The State of Florida is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 15

Violation of the Georgia Taxpayer Protection False Claims Act

Ga. Code Ann. §§23-3-120 – 23-3-127

239. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

240. This is a claim for treble damages and penalties under the Georgia Taxpayer Protection False Claims Act.

241. The Defendants violated the Georgia Taxpayer Protection False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

242. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Georgia for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

243. In addition, Defendants conspired with each other and with others to defraud Georgia by inducing its agencies to pay or approve false or fraudulent claims.

244. Georgia and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

245. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Georgia.

246. The State of Georgia is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 16

Violation of the Hawaii False Claims Act

Haw. Rev. Stat. §§661-21 – 661-29

247. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

248. This is a claim for treble damages and penalties under the Hawaii False Claims Act.

249. The Defendants violated the Hawaii False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e)

paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

250. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Hawaii for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

251. In addition, Defendants conspired with each other and with others to defraud Hawaii by inducing its agencies to pay or approve false or fraudulent claims.

252. Hawaii and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

253. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Hawaii.

254. The State of Hawaii is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 17

Violation of the Illinois Whistleblower Reward and Protection Act

740 Ill. Compo Stat. 175/1–175/8

255. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

256. This is a claim for treble damages and penalties under the Illinois Whistleblower Reward and Protection Act.

257. The Defendants violated the Illinois Whistleblower Reward and Protection Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

258. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Illinois for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by

Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

259. In addition, Defendants conspired with each other and with others to defraud Illinois by inducing its agencies to pay or approve false or fraudulent claims.

260. Illinois and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

261. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Illinois.

262. The State of Illinois is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 18

Violation of the Indiana False Claims and Whistleblower Protection Act

Ind. Code Ann. §§ 5-11-5.5-1 to 5-11-5.5-18

263. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

264. This is a claim for treble damages and penalties under the Indiana False Claims and Whistleblower Protection Act.

265. The Defendants violated the Indiana False Claims and Whistleblower Protection Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the

purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

266. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Indiana for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

267. In addition, Defendants conspired with each other and with others to defraud Indiana by inducing its agencies to pay or approve false or fraudulent claims.

268. Indiana and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

269. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Indiana.

270. The State of Indiana is entitled to the maximum penalty available for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 19

Violation of the Iowa False Claims Act

Iowa Code Ann. §685.5(i) et seq.

271. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

272. This is a claim for treble damages and penalties under the Iowa False Claims Act.

273. The Defendants violated the Iowa False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

274. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Iowa for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by

Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

275. In addition, Defendants conspired with each other and with others to defraud Iowa by inducing its agencies to pay or approve false or fraudulent claims.

276. Iowa and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

277. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Iowa.

278. The State of Iowa is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 20

Violation of the Louisiana Medical Assistance Programs Integrity Law

La. Rev. Stat. Ann. § 46:437.1 – 46.437.14

279. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

280. This is a claim for treble damages and penalties under the Louisiana Medical Assistance Programs Integrity Law.

281. The Defendants violated the Louisiana Medical Assistance Programs Integrity Law by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the

purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

282. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Louisiana for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

283. In addition, Defendants conspired with each other and with others to defraud Louisiana by inducing its agencies to pay or approve false or fraudulent claims.

284. Louisiana and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

285. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Louisiana.

286. The State of Louisiana is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 21

Violation of the Maryland False Health Claims Act

Md. Health-Gen Code Ann. §§ 2-601–2-611

287. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

288. This is a claim for treble damages and penalties under the Maryland False Health Claims Act.

289. The Defendants violated the Maryland False Health Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

290. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Maryland for payment or approval. Defendants knowingly made, used, or caused to be made or used false

records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

291. In addition, Defendants conspired with each other and with others to defraud Maryland by inducing its agencies to pay or approve false or fraudulent claims.

292. Maryland and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

293. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Maryland.

294. The State of Maryland is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 22

Violation of the Michigan Medicaid False Claims Act

Mich. Comp. Laws §§400.601 – 400.615

295. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

296. This is a claim for treble damages and penalties under the Michigan Medicaid False Claims Act.

297. The Defendants violated the Michigan Medicaid False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

298. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Michigan for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

299. In addition, Defendants conspired with each other and with others to defraud Michigan by inducing its agencies to pay or approve false or fraudulent claims.

300. Michigan and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

301. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Michigan.

302. The State of Michigan is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 23

Violation of the Minnesota False Claims Act

Minn. Stat. §§ 15C.01 – 15C.16

303. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

304. This is a claim for treble damages and penalties under the Minnesota False Claims Act.

305. The Defendants violated the Minnesota False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

306. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Minnesota for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

307. In addition, Defendants conspired with each other and with others to defraud Minnesota by inducing its agencies to pay or approve false or fraudulent claims.

308. Minnesota and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

309. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Minnesota.

310. The State of Minnesota is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 24

Violation of the Montana False Claims Act

Mont. Code Ann. §§ 17-8-401 – 17-8-416

311. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

312. This is a claim for treble damages and penalties under the Montana False Claims Act.

313. The Defendants violated the Montana False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

314. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Montana for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

315. In addition, Defendants conspired with each other and with others to defraud Montana by inducing its agencies to pay or approve false or fraudulent claims.

316. Montana and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

317. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Montana.

318. The State of Montana is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 25

Violation of the Nevada False Claims Act

Nev. Rev. Stat. Ann. §§ 357.010 – 357.250

319. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

320. This is a claim for treble damages and penalties under the Nevada False Claims Act.

321. The Defendants violated the Nevada False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

322. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Nevada for payment

or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

323. In addition, Defendants conspired with each other and with others to defraud Nevada by inducing its agencies to pay or approve false or fraudulent claims.

324. Nevada and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

325. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Nevada.

326. The State of Nevada is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 26

Violation of the New Hampshire False Claims Act

NH. Rev. Stat. Ann. §§ 167:61-b, et seq.

327. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

328. This is a claim for treble damages and penalties under the New Hampshire False Claims Act.

329. The Defendants violated the New Hampshire False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

330. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of New Hampshire for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

331. In addition, Defendants conspired with each other and with others to defraud New Hampshire by inducing its agencies to pay or approve false or fraudulent claims.

332. New Hampshire and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

333. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of New Hampshire.

334. The State of New Hampshire is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 27

Violation of the New Jersey False Claims Act

N.J. Stat. Ann. §§ 2A:32C-1 – 2A:32C-18

335. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

336. This is a claim for treble damages and penalties under the New Jersey False Claims Act.

337. The Defendants violated the New Jersey False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

338. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of New Jersey for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

339. In addition, Defendants conspired with each other and with others to defraud New Jersey by inducing its agencies to pay or approve false or fraudulent claims.

340. New Jersey and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

341. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of New Jersey.

342. The State of New Jersey is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 28

Violation of the New Mexico Medicaid False Claims Act

N.M. Stat. Ann. §27-14-1 et seq.

343. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

344. This is a claim for treble damages and penalties under the New Mexico Medicaid False Claims Act.

345. The Defendants violated the New Mexico Medicaid False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

346. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of New Mexico for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

347. In addition, Defendants conspired with each other and with others to defraud New Mexico by inducing its agencies to pay or approve false or fraudulent claims.

348. New Mexico and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

349. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of New Mexico.

350. The State of New Mexico is entitled to the maximum penalty for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 29

Violation of the New York False Claims Act

N.Y. State Fin. Law §§187 et seq.

351. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

352. This is a claim for treble damages and penalties under the New York False Claims Act.

353. The Defendants violated the New York False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

354. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of New York for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

355. In addition, Defendants conspired with each other and with others to defraud New York by inducing its agencies to pay or approve false or fraudulent claims.

356. New York and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

357. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of New York.

358. The State of New York is entitled to the maximum penalty of $12,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 30

Violation of the North Carolina False Claims Act

N.C. Gen. Stat. §§ 1-605 – 1-618

359. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

360. This is a claim for treble damages and penalties under the North Carolina False Claims Act.

361. The Defendants violated the North Carolina False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

362. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of North Carolina for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

363. In addition, Defendants conspired with each other and with others to defraud North Carolina by inducing its agencies to pay or approve false or fraudulent claims.

364. North Carolina and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

365. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of North Carolina.

366. The State of North Carolina is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 31

Violation of the Oklahoma Medicaid False Claims Act

Okla. Stat. tit. 63, §§ 5053.1 – 5053.7

367. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

368. This is a claim for treble damages and penalties under the Oklahoma Medicaid False Claims Act.

369. The Defendants violated the Oklahoma Medicaid False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

370. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Oklahoma for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

371. In addition, Defendants conspired with each other and with others to defraud Oklahoma by inducing its agencies to pay or approve false or fraudulent claims.

372. Oklahoma and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

373. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Oklahoma.

374. The State of Oklahoma is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 32

Violation of the Rhode Island False Claims Act

R.I. Gen. Laws §§9-1.1-1 – 9-1.1-8

375. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

376. This is a claim for treble damages and penalties under the Rhode Island False Claims Act.

377. The Defendants violated the Rhode Island False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

378. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Rhode Island for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

379. In addition, Defendants conspired with each other and with others to defraud Rhode Island by inducing its agencies to pay or approve false or fraudulent claims.

380. Rhode Island and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

381. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Rhode Island.

382. The State of Rhode Island is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 33

Violation of the Tennessee Medicaid False Claims Act

Tenn. Code. Ann. §§ 71-5-181 et seq.

383. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

384. This is a claim for treble damages and penalties under the Tennessee Medicaid False Claims Act.

385. The Defendants violated the Tennessee Medicaid False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

386. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Tennessee for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

387. In addition, Defendants conspired with each other and with others to defraud Tennessee by inducing its agencies to pay or approve false or fraudulent claims.

388. Tennessee and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

389. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Tennessee.

390. The State of Tennessee is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 34

Violation of the Texas Medicaid Fraud Prevention Act

Tex. Hum. Res. Code Ann. §§ 36.001–36.132

391. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

392. This is a claim for treble damages and penalties under the Texas Medicaid Fraud Prevention Act.

393. The Defendants violated the Texas Medicaid Fraud Prevention Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

394. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Texas for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

395. In addition, Defendants conspired with each other and with others to defraud Texas by inducing its agencies to pay or approve false or fraudulent claims.

396. Texas and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

397. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Texas.

398. The State of Texas is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 35

Violation of the Vermont False Claims Act

32 V.S.A. chapter 7, subchapter 8 et seq.

399. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

400. This is a claim for treble damages and penalties under the Vermont False Claims Act.

401. The Defendants violated the Vermont False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

402. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Vermont for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

403. In addition, Defendants conspired with each other and with others to defraud Vermont by inducing its agencies to pay or approve false or fraudulent claims.

404. Vermont and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

405. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Vermont.

406. The State of Vermont is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 36

Violation of the Washington State Medicaid Fraud False Claims Act

Chapter 77 RCW §§74.66 et seq.

407. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

408. This is a claim for treble damages and penalties under the Washington State Medicaid Fraud False Claims Act.

409. The Defendants violated the Washington State Medicaid Fraud False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

410. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Washington for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

411. In addition, Defendants conspired with each other and with others to defraud Washington by inducing its agencies to pay or approve false or fraudulent claims.

412. Washington and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

413. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Washington.

414. The State of Washington is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 37

Violation of the Wisconsin False Claims for Medical Assistance Law

Wis. Stat. §20.931 et seq.

415. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

416. This is a claim for treble damages and penalties under the Wisconsin False Claims for Medical Assistance Law.

417. The Defendants violated the Wisconsin False Claims for Medical Assistance Law by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

418. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of Wisconsin for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

419. In addition, Defendants conspired with each other and with others to defraud Wisconsin by inducing its agencies to pay or approve false or fraudulent claims.

420. Wisconsin and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

421. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the State of Wisconsin.

422. The State of Wisconsin is entitled to the maximum penalty of $10,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 38

Violation of the District of Columbia False Claims Act

D.C. Code §§ 2-381.01 et seq.

423. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

424. This is a claim for treble damages and penalties under the District of Columbia False Claims Act.

425. The Defendants violated the District of Columbia False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

426. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the District of Columbia for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

427. In addition, Defendants conspired with each other and with others to defraud the District of Columbia by inducing its agencies to pay or approve false or fraudulent claims.

428. The District of Columbia and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

429. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the District of Columbia.

