BEFORE THE DIVISION OF CONSUMER PROTECTION OF THE DEPARTMENT OF COMMERCE OF THE STATE OF UTAH

IN THE MATTER OF: **PURDUE PHARMA L.P.**, a Delaware limited partnership; **PURDUE PHARMA INC.**, a New York Corporation; **THE PURDUE FREDERICK COMPANY**, a Delaware corporation; **RICHARD SACKLER, M.D.**, individually and as an owner, officer, director, member, principal, manager, and/or key employee of the above named entities; and **KATHE SACKLER, M.D.**, individually and as an owner, officer, director, member, principal, manager, and/or key employee of the above named entities; **Respondents.**	**DCP Legal File No. CP-2019-005** **DCP Case No. 107102**

DECLARATION OF CHRISTOPHER J. STANLEY

Christopher J. Stanley hereby declares and states:

1. I am an attorney in good standing of the bar of the State of New York.

2. I am a partner in the law firm of Joseph Hage Aaronson LLC, counsel to Richard Sackler. I submit this declaration in support of Richard Sackler and Kathe Sackler's motion to dismiss the Administrative Citation filed by the Division of Consumer Protection of the Department of Commerce of the State of Utah in the above-captioned matter (the "**Citation**").

3. Attached as **Exhibit 1** is a true and correct copy of United States Patent No. 9,861,628 B2, dated January 9, 2018. This document is a publicly available government document and is referenced in the Citation at ¶ 150 n.103.

4. Attached as **Exhibit 2** is a true and correct copy of a letter to FDA Commissioner Hamburg from National Association of Attorneys General dated December 16, 2013. This document is a publicly available document.

5. Attached as **Exhibit 3** is a true and correct copy of the December 5, 1995 FDA-approved label for OxyContin 10mg Tablets, 20mg Tablets and 40mg Tablets.

Pursuant to Utah Code Ann. § 78B-18a-101, *et seq.*, I declare under criminal penalty under the law of Utah that the foregoing is true and correct.

Signed on the 9th day of April, 2019, at New York, New York.

CHRISTOPHER J. STANLEY

Exhibit 1

US009861628B2

(12) **United States Patent**
Oksche et al.

(10) **Patent No.: US 9,861,628 B2**
(45) **Date of Patent: *Jan. 9, 2018**

(54) **BUPRENORPHINE-WAFER FOR DRUG SUBSTITUTION THERAPY**

(71) Applicant: **Rhodes Pharmaceuticals L.P.**, Coventry, RI (US)

(72) Inventors: **Alexander Oksche**, Limburg (DE); **William Heath**, Cambridge (GB); **Timothy Holden**, Cambridge (GB); **Derek A. Prater**, Cambridge (GB); **Richard S. Sackler**, Greenwich, CT (US); **Malcolm Walden**, Cambridge (GB)

(73) Assignee: **RHODES PHARMACEUTICALS L.P.**, Coventry, RI (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/135,794**

(22) Filed: **Apr. 22, 2016**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) Continuation of application No. 14/800,270, filed on Jul. 15, 2015, now Pat. No. 9,370,512, which is a division of application No. 12/439,410, filed as application No. PCT/EP2007/058978 on Aug. 29, 2007, now Pat. No. 9,101,625.

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**

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A61K 31/485	(2006.01)
A61K 47/38	(2006.01)
A61K 9/00	(2006.01)
A61K 9/70	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/485*** (2013.01); ***A61K 9/006*** (2013.01); ***A61K 9/0056*** (2013.01); ***A61K 9/7007*** (2013.01); ***A61K 47/38*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to oral pharmaceutical dosage forms comprising buprenorphine with the dosage form releasing buprenorphine instantly upon oral, preferably sublingual, application of the dosage form. The present invention also relates to the use of such dosage forms for treating pain in a human or animal or for drug substitution therapy in drug-dependent human subjects.

15 Claims, No Drawings

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BUPRENORPHINE-WAFER FOR DRUG SUBSTITUTION THERAPY

The present invention relates to oral pharmaceutical dosage forms comprising buprenorphine with the dosage form releasing buprenorphine instantly upon oral, preferably sublingual, application of the dosage form. The present invention also relates to the use of such dosage forms for treating pain in a human or animal or for drug substitution therapy in drug-dependent human subjects.

BACKGROUND OF THE INVENTION

Chronic pain, which may be due to idiopathic reasons, cancer or other diseases such as rheumatism and arthritis, is typically treated with strong opioids.