430. The District of Columbia is entitled to the maximum penalty of $11,000 for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 39

Violation of the City of Chicago False Claims Act

Municipal Code of Chicago §1-22-010 - §1-22-060

431. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

432. This is a claim for treble damages and penalties under the City of Chicago False Claims Act.

433. The Defendants violated the City of Chicago False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

434. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the State of City of Chicago for

payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

435. In addition, Defendants conspired with each other and with others to defraud the City of Chicago by inducing its agencies to pay or approve false or fraudulent claims.

436. The City of Chicago and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

437. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the City of Chicago.

438. The City of Chicago is entitled to the maximum penalty for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 40

Violation of the City of New York False Claims Act

N.Y.C. Admin. Code §7-801, et seq.

439. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

440. This is a claim for treble damages and penalties under the City of New York False Claims Act.

441. The Defendants violated the City of New York False Claims Act by: a) engaging in the off label marketing of higher Suboxone and Subutex dosages than those lawfully permitted; b) engaging in the off label marketing of Suboxone and Subutex for the purposes of induction and use during pregnancy; c) making unlawful kickback payments to TA's; d) providing unlawful kickbacks in the form of things and services of value to prescribing physicians and TA's; e) paying unlawful kickbacks to state Medicaid agencies to obtain exclusive positions on state formularies; f) marketing Suboxone and Subutex to physicians in violation of DATA 2000 and for the off label use of pain treatment; and g) making false claims of superiority regarding the diversion and safety characteristics of Suboxone film.

442. In committing the acts described herein, Defendants knowingly presented, or caused to be presented, false or fraudulent claims to agencies of the City of New York for payment or approval. Defendants knowingly made, used, or caused to be made or used false records and statements, and omitted material facts, to induce these agencies to approve and pay such false and fraudulent claims. The false claims of superiority referenced above were made by Defendants in an intentional effort to destroy competition and potential competition for the Suboxone brand.

443. In addition, Defendants conspired with each other and with others to defraud the City of New York by inducing its agencies to pay or approve false or fraudulent claims.

444. The City of New York and its agencies, unaware of the falsity of the records, statements and claims made, used, presented, or caused to be made, used or presented by Defendants, paid and continues to pay claims that would not be paid but for Defendants' illegal inducements and/or business practices.

445. Defendants' conduct was the proximate and actual cause of very significant actual loss and damages to the City of New York.

446. The City of New York is entitled to the maximum penalty for each and every false or fraudulent claim, record or statement made, used, presented or caused to be made, used or presented by Defendants.

COUNT 41

Violation of the California Insurance Fraud Prevention Act

California Insurance Code § 1871.7

447. This is a claim for treble damages and penalties under the California Insurance Fraud Prevention Act.

448. This is a claim for treble damages and penalties under the California Insurance Frauds Prevention Act, Cal. Ins. Code §1871.7, as amended (referred to in this Count as "the Act"). The Act provides for civil recoveries against persons who violate the provisions of the Act or the provisions of California Penal Code sections 549 or 550, including recovery of up to three times the amount of any fraudulent claims, and fines of between $5,000 and $10,000 for each such claim. Cal. Ins. Code §1871.7(b).

449. Subsection (e) of Cal. Ins. Code §1871.8 provides for a *qui tam* civil action in order to create incentives for private individuals who are aware of fraud against insurers to help disclose and prosecute the fraud. Cal. Ins. Code §1871.1(e). The *qui tam* provision was patterned after the Federal False Claims Act, 31 U.S.C. §3729-32, and the California False Claims Act, Cal. Gov't Code §§12650 et seq.

450. Subsection (b) of Cal. Ins. Code §1871.7 provides for civil recoveries against persons who violate the provisions of Penal Code sections 549 or 550. Section 550 of the Penal Code prohibits the following activities, among others:

> (a) It is unlawful to do any of the following, or to aid, abet, solicit, or conspire with any person to do any of the following:
>
> (5) Knowingly prepare, make, or subscribe in writing, with the intent to present or use it, or to allow it to be presented, in support of any false or fraudulent claim.
>
> (6) Knowingly make or cause to be made any false or fraudulent claim for payment of a health care benefit.
>
> (b) It is unlawful to do, or to knowingly assist or conspire with any person to do so, any of the following:
>
> (1) Present or cause to be presented any written or oral statement as art of, or in support of or opposition to, a claim for payment or other benefit pursuant to an insurance policy, knowing that the statement contains any false or misleading information concerning any material fact.
>
> (2) Prepare or make any written or oral statement that is intended to be presented to any insurer or any insurance policy, knowing that the statement contains any false or misleading information concerning any material fact.
>
> (3) Conceal, or knowingly fail to disclose the occurrence of, an event that affects any person's initial or continued right or entitlement to any insurance benefit or payment, or the amount of any benefit or payment to which the person is entitled.

Cal. Penal Code §550.

451. By virtue of the acts described in this Complaint, Defendants knowingly presented or caused to be presented, false or fraudulent claims for health care benefits, in violation of Penal Code §550(a).

452. By virtue of the acts described in this Complaint, Defendants also concealed and/or failed to disclose information that would have affected the rights of pharmacies to receive reimbursement for prescriptions, in violation of Penal Code §550(b).

453. Each claim for reimbursement that was inflated as a result of Defendants' illegal practices represents a false or fraudulent record or statement, and a false or fraudulent claim for payment.

454. Private insurers, unaware of the falsity of the records, statements and claims made or caused to be made by Defendants, paid and continue to pay the claims that w2ould not be paid but for Defendants' unlawful conduct.

455. The California State Government is entitled to receive three times the amount of each claim for compensation submitted in violation of Cal. Ins. Code §1871.7. Additionally, the California State Government is entitled to the maximum penalty of $10,000 for each and every violation alleged herein.

COUNT 42

Violation of the Illinois Insurance Claims Fraud Prevention Act

740 Ill. Comp. Stat. §92/1

456. All allegations set forth in this Complaint are incorporated into this Count as if fully set forth herein.

457. This is a claim for treble damages and penalties under the Illinois Insurance Claims Fraud Prevention Act, 740 Ill. Comp. Stat. §92.

458. Subsection 5(b) of the Illinois Insurance Claims Fraud Prevention Act provides:

> A person who violates any provision of this Act or Article 46 of the Criminal Code of 1961 shall be subject, in addition to any other penalties that may be prescribed by law, to a civil penalty of not less than $5,000 nor more than $10,000, plus an assessment of not more than 3 times the amount of each claim for compensation under a contract of insurance.

740 Ill. Comp. Stat. §92/5(b).

459. Article 46 of the Illinois Criminal Code, referenced in the above-quoted section, provides criminal penalties for any person who commits the offense of insurance fraud, defined in the statute as follows:

> (a) A person commits the offense of insurance fraud when he or she knowingly obtains attempts to obtain, or causes to be obtained, by deception, control over the property of an insurance company or self-insured entity by the making of a false claim or by causing a false claim to be made on any policy of insurance issued by an insurance company . . . .

720 Ill. Comp. Stat. §5/46-1(a).

460. Subsection 15(a) of the Illinois Insurance Claims Fraud Prevent Act provides for a *qui tam* civil action in order to create incentives for private individuals to prosecute violations of the statute. Subsection 15(a) provides: "An interested person, including an insurer, may bring a civil action for a violation of the Act for the person and for the State of Illinois. The action shall be brought in the name of the State." 740 Ill. Comp. Stat. §92/15(a).

461. By virtue of the Conduct described in this Complaint, Defendants committed the following acts, or aided and abetted the commission of the following acts, in violation of the Illinois Insurance Claims Prevention Act: knowingly obtained, attempted to obtain, and caused to be obtained, by deception, control over the property of an insurance company or self-insured entity by the making of a false claim and by causing a false claim to be made on a policy of insurance issued by an insurance company, in violation of 740 Ill. Comp. Stat. §92/5(b) and 720 Ill. Comp. Stat. §5/46-1(a).

462. As a result of such conduct, Defendants have received illegal profits to which they were not entitled, at the expense of insurers and at the expense of the People of Illinois, in substantial amount to be determined at trial.

463. The Illinois State Government is entitled to receive three times the amount of each claim for compensation submitted by the Defendants in violation of 740 Ill. Comp. Stat. §92. Additionally, the Illinois State Government is entitled to the maximum penalty of $10,000 for each and every violation alleged herein.

WHEREFORE, Relator-Plaintiff, Ann Marie Williams, requests a jury trial on all issues raised herein and that judgment be entered against the Defendants for each Count set forth above ordering that:

1. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the United States has sustained because of Defendants' actions, plus a civil penalty of not less than $10,781 and not more than $21,563 for each violation of 31 U.S.C. §3729, et seq.;

2. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of California has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Cal. Govt. Code §12691(a);

3. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Colorado has sustained because of Defendants' action, plus the maximum civil penalty of $10,000 for each violation of the Colorado Medicaid False Claims Act, C.R.S. §25.5-4-304, et seq.

4. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Connecticut has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Chapter 319v Sec. 17b-301a et seq.;

5. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Delaware has sustained because of Defendants' actions, plus a civil penalty of $11,000 for each violation of 6 Del. C. §1201(a);

6. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Florida has sustained because of Defendants' actions, plus a civil penalty of $11,000 for each violation of Fla. Stat. Ann. §68.082;

7. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Georgia has sustained because of Defendants' actions, plus a civil penalty of $11,000 for each violation of O.C.G.A. §§49-4-158 et seq.;

8. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Hawaii has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Haw. Rev. Stat. §§661-21(a);

9. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Illinois has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of the Illinois False Claims Act, 740 Ill. Compt. Stat. §175/1 et seq., as amended 2010;

10. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Indiana has sustained because of Defendants' actions, plus civil penalties for each violation of I.C. §5-11-5.5;

11. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Iowa has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of the Iowa Medicaid False Claims Act;

12. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Louisiana has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of La. Rev. Stat. §437 et seq.;

13. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Maryland has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of the Maryland False Claims Health Act of 2010, Subtitle 6, False Claims Against State Health Plans and State Health Programs, §2-601 et seq.;

14. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Massachusetts has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Mass. Gen. L. Ch. §5B;

15. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Michigan has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of MCL 400.601 et seq.;

16. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Minnesota has sustained because of Defendants' actions, plus a civil penalty of $11,000 for each violation of Minn. Stat. §15C.01 et seq.;

17. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Montana has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of the Montana False Claims Act, Mont. Code Ann. §17-8-401 et seq.;

18. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Nevada has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Nev. Rev. Stat. Ann. §357.040(1);

19. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of New Hampshire has sustained because of Defendants' actions, plus civil penalties for each violation of N.H. Rev. Stat. Ann. §167:61-b(I);

20. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of New Jersey has sustained because of Defendants' actions, plus civil penalties for each violation of N.J. Stat. §2A:32C-1 et seq.;

21. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of New Mexico has sustained because of Defendants' actions, plus civil penalties for each violation of N.M. Stat. Ann. §27-14-1 et seq. and N.M. Stat. Ann. §44-9-1 et seq.;

22. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of New York has sustained because of Defendants' actions, plus a civil penalty of $12,000 for each violation of N.Y. Fin. §§187 et seq.;

23. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of North Carolina has sustained because of Defendants' actions, plus a civil penalty of $11,000 for each violation of N.C. Gen. Stat. §§1-605 et seq.;

24. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Oklahoma has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of 2007 OK. ALS 137;

25. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Rhode Island has sustained because of Defendants' actions, plus civil penalties for each violation of R.I. Gen. Laws §9-1.1-1 et seq.;

26. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Tennessee has sustained because of Defendants' actions, plus a civil penalty for each violation of Tenn. Code Ann. §71-5-182(a);

27. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Texas has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Tex. Hum. Res. Code Ann. §36.002;

28. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Vermont has sustained because of Defendants' actions, plus a civil penalty of between $5,500 and $11,000 for each violation of 32 V.S.A. Chapter 7, subchapter 8, et seq.;

29. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the Commonwealth of Virginia has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Va. Code Ann. §8.01-216.3(A);

30. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Washington has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of the Washington Medicaid False Claims Act;

31. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the State of Wisconsin has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of Wis. Stat. §20.931 et seq.;

32. That this Court enter judgment against Defendants in an amount equal to three times the amount of damages the District of Columbia has sustained because of Defendants' actions, plus a civil penalty of $10,000 for each violation of D.C. Code Ann. §2-308.14(a);

33. That by reason of the aforementioned violations of the Chicago False Claims Act provisions that this Court enter judgment in Relator-Plaintiff's favor and against Defendants in an amount equal to not less than two times and not more than three times the amount of damages that the City of Chicago has sustained because of Defendants' action, plus a civil penalty of not less than $5,000 and not more than $10,000 for each violation of the Municipal Code of Chicago, §1-22-010 - §1-22-060;

34. That by reason of the aforementioned violations of the New York City False Claims Act provisions that this Court enter judgment in Relator-Plaintiff's favor and against Defendants in an amount equal to not less than two times and not more than three times the amount of damages that the City of New York has sustained because of Defendants' action, plus a civil penalty of not less than $5,000 and not more than $10,000 for each violation of the New York City False Claims Act, New York City Administrative Code §7-801 - §7-810;

35. That this Court enter judgment against Defendants in an amount of three times the amount of each claim for compensation submitted in violation of Cal. Ins. Code §1871.7 plus the maximum penalty of $10,000 for each and every violation of the statute;

36. That this Court enter judgment against Defendants in an amount equal to three times the amount of each claim for compensation by Defendants in violation of 740 Ill. Comp. Stat. §92, plus the maximum penalty of $10,000 for each and every violation of the statute;

37. That Relator be awarded the maximum amount allowed as a Relator's Share pursuant to §3730(d) of the federal False Claims Act;

38. That Relator be awarded the maximum amount allowed as Relator's Share under the equivalent provisions of the state statutes set forth above;

39. That Relator be awarded the maximum amount allowed as a Relator's share under statutes of the City of Chicago and New York City, and insurance fraud statutes of California and Illinois as set forth above;

40. That Relator be awarded all costs of this action, including attorney's fees, costs and expenses pursuant to §3730(d) and the state statutes set forth above; and

41. That the United States, the individual States and Relator recover such other relief as the Court deems just and proper.

Respectfully submitted,

ANN MARIE WILLIAMS

By: _____
Of Counsel

James H. Shoemaker, Jr., VSB No. 33148
Scott R. Reichle, VSB No. 40016
Patten, Wornom, Hatten & Diamonstein, L.C.
12350 Jefferson Avenue, Suite 300
Newport News, Virginia 23602
(757) 223-4500
(757) 223-4518 (facsimile)
jshoemaker@pwhd.com
sreichle@pwhd.com

Kenneth R. Yoffy
Virginia State Bar No. 20549
C. Thomas Turbeville, Jr.
Virginia State Bar No. 30641
Yoffy and Turbeville, P.L.C.
4805 Courthouse Street
Williamsburg, Virginia 23188
(757) 259-0800
757-259-4408
kyoffy@mac.com
tomtlaw@mac.com

EXHIBIT A

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Pharmaceutical Sales 2010

The following is a list of the top 200 pharmaceutical drugs by retail sales in 2010, listed by U.S. sales value and brand name.

New: Quarterly Top 100 prescription sales data now available, from Q1 2011 **more....**

Top 200 Drugs for 2010 by Sales

View data for: **2003** | **2004** | **2005** | **2006** | **2007** | **2008** | **2009** | 2010 | **2011** | **2012** **(By Units)**

Rank	Drug	Current Manufacturer	Total Sales ($000)	% Change 2009
1 (↑1)	**Nexium**	**AstraZeneca Pharmaceuticals LP**	5,276,153	4.9%
2 (↓1)	**Lipitor**	**Pfizer Inc.**	5,272,576	-2.3%
3	**Plavix**	**Bristol-Myers Squibb Company**	4,675,483	10.2%
4	**Advair Diskus**	**GlaxoSmithKline**	3,655,206	-1.0%
5 (↑3)	**OxyContin**	**Purdue Pharma LP**	3,554,751	13.1%
6	**Abilify**	**Bristol-Myers Squibb Company**	3,514,265	12.7%
7	**Singulair**	**Merck & Co., Inc.**	3,324,909	8.9%
8 (↓3)	**Seroquel**	**AstraZeneca Pharmaceuticals LP**	3,222,055	2.4%
9 (↑5)	**Crestor**	**AstraZeneca Pharmaceuticals LP**	2,922,687	27.0%
10 (↑1)	**Cymbalta**	**Eli Lilly and Company**	2,638,536	7.6%
11 (↓2)	**Actos**	**Takeda Pharmaceuticals U.S.A., Inc.**	2,631,930	4.2%
12 (↑1)	**Lexapro**	**Actavis Pharma, Inc.**	2,483,391	4.6%
13 (↑2)	**Zyprexa**	**Eli Lilly and Company**	2,036,092	7.7%
14 (↑9)	**Spiriva**	**Boehringer Ingelheim Pharmaceuticals, Inc.**	1,593,593	19.3%
15 (↑3)	**Lantus**	**Sanofi-Aventis U.S. LLC**	1,525,697	0.3%
16 (↑6)	**Aricept**	**Eisai Inc.**	1,522,517	13.3%
17 (↑2)	**Lyrica**	**Pfizer Inc.**	1,478,158	-0.1%
	Diovan	**Novartis Pharmaceuticals Corporation**	1,443,539	7.0%

EXHIBIT A

18 (↑6)				
19 (↓7)	Effexor XR	Pfizer Inc.	1,431,042	-40.1%
20 (↑7)	Concerta	Janssen Pharmaceuticals, Inc.	1,407,962	16.9%
21	Levaquin	Janssen Pharmaceuticals, Inc.	1,355,350	-0.6%
22 (↓2)	Celebrex	Pfizer Inc.	1,349,833	-6.9%
23 (↑2)	Diovan HCT	Novartis Pharmaceuticals Corporation	1,314,507	3.7%
24 (↑4)	Januvia	Merck & Co., Inc.	1,294,408	13.0%
25 (↑16)	Suboxone	Reckitt Benckiser Pharmaceuticals Inc.	1,164,872	26.6%
26 (↑14)	NovoLog	Novo Nordisk	1,101,447	20.6%
27 (↑9)	Viagra	Pfizer Inc.	1,028,769	5.5%
28 (↑4)	Atripla	Bristol-Myers Squibb Company	1,028,753	-6.5%
29 (↓3)	Tricor	Abbott Laboratories	1,015,682	-17.2%
30 (↑13)	Provigil	Cephalon, Inc.	999,975	6.7%
31 (↑2)	Zetia	Merck & Co., Inc.	985,823	-4.3%
32 (↑12)	Geodon oral	Pfizer Inc.	959,057	8.7%
33 (↓4)	Vytorin	Merck & Co., Inc.	953,625	-16.3%
34 (↑1)	Ambien CR	Sanofi-Aventis U.S. LLC	951,108	-2.5%
35 (↑11)	Lunesta	Sepracor Inc.	948,621	17.6%
36 (↑2)	Lidoderm	Endo Pharmaceuticals Inc.	934,418	-1.1%
37 (↑22)	Lantus SoloSTAR	Sanofi-Aventis U.S. LLC	933,589	50.5%
38 (↑15)	Vyvanse	Shire US, Inc.	931,421	40.9%
39 (↓5)	Aciphex	Eisai Inc.	915,796	-8.8%
40 (↑2)	Nasonex	Merck & Co., Inc.	886,446	-1.9%
41 (↓10)	Lovenox	Sanofi-Aventis U.S. LLC	867,240	-20.4%
42 (↓12)	Adderall XR	Shire US, Inc.	837,448	-27.0%
43 (↓4)	ProAir HFA	Teva Pharmaceuticals USA, Inc.	818,903	-12.6%
44 (↑1)	Truvada	Gilead Sciences, Inc.	813,944	-8.5%
45 (↑3)	Niaspan	Abbott Laboratories	793,882	11.0%

EXHIBIT A

46 (↑1)	Humalog	Eli Lilly and Company	783,294	3.2%
47 (↑8)	Cialis	Eli Lilly and Company	756,576	15.9%
48 (↑4)	Namenda	Actavis Pharma, Inc.	744,296	10.9%
49 (↑27)	Symbicort	AstraZeneca Pharmaceuticals LP	707,468	47.4%
50 (↑8)	Flovent HFA	GlaxoSmithKline	704,631	13.2%
51 (↑52)	Seroquel XR	AstraZeneca Pharmaceuticals LP	695,560	92.1%
52 (↑8)	Combivent	Boehringer Ingelheim Pharmaceuticals, Inc.	693,068	14.3%
53 (↑)	Lovaza	GlaxoSmithKline	682,384	15.5%
54 (↑24)	Solodyn	Medicis Pharmaceutical Corporation	673,427	40.7%
55 (↓6)	Detrol LA	Pfizer Inc.	620,231	-13.6%
56 (↑8)	AndroGel	Abbott Laboratories	593,780	10.1%
57 (↑10)	Benicar	Daiichi Sankyo	567,636	10.0%
58 (38)	Levemir	Novo Nordisk	567,341	41.1%
59 (2)	Enbrel	Amgen Inc.	546,814	-15.8%
60 (44)	Valtrex	GlaxoSmithKline	533,961	-69.9%
61 (2)	Benicar HCT	Daiichi Sankyo	526,177	-3.1%
62 (7)	Gleevec	Novartis Pharmaceuticals Corporation	517,967	-3.7%
63 (14)	Humira Pen	Abbott Laboratories	514,735	10.1%
64 (10)	Synthroid	Abbott Laboratories	506,859	2.5%
65 (20)	Xalatan	Pfizer Inc.	502,227	9.1%
66 (2)	Premarin tabs	Pfizer Inc.	497,757	-6.5%
67 (5)	Strattera	Eli Lilly and Company	496,960	-3.9%
68 (46)	Ventolin HFA	GlaxoSmithKline	496,659	65.4%
69 (52)	Flomax	Boehringer Ingelheim Pharmaceuticals, Inc.	486,106	-68.9%
70 (52)	Loestrin 24 Fe	Teva Pharmaceuticals USA, Inc.	483,754	82.3%
71 (13)	Protonix	Pfizer Inc.	481,429	3.5%
72 (1)	Boniva	Genentech, Inc.	480,470	-5.3%

73 (22)	Restasis	Actavis Pharma, Inc.	480,414	19.0%
74 (14)	Femara	Novartis Pharmaceuticals Corporation	477,256	12.7%
75 (18)	Enbrel Sureclick	Amgen Inc.	474,602	2.6%
76 (17)	NovoLog Mix 70/30	Novo Nordisk	470,786	16.8%
77 (6)	Evista	Eli Lilly and Company	469,013	0.3%
78 (16)	Byetta	Amylin Pharmaceuticals, Inc.	459,454	-17.8%
79 (20)	Janumet	Merck & Co., Inc.	459,068	22.7%
80 (5)	Asacol	Actavis Pharma, Inc.	450,645	-8.3%
81 (9)	Avodart	GlaxoSmithKline	441,486	5.5%
82 (16)	Vesicare	Astellas Pharma US, Inc.	440,862	15.3%
83 (68)	Trilipix	Abbott Laboratories	428,978	104.5%
84 (3)	Copaxone	Accredo Health Group, Inc.	421,758	1.3%
85 (19)	Focalin XR	Novartis Pharmaceuticals Corporation	416,245	18.6%
86 (16)	Reyataz	Bristol-Myers Squibb Company	412,293	-20.9%
87 (37)	Pristiq	Pfizer Inc.	411,715	58.4%
88 (32)	Arimidex	AstraZeneca Pharmaceuticals LP	403,891	-37.5%
89 (9)	Chantix	Pfizer Inc.	394,944	-14.3%
90 (10)	Sensipar	Amgen Inc.	382,232	-0.5%
91 (3)	Avapro	Bristol-Myers Squibb Company	369,596	-6.2%
92 (49)	Opana ER	Endo Pharmaceuticals Inc.	366,417	52.5%
93 (43)	Yaz	Bayer HealthCare Pharmaceuticals Inc.	361,958	-49.1%
94 (27)	Doryx	Actavis Pharma, Inc.	361,662	35.7%
95 (13)	Actoplus Met	Takeda Pharmaceuticals U.S.A., Inc.	359,790	4.7%
96 (19)	Humira	Abbott Laboratories	358,012	-12.5%
97	Avelox	Bayer HealthCare Pharmaceuticals Inc.	353,130	-8.4%
98 (13)	NuvaRing	Merck & Co., Inc.	349,014	11.0%
99 ( )	Renvela	Genzyme Corporation	333,987	111.5%

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100 (35)	Ortho Tri-Cyclen Lo	Janssen Pharmaceuticals, Inc.	331,730	33.9%
101 (28)	Lamictal	GlaxoSmithKline	326,331	-35.2%
102 (4)	Avalide	Bristol-Myers Squibb Company	324,571	-6.4%
103 (1)	Xopenex	Akorn, Inc.	316,162	-13.0%
104 (18)	Actonel	Actavis Pharma, Inc.	313,904	-29.0%
105 ( )	Dexilant/Kapidex		313,386	254.8%
106 (4)	Lotrel	Novartis Pharmaceuticals Corporation	306,010	-6.8%
107 (9)	Invega	Janssen Pharmaceuticals, Inc.	304,182	5.1%
108 (24)	Welchol	Daiichi Sankyo	303,392	19.7%
109 (11)	Avonex	Biogen	303,147	0.2%
110 (73)	Topamax	Janssen Pharmaceuticals, Inc.	287,186	-70.5%
111 (1)	Norvir	Abbott Laboratories	287,102	-10.0%
112 (46)	Entocort EC	AstraZeneca Pharmaceuticals LP	282,547	38.6%
113 (15)	Aggrenox	Boehringer Ingelheim Pharmaceuticals, Inc.	277,144	6.5%
114 (51)	Travatan Z	Alcon	273,598	44.1%
115	Isentress	Merck & Co., Inc.	272,132	-9.8%
116 (25)	Avandia	GlaxoSmithKline	269,213	-33.8%
117	Prevacid SoluTab	Takeda Pharmaceuticals U.S.A., Inc.	268,284	-1.4%
118 (27)	Exforge	Novartis Pharmaceuticals Corporation	267,771	16.6%
119 (68)	Cozaar	Merck & Co., Inc.	267,081	-62.4%
120 (9)	Lumigan	Actavis Pharma, Inc.	267,047	7.0%
121 (12)	Caduet	Pfizer Inc.	266,967	-18.6%
122 (36)	Actonel 150	Actavis Pharma, Inc.	264,858	26.2%
123 (5)	Risperdal Consta	Janssen Pharmaceuticals, Inc.	262,054	-8.2%
124 (59)	Prograf	Astellas Pharma US, Inc.	260,885	-56.2%
125 (27)	Ciprodex otic	Alcon	254,888	13.8%
126 (23)	Vigamox	Alcon	252,864	11.3%

127 (7)	Kadian	Actavis Pharma, Inc.	251,858	-0.8%
128 (2)	Coreg CR	GlaxoSmithKline	251,440	-1.6%
129 (4)	Levitra	Bayer HealthCare Pharmaceuticals Inc.	242,446	-5.9%
130 (8)	Maxalt	Merck & Co., Inc.	242,237	0.5%
131 (24)	Keppra	UCB, Inc.	241,737	-33.0%
132 (122)	Prevacid	Takeda Pharmaceuticals U.S.A., Inc.	241,374	-90.6%
133 (27)	Micardis	Boehringer Ingelheim Pharmaceuticals, Inc.	238,335	23.9%
134 ( )	Bystolic	Actavis Pharma, Inc.	231,449	72.2%
135 (28)	Prezista	Janssen Biotech, Inc.	230,406	13.8%
136 (52)	Exelon Patch	Novartis Pharmaceuticals Corporation	229,601	38.2%
137 ( )	Nuvigil	Cephalon, Inc.	223,885	239.6%
138 (2)	Zyvox	Pfizer Inc.	222,554	-7.5%
139 (41)	Lialda	Shire US, Inc.	222,201	29.3%
140 (15)	Epzicom	GlaxoSmithKline	221,406	-17.0%
141 (20)	Enablex	Actavis Pharma, Inc.	220,478	11.0%
142 (19)	Forteo	Eli Lilly and Company	219,387	-25.1%
143 (7)	Viread	Gilead Sciences, Inc.	216,264	-6.2%
144 (31)	Kaletra	Abbott Laboratories	212,723	-32.9%
145 (17)	Micardis HCT	Abbott Laboratories	211,575	10.4%
146 (8)	Maxalt MLT	Merck & Co., Inc.	211,230	-1.1%
147	Humalog Mix 75/25 Pen	Eli Lilly and Company	211,021	-6.9%
148 (12)	Xeloda	Genentech, Inc.	209,499	-11.7%
149 (7)	Asmanex	Merck & Co., Inc.	208,839	3.8%
150 (84)	Hyzaar	Merck & Co., Inc.	207,471	-62.3%
151 (20)	Fentora	Cephalon, Inc.	207,376	11.2%
152 (91)	Pulmicort Respules	AstraZeneca Pharmaceuticals LP	205,218	-68.0%
153 ( )	Ranexa	Gilead Sciences, Inc.	200,622	41.5%

154 (49)	RenaGel	Genzyme Corporation	199,275	-48.2%
155 (34)	Prempro	Pfizer Inc.	198,132	22.2%
156 (1)	Relpax	Pfizer Inc.	197,341	-3.4%
157 (12)	Patanol	Alcon	196,500	2.6%
158 (8)	Amitiza	Takeda Pharmaceuticals U.S.A., Inc.	195,132	1.4%
159 (4)	Duragesic	Johnson & Johnson	194,599	-14.5%
160 ( )	Vancocin HCl	Eli Lilly and Company	192,066	23.4%
161 (22)	Nasacort AQ	Sanofi-Aventis U.S. LLC	192,035	-19.0%
162 (35)	Proventil HFA	Merck & Co., Inc.	191,839	-26.5%
163 ( )	Advair HFA	GlaxoSmithKline	191,245	26.4%
164 (14)	Valcyte	Genentech, Inc.	191,160	-0.9%
165 (21)	Wellbutrin XL	Valeant Pharmaceuticals International, Inc.	189,026	-21.2%
166 ( )	Oracea	Galderma Laboratories, L.P.	187,182	67.9%
167 (18)	Vivelle-DOT	Novartis Pharmaceuticals Corporation	185,860	12.4%
168 (11)	Uroxatral	Concordia Pharmaceuticals Inc.	185,624	6.2%
169 (8)	Zovirax topical	GlaxoSmithKline	184,377	2.6%
170 (27)	Epipen	King Pharmaceuticals, Inc.	182,785	20.8%
171 ( )	Creon	Abbott Laboratories	181,303	358.6%
172 ( )	Azor	Daiichi Sankyo	179,647	33.0%
173 (9)	Pentasa	Sanofi-Aventis U.S. LLC	178,068	4.5%
174 (32)	Procrit	Janssen Biotech, Inc.	174,622	-25.9%
175 ( )	Pataday	Alcon	173,553	25.5%
176 (30)	Differin	Galderma Laboratories, L.P.	171,454	-24.8%
177 (10)	Premarin vaginal	Pfizer Inc.	170,860	3.5%
178 ( )	Zyprexa Zydis	Eli Lilly and Company	169,714	6.7%
179 (36)	Tussionex	Sanofi-Aventis U.S. LLC	169,611	-29.8%
180 ( )	Victoza	Novo Nordisk	168,943	0.0%

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181 ( )	**Humalog KwikPen**	**Eli Lilly and Company**	168,270	79.6%
182 ( )	**Arixtra**	**GlaxoSmithKline**	165,530	19.9%
183 ( )	**Qvar**	**Janssen Pharmaceuticals, Inc.**	163,697	41.1%
184 (36)	**Combivir**	**GlaxoSmithKline**	163,406	-27.8%
185 ( )	**Testim**	**Endo Pharmaceuticals Inc.**	163,015	12.2%
186 (60)	**Tarceva**	**Astellas Pharma US, Inc.**	160,591	-38.2%
187 (17)	**Xyzal**	**Sanofi-Aventis U.S. LLC**	160,237	-15.6%
188 (12)	**Elmiron**	**Janssen Pharmaceuticals, Inc.**	158,274	4.3%
189 (5)	**Propecia**	**Merck & Co., Inc.**	157,892	-5.7%
190 (108)	**CellCept**	**Genentech, Inc.**	157,743	-68.3%
191 (110)	**Skelaxin**	**Elan Corporation, plc**	156,372	-67.7%
192 ( )	**Betaseron**	**Bayer HealthCare Pharmaceuticals Inc.**	155,952	-6.8%
193 (12)	**Temodar**	**Merck & Co., Inc.**	154,466	-14.9%
194 ( )	**Flector**	**Actavis Pharma, Inc.**	153,814	0.2%
195 (27)	**Pegasys**	**Genentech, Inc.**	153,101	-8.4%
196 (6)	**Prandin**	**Novo Nordisk**	151,678	-5.9%
197 (5)	**Veramyst**	**GlaxoSmithKline**	150,582	-7.8%
198 ( )	**Intuniv**	**Shire US, Inc.**	150,346	NA
199 ( )	**Clobex**	**Galderma Laboratories, L.P.**	150,230	20.6%
200 ( )	**Humulin N**	**Eli Lilly and Company**	149,945	4.4%

Source: Verispan, VONA

View data for: **2003** | **2004** | **2005** | **2006** | **2007** | **2008** | **2009** | 2010 | **2011** | **2012** **(By Units)**

SUBOXONE (CIII)
(buprenorphine HCl and naloxone HCl dihydrate sublingual tablets)

SUBUTEX (CIII)
(buprenorphine HCl sublingual tablets)

Rx only

Under the Drug Addiction Treatment Act of 2000 (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 have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence.

DESCRIPTION

SUBOXONE sublingual tablets contain buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

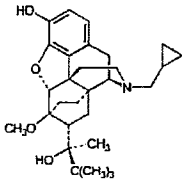
SUBUTEX sublingual tablets contain buprenorphine HCl.

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (17mg/mL). Chemically, buprenorphine is 17-(cyclopropylmethyl)-α-(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy-α-methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)]-. Buprenorphine hydrochloride has the molecular formula $C_{29}H_{41}NO_4$ HCl and the molecular weight is 504.10.

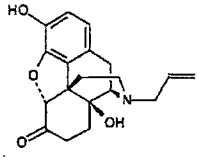
STRUCTURAL FORMULA OF BUPRENORPHINE



.HCl

Naloxone hydrochloride is a white to slightly off-white powder and is soluble in water, in dilute acids and in strong alkali. Chemically, naloxone is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride. Naloxone Hydrochloride has the molecular formula $C_{19}H_{21}NO_4$ HCl .$2H_2O$ and the molecular weight is 399.87.

STRUCTURAL FORMULA OF NALOXONE



.HCl

SUBOXONE is an uncoated **hexagonal orange tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine with 0.5mg naloxone, and 8mg buprenorphine with 2mg naloxone free bases. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon / lime flavor.

SUBUTEX is an uncoated **oval white tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine and 8mg buprenorphine free base. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate.

CLINICAL PHARMACOLOGY

Subjective Effects:
Comparisons of buprenorphine with full agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In non-dependent subjects, acute sublingual doses of SUBOXONE tablets produced opioid agonist effects, which reached a maximum between doses of 8 mg and 16mg of SUBUTEX. The effects of 16mg SUBOXONE were similar to those produced by 16mg SUBUTEX (buprenorphine alone).

Opioid agonist ceiling effects were also observed in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo, and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced, non-dependent subjects. Both drugs produced typical opioid agonist effects. For all the measures for which the drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administrations. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:
Buprenorphine in intravenous (2mg, 4mg, 8mg, 12mg and 16 mg) and sublingual (12mg) doses has been administered to non-dependent subjects to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared with placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:
Physiologic and subjective effects following acute sublingual administration of SUBOXONE and SUBUTEX tablets were similar at equivalent dose levels of buprenorphine. Naloxone, in the SUBOXONE formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. SUBOXONE, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In methadone-maintained patients and heroin-dependent subjects, intravenous administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio. SUBOXONE tablets contain buprenorphine with naloxone at a ratio of 4:1.

Pharmacokinetics:
Absorption:
Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX and SUBOXONE, and plasma levels of naloxone increased with the sublingual dose of SUBOXONE (Table 1). There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

Naloxone did not affect the pharmacokinetics of buprenorphine and both SUBUTEX and SUBOXONE deliver similar plasma concentrations of buprenorphine. The levels of naloxone were too low to assess dose-proportionality. At the three naloxone doses of 1 mg, 2 mg, and 4 mg, levels above the limit of quantitation (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects. In one individual, at the 4mg dose, the last measurable concentration was at 8 hours. Within each subject (for most of the subjects), across the doses there was a trend toward an increase in naloxone concentrations with increase in dose. Mean peak naloxone levels ranged from 0.11 to 0.28ng/mL in the dose range of 1-4 mg.

Table 1. Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone® doses and 16mg Subutex® dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone® 4 mg	Suboxone® 8 mg	Suboxone® 16 mg	Subutex® 16 mg
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour. ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

Distribution:
Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:
Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:
A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Buprenorphine has a mean elimination half-life from plasma of 37 h.

Naloxone has a mean elimination half-life from plasma of 1.1 h.

Special Populations:
Hepatic Disease:
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, in patients with hepatic impairment dosage should be adjusted and patients should be observed for symptoms of precipitated opioid withdrawal.

Renal Disease:
No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following intravenous administration of 0.3mg buprenorphine.

The effects of renal failure on naloxone pharmacokinetics are unknown.

Appendix 1: Product Information

Drug-drug Interactions:
CYP 3A4 Inhibitors and Inducers: A pharmacokinetic interaction study of ketoconazole (400 mg/day), a potent inhibitor of CYP 3A4, in 12 patients stabilized on SUBOXONE [8mg (n=1) or 12mg (n=5) or 16mg (n=6)] resulted in increases in buprenorphine mean C_{max} values (from 4.3 to 9.8, 6.3 to 14.4 and 9.0 to 17.1) and mean AUC values (from 30.9 to 46.9, 41.9 to 83.2 and 52.3 to 120) respectively. Subjects receiving SUBUTEX or SUBOXONE should be closely monitored and may require dose-reduction if inhibitors of CYP 3A4 such as azole antifungal agents (e.g. ketoconazole), macrolide antibiotics (e.g., erythromycin) and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) are co-administered. The interaction of buprenorphine with CYP 3A4 inducers has not been investigated; therefore it is recommended that patients receiving SUBUTEX or SUBOXONE should be closely monitored if inducers of CYP 3A4 (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered (SEE WARNINGS).

CLINICAL STUDIES
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.

SUBOXONE tablets have been studied in 575 patients, SUBUTEX tablets in 1834 patients and buprenorphine sublingual solutions in 2470 patients. A total of 1270 females have received buprenorphine in clinical trials. Dosing recommendations are based on data from one trial of both tablet formulations and two trials of the ethanolic solution. All trials used buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

In a double blind placebo- and active controlled study, 326 heroin-addicted subjects were randomly assigned to either SUBOXONE 16 mg per day, 16 mg SUBUTEX per day or placebo tablets. For subjects randomized to either active treatment, dosing began with one 8 mg tablet of SUBUTEX on Day 1, followed by 16 mg (two 8 mg tablets) of SUBUTEX on Day 2. On Day 3, those randomized to receive SUBOXONE were switched to the combination tablet. Subjects randomized to placebo received one placebo tablet on Day 1 and two placebo tablets per day thereafter for four weeks. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. Subjects were instructed to hold the medication under the tongue for approximately 5 to 10 minutes until completely dissolved. Subjects received one hour of individual counseling per week and a single session of HIV education. The primary study comparison was to assess the efficacy of SUBUTEX and SUBOXONE individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBUTEX and SUBOXONE, than for placebo.

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomized to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of SUBUTEX or SUBOXONE), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3-10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually.

Maintenance dosing continued through Week 17, and then medications were tapered by approximately 20-30% per week over Weeks 18-24, with placebo dosing for the last two weeks. Subjects received individual and/or group counseling weekly.

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

In a dose-controlled, double-blind, parallel-group, 16-week study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution. Buprenorphine was titrated to maintenance doses over 1-4 days (Table 2) and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site.

Table 2. Doses of Sublingual Buprenorphine Solution used for Induction in a Double-Blind Dose Ranging Study

Target dose of Buprenorphine *	Induction Dose			Maintenance dose
	Day 1	Day 2	Day 3	
1 mg	1 mg	1 mg	1 mg	1 mg
4 mg	2 mg	4 mg	4 mg	4 mg
8 mg	2 mg	4 mg	8 mg	8 mg
16 mg	2 mg	4 mg	8 mg	16 mg

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
2 mg solution would be roughly equivalent to 3 mg tablet
4 mg solution would be roughly equivalent to 6 mg tablet
8 mg solution would be roughly equivalent to 12 mg tablet
16 mg solution would be roughly equivalent to 24 mg tablet

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, the three highest tested doses were superior to the 1mg dose. Therefore, this study showed that a range of buprenorphine doses may be effective. The 1mg dose of buprenorphine sublingual solution can be considered to be somewhat lower than a 2 mg tablet dose. The other doses used in the study encompass a range of tablet doses from approximately 6 mg to approximately 24 mg.

INDICATIONS AND USAGE
SUBOXONE and SUBUTEX are indicated for the treatment of opioid dependence.

CONTRAINDICATIONS
SUBOXONE and SUBUTEX should not be administered to patients who have been shown to be hypersensitive to buprenorphine, and SUBOXONE should not be administered to patients who have been shown to be hypersensitive to naloxone.

WARNINGS
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 have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with SUBUTEX or SUBOXONE.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

SUBOXONE and SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

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. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset.

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. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Measurements of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, the drug should be carefully discontinued to prevent withdrawal symptoms and a return to illicit drug use, and strict monitoring of the patient should be initiated.

Allergic Reactions:
Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex or Suboxone use. A history of hypersensitivity to naloxone is a contraindication to Suboxone use.

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, SUBOXONE and SUBUTEX may produce orthostatic hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure:
SUBOXONE and SUBUTEX, like other potent opioids, 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. SUBOXONE and SUBUTEX can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opioid withdrawal effects:
Because it contains naloxone, SUBOXONE is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, SUBOXONE may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

PRECAUTIONS
General:
SUBOXONE and SUBUTEX 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.

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for symptoms of precipitated opioid withdrawal.

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.

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Drug Interactions:
Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP 3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. erythromycin), and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) should have their dose of SUBUTEX or SUBOXONE adjusted.

Based on anecdotal reports, there may be an interaction between buprenorphine and benzodiazepines. There have been a number of reports in the post-marketing experience of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts. In many of these cases, buprenorphine was misused by self-injection of crushed SUBUTEX tablets. SUBUTEX and SUBOXONE should be prescribed with caution to patients on benzodiazepines or other drugs that act on the central nervous system, regardless of whether these drugs are taken on the advice of a physician or are taken as drugs of abuse. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines while under treatment with SUBOXONE or SUBUTEX.

Information for Patients:
Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on narcotics and that the patient is being treated with SUBOXONE or SUBUTEX.

Patients should be cautioned that a serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken at the same time as SUBOXONE or SUBUTEX.

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, SUBOXONE and SUBUTEX may produce orthostatic hypotension in ambulatory patients.

Patients should consult their physician if other prescription medications are currently being used or are prescribed for future use.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Carcinogenicity: Carcinogenicity data on SUBOXONE are not available. Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) for 27 months. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Mutagenicity:
SUBOXONE: The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes, or in an intravenous micronucleus test in the rat.

SUBUTEX: Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast *(Saccharomyces cerevisiae)* for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets *(E. coli)* survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:
SUBOXONE: Dietary administration of SUBOXONE in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure was approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) had no adverse effect on fertility.

SUBUTEX: Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or up to 5mg/kg/day *im* or *sc* (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Pregnancy:
Pregnancy Category C:
Teratogenic effects:
SUBOXONE: Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure was approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at intramuscular doses up to 30 mg/kg/day (estimated exposure was approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphacele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration to the rat, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following intramuscular administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

SUBUTEX: Buprenorphine was not teratogenic in rats or rabbits after *im* or *sc* doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after *iv* doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). 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. Increases in skeletal abnormalities in rabbits after *im* administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at *iv* doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

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 potential risk to the fetus.

Non-teratogenic effects.
Dystocia was noted in pregnant rats treated *im* with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Both fertility and peri- and postnatal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after *im* doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after *sc* doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Neonatal Withdrawal:
Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnea and bradycardia were also reported.

Nursing Mothers:
An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices. 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 SUBUTEX or SUBOXONE.

Pediatric Use:
SUBOXONE and SUBUTEX are not recommended for use in pediatric patients. The safety and effectiveness of SUBOXONE and SUBUTEX in patients below the age of 16 have not been established.

ADVERSE REACTIONS
The safety of SUBOXONE has been evaluated in 497 opioid-dependent subjects. The prospective evaluation of SUBOXONE was supported by clinical trials using SUBUTEX (buprenorphine tablets without naloxone) and other trials using buprenorphine sublingual solutions. In total, safety data are available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction.

Few differences in adverse event profile were noted between SUBOXONE and SUBUTEX or buprenorphine administered as a sublingual solution.

In a comparative study, adverse event profiles were similar for subjects treated with 16 mg SUBOXONE or 16mg SUBUTEX. The following adverse events were reported to occur by at least 5% of patients in a 4-week study (Table 3).

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

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

Appendix 1: Product Information

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. Table 4 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controled study.

Table 4. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study

Body System / Adverse Event (COSTART Terminology)	Buprenorphine Dose*				
	Very Low* (N=184)	Low* (N=180)	Moderate* (N=186)	High* (N=181)	Total* (N=731)
	N (%)	N (%)	N (%)	N (%)	N (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin And Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
"Very low" dose (1mg solution) would be less than a tablet dose of 2 mg
"Low" dose (4mg solution) approximates a 6 mg tablet dose
"Moderate" dose (8mg solution) approximates a 12 mg tablet dose
"High" dose (16mg solution) approximates a 24 mg tablet dose

DRUG ABUSE AND DEPENDENCE
SUBOXONE and SUBUTEX are controlled as Schedule III narcotics under the Controlled Substances Act.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces dependence of the opioid type, characterized by moderate withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset (SEE WARNINGS)

Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pregnancy (See PRECAUTIONS)

SUBOXONE contains naloxone and if misused parenterally, is highly likely to produce marked and intense withdrawal symptoms in subjects dependent on other opioid agonists.

OVERDOSAGE
Manifestations:
Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

Treatment:
The respiratory and cardiac status of the patient should be monitored carefully. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

High doses of naloxone hydrochloride, 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose. Doxapram (a respiratory stimulant) also has been used.

DOSAGE AND ADMINISTRATION
SUBUTEX or SUBOXONE is administered sublingually as a single daily dose in the range of 12 to 16mg/day. When taken sublingually, SUBOXONE and SUBUTEX have similar clinical effects and are interchangeable. There are no adequate and well-controlled studies using SUBOXONE as initial medication. SUBUTEX contains no naloxone and is preferred for use during induction. Following induction, SUBOXONE, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of SUBUTEX for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE, for example those patients who have been shown to be hypersensitive to naloxone.

Method of administration:
SUBOXONE and SUBUTEX tablets should be placed under the tongue until they are dissolved.
For doses requiring the use of more than two tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than two tablets comfortably) place two tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

Induction:
Prior to induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with SUBUTEX should be undertaken when objective and clear signs of withdrawal are evident.

In a one-month study of SUBOXONE tablets induction was conducted with SUBUTEX tablets. Patients received 8mg of SUBUTEX on day 1 and 16mg SUBUTEX on day 2. From day 3 onward, patients received SUBOXONE tablets at the same buprenorphine dose as day 2. Induction in the studies of buprenorphine solution was accomplished over 3-4 days, depending on the target dose.
In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period. Therefore it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms.

Patients taking heroin or other short-acting opioids:
At treatment initiation, the dose of SUBUTEX should be administered at least 4 hours after the patient last used opioids or preferably when early signs of opioid withdrawal appear.

Patients on methadone or other long-acting opioids:
There is little controlled experience with the transfer of methadone-maintained patients to buprenorphine. Available evidence suggests that withdrawal symptoms are possible during induction to buprenorphine treatment. Withdrawal appears more likely in patients maintained on higher doses of methadone (>30mg) and when the first buprenorphine dose is administered shortly after the last methadone dose.

Maintenance:
SUBOXONE is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation.

Adjusting the dose until the maintenance dose is achieved:
The recommended target dose of SUBOXONE is 16 mg/day. Clinical studies have shown that 16mg of SUBUTEX or SUBOXONE is a clinically effective dose compared with placebo and indicate that doses as low as 12 mg may be effective in some patients. The dosage of SUBOXONE should be progressively adjusted in increments / decrements of 2mg or 4mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4mg to 24mg per day depending on the individual.

Reducing dosage and stopping treatment:
The decision to discontinue therapy with SUBOXONE or SUBUTEX after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

HOW SUPPLIED
SUBOXONE is supplied as sublingual tablets in white HDPE bottles.

Hexagonal orange tablets containing 2mg buprenorphine with 0.5mg naloxone
NDC 12496-1283-2 30 tablets per bottle

Hexagonal orange tablets containing 8mg buprenorphine with 2mg naloxone

NDC 12496-1306-2 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15-30°C
(59-86°F) [see USP Controlled Room Temperature]

SUBUTEX is supplied as sublingual tablets in white HDPE bottles.

Oval white tablets containing 2mg buprenorphine
NDC 12496-1278-2 30 tablets per bottle

Oval white tablets containing 8mg buprenorphine
NDC 12496-1310-2 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15-30°C
(59-86°F) [see USP Controlled Room Temperature]

Manufactured by:
Reckitt Benckiser Healthcare (UK) Ltd
Hull, UK, HU8 7DS

Distributed by:
Reckitt Benckiser Pharmaceuticals, Inc.
Richmond, VA 23235

Last revised June 2005

#0044284

Reckitt Benckiser Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SUBOXONE® sublingual film safely and effectively. See full prescribing information for SUBOXONE sublingual film.

SUBOXONE (buprenorphine and naloxone) sublingual film for sublingual administration CIII.

Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act. (1)

----------DOSAGE AND ADMINISTRATION----------

Administer SUBOXONE sublingual film sublingually as a single daily dose. (2)

The recommended daily dose for maintenance treatment is 16 mg/4 mg buprenorphine and naloxone. Advise patients not to cut, chew, or swallow SUBOXONE sublingual film.

----------DOSAGE FORMS AND STRENGTHS----------

Sublingual film: 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to buprenorphine or naloxone. (4)

----------WARNINGS AND PRECAUTIONS----------

- Buprenorphine can be abused in a similar manner to other opioids. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Significant respiratory depression and death have occurred in association with buprenorphine, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). (5.2)
- Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. (5.3)
- Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Chronic administration produces opioid-type physical dependence. Abrupt discontinuation or rapid dose taper may result in opioid withdrawal syndrome. (5.5)
- Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.6)
- Do not administer SUBOXONE sublingual film to patients with known hypersensitivity to buprenorphine or naloxone. (5.7)
- A marked and intense opioid withdrawal syndrome is highly likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists or by sublingual administration before the agonist effects of other opioids have subsided. (5.8)
- Neonatal withdrawal has been reported following use of buprenorphine by the mother during pregnancy. (5.9)
- SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.10)
- Caution patients about the risk of driving or operating hazardous machinery. (5.11)

----------ADVERSE REACTIONS----------

Adverse events commonly observed with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Reckitt Benckiser Pharmaceuticals Inc. at 1-877-782-6966, FDA at 1-800-FDA-1088, or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over or under dosing. (7.1)
- Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- SUBOXONE sublingual film is not indicated for use during pregnancy unless potential benefit justifies potential risk. (8.1)
- Buprenorphine passes into the mother's milk. Breast-feeding is not advised while taking SUBOXONE sublingual film. (8.3)
- Safety and effectiveness of SUBOXONE sublingual film in patients below the age of 16 has not been established. (8.4)
- Administer SUBOXONE sublingual film with caution to elderly or debilitated patients. (8.5)
- Administer SUBOXONE sublingual film with caution to patients with liver dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Approved August 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections and subsections omitted from the full prescribing information are not listed.

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See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Approved August 2012

ENTS*

ıaloxone) Sublingual Tablets

ublingual Film

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

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.

2 DOSAGE AND ADMINISTRATION

SUBOXONE sublingual film is administered sublingually as a single daily dose. SUBOXONE sublingual film should be used in patients who have been initially inducted using buprenorphine sublingual tablets.

2.1 Maintenance

- SUBOXONE sublingual film is indicated for maintenance treatment. The recommended target dosage of SUBOXONE sublingual film is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose.
- The dosage of SUBOXONE sublingual film should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- The maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage.

2.2 Method of Administration

Do not cut, chew, or swallow SUBOXONE sublingual film. Place a sublingual film under the tongue. If an additional sublingual film is necessary to achieve the prescribed dose, place an additional sublingual film sublingually on the opposite side from the first film. Place the sublingual film in a manner to minimize overlapping as much as possible. The sublingual film must be kept under the tongue until the film is completely dissolved. **SUBOXONE sublingual film should NOT be moved after placement.**

Proper administration technique should be demonstrated to the patient.

2.3 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the physician's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

If treatment goals are not being achieved, the physician should re-evaluate the appropriateness of continuing the current treatment.

2.4 Unstable Patients

Physicians will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the physician does not feel that he/she has the expertise to manage the patient. In such cases, the physician may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.5 Stopping Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation of buprenorphine has been used, but the data are insufficient to determine the best method of dose taper at the end of treatment.

2.6 Switching between SUBOXONE Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between SUBOXONE sublingual tablets and SUBOXONE sublingual film should be started on the same dosage as the previously administered product. However, dosage adjustments may be necessary when switching between products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to the SUBOXONE sublingual tablets as observed in pharmacokinetic studies *[see Clinical Pharmacology (12.3)]*. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to strips or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

2.7 Switching between SUBOXONE Sublingual Film strengths

As indicated in Table 1, the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e., 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual films to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Table 1. Comparison of available SUBOXONE film strengths by dimensions and drug concentrations.

SUBOXONE film unit strength (buprenorphine/naloxone)	SUBOXONE film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22.0 mm x 19.2 mm	17.2	4.88

3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg,
- buprenorphine/naloxone 4 mg/1 mg,
- buprenorphine/naloxone 8 mg/2 mg, and
- buprenorphine/naloxone 12 mg/3 mg

4 CONTRAINDICATIONS

SUBOXONE sublingual film should not be administered to patients who have been shown to be hypersensitive to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

Buprenorphine can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. *[see Drug Abuse and Dependence (9.2)]*.

5.2 Respiratory Depression

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other CNS depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs. Patients should be warned of the potential danger of self-administration of benzodiazepines or other depressants while under treatment with SUBOXONE sublingual film. [see *Drug Interactions* (7.3)].

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

SUBOXONE sublingual film should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 CNS Depression

Patients receiving buprenorphine in the presence of opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. Consider dose reduction of CNS depressants, SUBOXONE sublingual film, or both in situations of concomitant prescription. *[see Drug Interactions (7.3)]*.

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children.

5.5 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. *[see Drug Abuse and Dependence (9.3)]*

5.6 Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.7 Allergic Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

5.8 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, SUBOXONE sublingual film is highly likely to produce marked and intense 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 sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered sublingually before the agonist effects of the opioid have subsided.

5.9 Neonatal Withdrawal

Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal signs ranged from Day 1 to Day 8 of life with most cases occurring on Day 1. Adverse events associated with the neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus, and there have been reports of convulsions, apnea, respiratory depression, and bradycardia.

5.10 Use in Opioid Naïve Patients

There have been reported deaths of opioid naive individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

5.11 Impairment of Ability to Drive or Operate Machinery

SUBOXONE sublingual film 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 treatment induction and dose adjustment. Patients should be cautioned about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

5.12 Orthostatic Hypotension

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

5.13 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.14 Elevation of Intracholedochal Pressure

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.

5.15 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

5.16 General Precautions

SUBOXONE sublingual film should be administered with caution in debilitated patients and those with 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.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Events in Clinical Trials - SUBOXONE sublingual film

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted among SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, SUBUTEX (buprenorphine) sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

Other adverse event data were derived from larger, controlled studies of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE (buprenorphine and naloxone) and SUBUTEX (buprenorphine) sublingual tablets, adverse event profiles were similar for subjects treated with 16 mg/4 mg SUBOXONE (buprenorphine and naloxone) sublingual tablets or 16 mg SUBUTEX (buprenorphine) sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4-week study of SUBOXONE (buprenorphine and naloxone) sublingual tablets and SUBUTEX (buprenorphine) sublingual tablets.

Table 2. Adverse Events (≥5%) by Body System and Treatment Group in a 4-week Study

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

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 16-week Study

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)

Body System/ Adverse Event (COSTART Terminology)	Buprenorphine Dose				
	Very Low* N=184 n (%)	Low* N=180 n (%)	Moderate* N=186 n (%)	High* N=181 n (%)	Total* N=731 n (%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:

1 mg solution would be less than a tablet dose of 2 mg

4 mg solution approximates a 6 mg tablet dose

8 mg solution approximates a 12 mg tablet dose

16 mg solution approximates a 24 mg tablet dose

6.2 Adverse Events – Post-marketing Experience with SUBOXONE Sublingual Tablets

The most frequently reported post-marketing adverse event not observed in clinical trials was peripheral edema.

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

Buprenorphine is metabolized to norbuprenorphine primarily by cytochrome CYP3A4; therefore, potential interactions may occur when SUBOXONE sublingual film is given concurrently with agents that affect CYP3A4 activity. The concomitant use of SUBOXONE sublingual film with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored and may require dose-reduction of one or both agents.

The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered [see Clinical Pharmacology (12.3)].

7.2 Antiretrovirals

Three classes of antiretroviral agents have been evaluated for CYP3A4 interactions with buprenorphine. Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine and etravirine are known CYP3A inducers whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. It is recommended that patients who are on chronic buprenorphine treatment have their dose monitored if NNRTIs are added to their treatment regimen. Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. Monitoring of patients taking buprenorphine and atazanavir with and without ritonavir is recommended, and dose reduction of buprenorphine may be warranted.

7.3 Benzodiazepines

There have been a number of post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many, but not all, of these cases, buprenorphine was misused by self-injection. Preclinical studies have shown that the combination of benzodiazepines and buprenorphine altered the usual ceiling effect on buprenorphine-induced respiratory depression, making the respiratory effects of buprenorphine appear similar to those of full opioid agonists. SUBOXONE sublingual film should be prescribed with caution to patients taking benzodiazepines or other drugs that act on the CNS, regardless of whether these drugs are taken on the advice of a physician or are being abused/misused. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking SUBOXONE sublingual film, and should also be cautioned to use benzodiazepines concurrently with SUBOXONE sublingual film only as directed by their physician.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies of SUBOXONE sublingual film or buprenorphine/naloxone in pregnant women. SUBOXONE sublingual film should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic Effects:

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). 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. Increases in skeletal abnormalities in rabbits after IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m² basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Non-teratogenic Effects:

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Fertility, peri-, and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

8.3 Nursing Mothers

Buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products.

An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices.

8.4 Pediatric Use

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients.

8.5 Geriatric Use

Clinical studies of SUBOXONE sublingual film, SUBOXONE (buprenorphine and naloxone) sublingual tablets, or SUBUTEX (buprenorphine) sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for signs and symptoms of precipitated opioid withdrawal.

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

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.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The physician may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.5)]*.

A neonatal withdrawal syndrome has been reported in the infants of women treated with buprenorphine during pregnancy *[see Warnings and Precautions (5.9)]*.

10 OVERDOSAGE

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

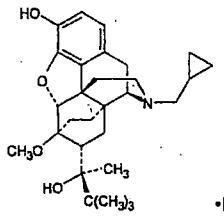
In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary.

11 DESCRIPTION

SUBOXONE (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist and a kappa-opioid receptor antagonist, and naloxone HCl dihydrate, an opioid receptor antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual administration and is available in four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone, and 12 mg buprenorphine with 3 mg naloxone. Each sublingual film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

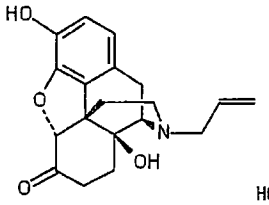
Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



•HCl

Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4$ • HCl and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



HCl • $2H_2O$

Naloxone hydrochloride dihydrate has the molecular formula $C_{19}H_{21}NO_4$ • HCl • $2H_2O$ and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

12.2 Pharmacodynamics

Subjective Effects:

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3-hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

12.3 Pharmacokinetics

Absorption:

In pharmacokinetic studies, the 2 mg/0.5 mg and 4 mg/1 mg doses administered as SUBOXONE sublingual films showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets, whereas the 8 mg/2 mg and 12 mg/3 mg doses administered as SUBOXONE sublingual films showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE sublingual tablets. A combination

of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films (total dose of 12 mg/3 mg) showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets *[See Dosage and Administration (2.6 and 2.7)]*.

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in-vitro*; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug-drug Interactions:

CYP3A4 Inhibitors and Inducers: Subjects receiving SUBOXONE sublingual film should be monitored if inhibitors of CYP3A4 such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin) or HIV protease inhibitors and may require dose-reduction of one or both agents. The interaction of buprenorphine with all CYP3A4 inducers has not been studied, therefore it is recommended that patients receiving SUBOXONE sublingual film be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered *[See Drug Interactions (7.1)]*.

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in *in-vitro* studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity:

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rat, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Mutagenicity:

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli*. The combination was not clastogenic in an *in-vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in-vivo* and *in-vitro* incorporation of [³H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis) had no adverse effect on fertility.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBOXONE sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine/naloxone 2 mg/0.5 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1204-3 (buprenorphine/naloxone 4 mg/1 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine/naloxone 8 mg/2 mg/film; content expressed in terms of free base) - 30 films per carton
- NDC 12496-1212-3 (buprenorphine/naloxone 12 mg/3 mg/film; content expressed in terms of free base) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Patients should be advised to store buprenorphine-containing medications safely and out of sight and reach of children.

Rx only

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Patients should be advised NOT to cut, chew or swallow SUBOXONE sublingual film.

17.1 Safe Use

Before initiating treatment with SUBOXONE, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBOXONE is dispensed because new information may be available.

- Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines or other CNS depressants (including alcohol) while taking SUBOXONE sublingual film. Patients prescribed benzodiazepines or other CNS depressants should be cautioned to use them only as directed by their physician. *[see Warnings and Precautions (5.2), Drug Interactions (7.3)]*
- Patients should be advised that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Patients should be cautioned to keep their films in a safe place, and to protect them from theft.
- Patients should be instructed to keep SUBOXONE sublingual film in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in death. Patients should be advised that if a child is exposed to SUBOXONE sublingual film, medical attention should be sought immediately.
- Patients should be advised never to give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Patients should be advised that selling or giving away this medication is against the law.
- Patients should be cautioned that SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. *[see Warnings and Precautions (5.11)]*
- Patients should be advised not to change the dosage of SUBOXONE sublingual film without consulting their physician.
- Patients should be advised to take SUBOXONE sublingual film once a day.
- Patients should be informed that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Patients seeking to discontinue treatment with buprenorphine for opioid dependence should be advised to work closely with their physician on a tapering schedule and should be apprised of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Patients should be cautioned that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals. *[see Warnings and Precautions. (5.12)]*
- Patients should inform their physician if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used. *[see Drug Interactions (7.1, 7.2 and 7.3)]*
- Women of childbearing potential who become pregnant or are planning to become pregnant, should be advised to consult their physician regarding the possible effects of using SUBOXONE sublingual film during pregnancy. *[see Use in Specific Populations (8.1)]*
- Patients should be warned that buprenorphine passes into breast milk. Breast-feeding is not advised in mothers treated with buprenorphine products. *[see Use in Specific Populations (8.3)]*.
- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.
- Refer to the Medication Guide for additional information regarding the counseling information.

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Buprenorphine Pilot Project with Parolees in Illinois: Early Results and Lessons Learned

Dona Howell-IDOC Manager of Addiction and Recovery Service
Janelle Prueter, Director-TASC Corrections Program
Arturo Valdez- HAS

GOALS

- Explain the process of gaining acceptance of Medication Assisted Treatment as a viable treatment option within the criminal justice system
- Share the lessons learned as pilot program implementation moved forward
- Identify strategies for improving outcomes for MAT for opiate dependent parolees

PARTNERS

- Reckitt Benckiser Pharmaceutical Company
- HAS- Healthcare Alternative Systems
- TASC- Treatment Alternatives for Safe Communities
- Haymarket
- Westcare
- IDOC-including Sheridan Correctional Center, Parole, Placement Resource Unit, Addiction Management and Recovery Services

PROCESS

- Building on an existing structure to expand successful programming for IDOC parolees leaving one of the national model programs- Sheridan Correctional Center
- Reentry Program Council
- NIDA- CJDATS Program

PROCESS

- Evaluation of parolee success in the community
- Longitutidinally, Opiate addicts were found to have some of the lowest success rates in the transition from facility based treatment to the community
- Utilization of existing partners, supported by a grant from Reckitt Benckiser to develop alternative programming options

IDOC

- Sheridan has 950 totally dedicated substance abuse treatment beds at Sheridan with another 300 Pre Treatment and 206 Pre Release beds on site for offenders either getting ready to transition to the community or move into the treatment.
- Safer provides job preparedness training, job coaching, and vocational services
- TASC provides the pre release clinical case management and Inner Circle groups on site
- Both Safer and TASC focus the majority of their services toward the end of an offender's stay at Sheridan

IDOC

- Already invested in evidence based practices and exploring ways to improve outcomes as offenders transition into the community
- 6 years worth of research on the National Model Treatment Program at Sheridan
- Partnerships between IDOC, TASC, SAFER, HAS, and Haymarket already in existence
- Lessons already learned and shared

IDOC

- Sheridan parolees have a significant amount of services available to them in the community
- TASC provides the clinical case management both pre and post services for Sheridan
- Westcare provides the "in-house" substance abuse treatment for offenders and is part of the process to make clinical continuing care recommendations for offenders paroling to the community

TASC

- Responsible for providing clinical reentry management both pre and post release
- Involved in advocating for medication assisted therapy for offenders struggling with opiate addiction
- The bridge for offenders leaving Sheridan and transitioning to the community
- Monitors parolees' progress in treatment in the community

TASC

- Advocate for treatment
- Case manager that works with individual parolees to ensure that they follow their discharge summary and help modify programming when things are not working
- Explores with parolees other options for programming
- A partner along with parole, PRU, the community treatment providers, and SAFER

HAS

- A community based substance abuse treatment agency already familiar with both the treatment population and the treatment regime
- HAS has contracts with both IDOC and TASC to provide substance abuse treatment for parolees
- 35 years of experience in the treatment of addiction

HAYMARKET

- Contracted by IDOC to provide an array of treatment services to parolees
- Already using Suboxone in the detoxification of opiate-dependent offenders.

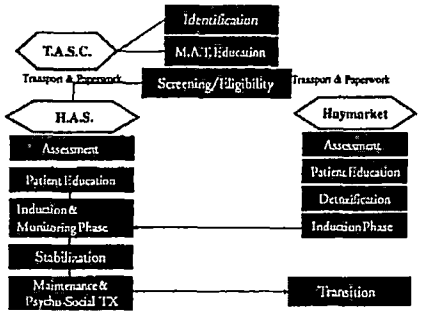
A New Treatment Model including MAT

- The population included opiate affected former offenders released from Sheridan that relapsed during or following a course of community based treatment.
- Offenders motivated to change and struggling in their recovery.
- TASC staff and/or parole agents meet with the offender to talk about the option for treatment combined with MAT-suboxone.

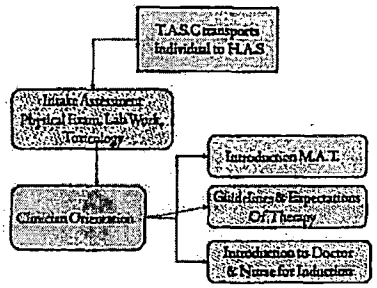
A New Treatment Model including MAT

- Those that agreed to participate in the pilot either entered detox at Haymarket or began induction to suboxone at HAS.
- Treatment services and medication management conducted by HAS.
- TASC continues to provide intensive case management services coupled with supervision by parole.

THE PROCESS



Patient Education



Suboxone Induction & Stabilization

- Administered when an opioid-addicted individual has mild to moderate withdrawal symptoms
- Individual is seen by the Doctor and Nurse for first dose in the office
- Individual is then assessed immediately or within a few hours of effects
- Prescription is given extending until the next appointment
- Adjustment period until stabilized
- Enter patient education and psycho-social phase

Outpatient Psychosocial Treatment

I. *Thinking for Change*
- National Institute of Corrections Cognitive Behavioral Curriculum

II. *Strategies for Self-Improvement and Change (SSC)*
(Wanberg & Milkman Criminal Conduct and Substance Abuse Treatment)
- Chemical dependency Treatment I
- Criminogenic Risk and Needs Emphasis

III. *Relapse Prevention* (Wanberg & Milkman Criminal Conduct and Substance Abuse Treatment)

CASE STUDY

47 year old African American Male:

Recovery Capital: sober living environment, participated in 12 step groups, tested negative at treatment assessment; part-time employment, some family support

Characteristics of Drug Challenges:

- 20 year history heroin/cocaine use
- Relapsed 5 months post release
- 3rd treatment episode within 13 months
- Acute episodes of depression

Process

-February 10th referral communication from TASC
- Seen by HAS next day
-Induction 1st dose 8 mg February 11th (inclusive of assessment, physical)
- 2 more doctor follow ups
- Treatment participation started March 15th did not complete due to ongoing transportation issues. Completed 55 hours of treatment

CASE STUDY

Prior case continued:

Current status:

Client continues on suboxone and has had some ups and downs related to continued use. Mostly recently is drug free and continuing suboxone.

CASE STUDY

40 year old African American Male:

Reason for Referral: Client was AWOL from parole and TASC for 3 months. When found, admitted daily use of opiates.

Recovery Capital:

Married 14 years, high school diploma, primary care doctor, high level of awareness of drug challenges, previous successful treatment completions, employment skills, also aware of triggers. Engaged in process and willingness to participate.

Characteristics of Drug Challenges:

13 year heroin use history

Client dropped out suddenly after completing 15 hours of treatment and taking suboxone consistently

CASE STUDY

- Inducted into the Suboxone program March of 2010.
- Struggled initially with both treatment compliance and abstaining from other drugs (cocaine and marijuana);
- Admitted to Detox at Haymarket; and stepped down through Haymarket 's Residential Program for 28 days and then to Haymarket's CIP Program (90 day recovery home).
- Participant has since been stepped down on his medication dosage, to where now, he no longer takes Suboxone.
- He suggested a Suboxone Support Group for the clients currently in the program stating they have similar backgrounds (drug and criminal) which currently meets one time per week.
- Participant completed treatment at H.A.S. and has begun working with the Department of Streets and Sanitation.

LESSONS LEARNED

- Educating all involved systems, staff and offenders on the role, purpose, and intentions of MAT is critical.
- Understanding the role and significance of treatment combined within MAT needs to be defined early on in the process.
- Continuity of contact over time with all team members and participant is vital to prevention, intervention, and ongoing participation.

LESSONS LEARNED

- Focus on a very difficult to treat population that had already relapsed and in jeopardy of returning to prison.

NEXT STEPS

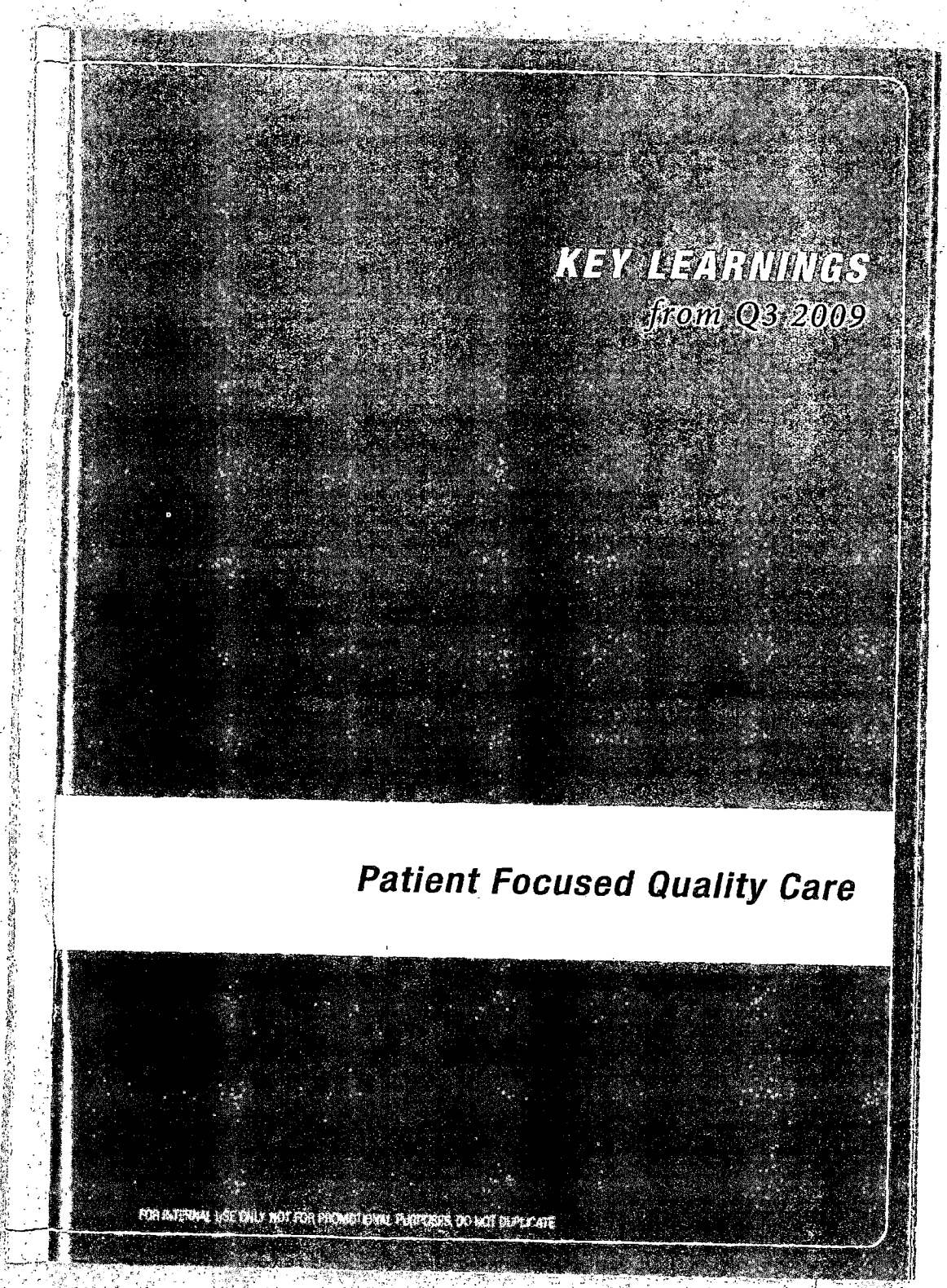
- Modify criteria to determine most appropriate participants for the program
- Introduce program and educate potential participants while in reentry phase of incarceration.
- Introduce MAT combined with appropriate treatment services immediately following release from prison
- Increase education to participants , their families and staff regarding MAT

Next Steps

- Increase resources and expand recovery initiation and planning for participants within the community to address the multiple challenges people face such as vocational training, education, employment, housing, and recreation.

NEXT STEPS

- Create a more efficient data access system to the participants file by all partners.
- Create an participant advisory council comprised of current and discharged MAT clients to serve as adjuncts to direct service staff (peers).
- Increase telephone recovery check ins and follow up (rapid, assertive, and ongoing engagement and communication).


KEY LEARNINGS
from Q3 2009
Patient Focused Quality Care
FOR INTERNAL USE ONLY NOT FOR PROMOTIONAL PURPOSES DO NOT DUPLICATE

Key Learnings from Q3 2009

Your efforts in promoting the Here to Help® program have further demonstrated Reckitt Benckiser Pharmaceuticals' commitment to the treatment of opioid dependence and Patient Focused Quality Care by addressing the many barriers that physicians and patients experience.

We have built a strong foundation with Here to Help® providers, physicians, and counselors. You are building their hands-on experience with the difference Here to Help® makes for their patients. Patient enrollment in the Here to Help® program continues to grow as of October 5, 2009:

- Over **12,971** Patients have been assisted in finding treatment through Here to Help®
- **3,885** Patients have enrolled in Here to Help®
  - ***2,648 patients have completed at least one Care Coach call***
  - ***1,237 patients have enrolled in email support through a Care Coordinator***
- Another **1,275** patients enrolled in Here to Help® email through the website

The value the Here to Help® program provides is evident in the feedback we are receiving from both physicians and patients. Physicians with enrolled patients actively engaged in the Here to Help® program are able to recognize the benefits the program brings to their patients and their practice.

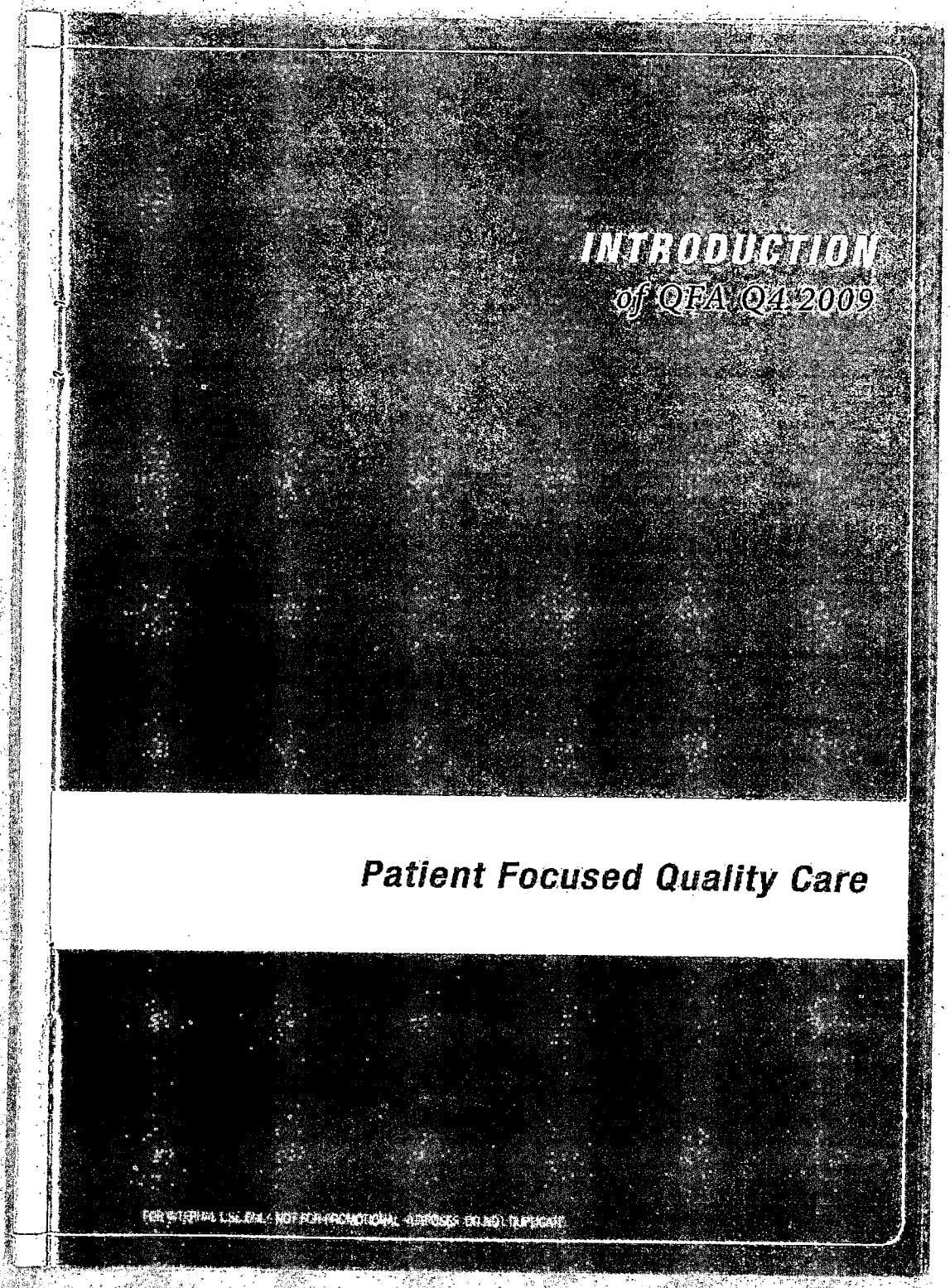
- "We tell our patients that if they have a question after office hours or on weekends, to call their Care Coach first, write down the information or concern in their Everyday Success Planner, and then bring it in to their next appointment. This has worked well for them and has cut back on after-hour paging to the doctor and calls to the office."
- "I have been reluctant to expand beyond 30 patients because these patients demand a lot from my staff in terms of phone time, education and treatment follow up. The Here to Help® program will provide me with the kind of resource that I now believe I can increase my number of patients to 55-60."
- "I like having this program Here to Help® available because I feel like I have the assurance that I could always talk to somebody and that's better than to fall back."

Key Learnings from Q3 2009

Key Learnings (continued):

It is important for all of your physicians to experience the positive impact Here to Help® can have on their patients and their practice. As each new patient experiences the benefits of Here to Help®, it becomes an indispensible part of treatment and further reinforces the important contribution that RBP is making to promote *Patient Focused Quality Care.*

[Notes]


INTRODUCTION
of QFA Q4 2009
Patient Focused Quality Care

Introduction to QFA Q4 2009

As Clinical Liaisons, you are trusted advisors to many of your physicians because of your ongoing commitment to improving the lives of patients by advocating for Patient Focused Quality Care beyond just the medication.

The last two quarters have focused on introducing Here to Help® and promoting the value of the program to improve the quality of care for opioid dependence. We need to continue to build upon these efforts by reinforcing the value that you bring to your matrix members through the promotion of SUBOXONE® (buprenorphine and naloxone) + Counseling + Here to Help® as the new model of Patient Focused Quality Care. Your efforts will make SUBOXONE® synonymous with quality care and further strengthen our brand equity.

This effort is critical given that our marketplace has expanded to include a generic buprenorphine-only product. On October 9, 2009, Roxane Laboratories received FDA approval for generic Subutex® (buprenorphine) sublingual tablets CIII. Following the recent approval of this generic buprenorphine tablet there will likely be a push from patients to request a switch from SUBOXONE® to generic buprenorphine - only to reduce their medication costs. Physicians may be likely to comply with this request if they do not understand the importance or value of the naloxone component of SUBOXONE® to their patients and their practice, and the value of the Here to Help® program.

Now and in the future it is critical that your physicians understand and believe in the role that SUBOXONE® and Here to Help® play to ensure Patient Focused Quality Care.

Care Coordination: Successfully Opening Up Access to Care

- In the first 6 months*, HTH Care Coordinators helped 18,692 people connect with a physician's office
- Currently ~2400 patients per week call the HTH line seeking treatment
- An additional ~16,000 people per week use the online HTH locator

*HTH launched 4/27/09

Suboxone (buprenorphine HCl/naloxone HCl dihydrate) C-III

Care Coordination: Providing Value to Enrolled Physicians

"A Care Coordinator called in with the patient, stayed on the line to introduce the patient, then left the line. The patient and I talked for a short while and an appointment was set up for next week for the patient to come to the office. I was impressed with the knowledge the patient had about Suboxone and her openness about her disease. If [Here to Help] is able to help bring patients to me like this, I will continue accepting new patients." - HTH enrolled physician

"I've had patients come from two hours away and they are being referred to me through Here to Help®, and so that's been a very good resource." - Dr Gregory Dobash

Suboxone

Here to Help® Care Coordination

- Here to Help (HTH) Care Coordinators help patients find treatment and encourage them to access it
- Care Coordinators provide
  - Up-to-date information on HTH enrolled treatment providers
  - Assistance in making the first appointment
  - Follow-up with patient that an appointment has been scheduled
  - Enrollment in Here to Help Care Coaching
  - Support in overcoming the barriers to finding treatment
  - Referrals to email support and internet resources
- These services are designed to increase the likelihood that the patient makes and keeps their first appointment

Suboxone (buprenorphine HCl and naloxone HCl dihydrate) C

How can you ensure that your patients benefit from Here to Help®?

- How can we work together to facilitate more patients enroll in HTH?
- How can we make sure they are engaged in HTH?

"Now if I have patients who are kind of reluctant to use Here to Help, I'm wondering how seriously they're taking their treatment. Patients who are using Here to Help want to do the extra things it takes." – Dr. Brian Rodgers

Suboxone®

Accessing Treatment is Only the First Step

- Once in treatment, patients face additional barriers to being successful in treatment
  - Lack of ongoing support
  - Lack of personalized resources to help them take a more active role in their treatment and be successful
  - Lack of support outside office hours and on weekends
- Here to Help® Care Coaching is designed to assist patients in overcoming the barriers to treatment success

Suboxone
buprenorphine HCl/naloxone HCl dihydrate

EXHIBIT G

Counselor's Clinical Cottage, PSC

1205 MONTGOMERY PLAZA, SUITE # 3
ASHLAND, KY 41101
PH: 606-329-0727 FX: 606-329-1327
BUSINESS LICENSE ID# BL-2011-12
GROUP NPI # 1831366327

Jade A. Maddox, MA, LPCC, NCC / Executive Director /
Past President of the Kentucky Counselor's Association

Dr. Rodney Crock, Board Certified Family Practice, Expect in Chemical Dependency Treatment
DEA XC # XC832464, NPI # 1891738357

April 4, 2013

To Whom It May Concern:

The preferred medication (buprenorphine and naloxone tablet) that is recommended by this patient's insurance company is not acceptable.

This tablet is unacceptable due to patient risk of misuse, abuse, and diversion. I am recommending the patient use Suboxone Sublingual Film Therapy.

Sincerely,

Dr. Rodney Crock