Over the last decades prejudices in the medical community as to the use of strong opioids for treating chronic pain in patients has significantly decreased. Many of the se prejudices were due to some of the characteristics being inherent to opioids.

While opioids have always been known to be useful in pain treatment, they also display an addictive potential in view of their euphorigenic activity. Thus, if opioids are taken by healthy human subjects with a drug seeking behaviour they may lead to psychological as well as physical dependence.

These usually undesired characteristics of opioids can however become important in certain scenarios such as drug substitution therapies for drug addicts. One of the fundamental problems of illicit drug abuse by drug addicts ("junkies") who are dependent on the constant intake of illegal drugs such as heroin is the drug-related criminal activities resorted to by such addicts in order to raise enough money to fund their addiction. The constant pressures upon addicts to procure money for buying drugs and the concomitant criminal activities have been increasingly recognised as a major factor that counteracts efficient and long-lasting withdrawal and abstinence from drugs.

Therefore, programmes have been developed, particularly in the United States and western European countries, in which drug addicts are allowed to take prescription drugs under close supervision of medical practitioners instead of illegal drugs such as street heroin.

The aim of drug substitution theory is thus to first enable addicts to lead a regular life by administering legal drugs to prevent withdrawal symptoms, but because of their legal character and prescription by medical practitioners do not lead to the aforementioned described drug-related criminal activities. In a second and/or alternate step in the treatment of drug addiction may be to slowly make the drug addict less dependent on the drug by gradually reducing the dose of the substitution drug or to bridge the time until a therapy place in a withdrawal programme is available.

The standard drug used in drug substitution therapy programmes has for a long time been methadone. However, in recent years the potential of other opioids as substitution drugs in substitution therapy has been recognised. A particularly suitable drug for that purpose is the opioid buprenorphine, which is a mixed opioid agonist/antagonist.

Nowadays, buprenorphine preparations are administered in drug substitution programmes in the form of a tablet for sublingual administration. One of the reasons that the tablets are formulated for sublingual administration is that this the preferred route of administration for buprenorphine. Furthermore, if a patient swallows such tablets they will not provide euphorigenic activity.

One example of sublingual tablets for drug substitution therapy is the preparation Subutex® (being marketed in Germany by Essex Pharma).

Nevertheless, drug addicts sometimes still try to divert these sublingual buprenorphine tablets by removing them from the mouth when the supervising healthcare professional's attention is directed to other activities. Later the tablets may be sold or the active agent buprenorphine isolated/extracted to apply it parenterally.

Another buprenorphine preparation aimed at preventing this potential possibility of abuse has recently gained administrative approval in the United States (Suboxone®). The Suboxone® preparation comprises buprenorphine hydrochloride and the opioid antagonist naloxone hydrochloride dihydrate. The presence of naloxone is intended to prevent parenteral abuse of buprenorphine as parenteral co-administration of buprenorphine and naloxone in e.g. an opioid-dependent addict will lead to serious withdrawal symptoms.

However, there remains a need for other diversion and/or abuse-resistant dosage forms of buprenorphine, which can be used in drug substitution therapy as described above. Additionally, it would be desirable to have a buprenorphine preparation available which is diversion and/or abuse-resistant in cases where the preparation is used for drug substitution therapy and which could also provide efficient analgesia in cases where the preparation is administered to alleviate pain in a patient.

OBJECT AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide an oral pharmaceutical dosage form of the active agent buprenorphine that is less prone to diversion and/or abuse in drug substitution therapy. It is another object of the present invention to provide an oral dosage form of the active agent buprenorphine that can be used for drug substitution therapy and/or pain treatment.

In one embodiment the present invention relates to an oral pharmaceutical dosage form comprising at least buprenorphine or a pharmaceutically acceptable salt thereof with a dosage form releasing buprenorphine or said pharmaceutically acceptable salt thereof instantly upon or oral, preferably sublingual, application of the dosage form. It is, however, understood that the invention and its various embodiments which are set out below, can be extended to any opioid or analgesic whose preferred route of administration is oral, prefereably sublingual, as is the case for buprenorphine.

An instant release of buprenorphine or a pharmaceutically acceptable salt thereof upon oral, preferably sublingual, application means that substantially all of the buprenorphine or said pharmaceutically acceptable salt thereof will be released within less than three minutes, preferably within less than two minutes or less than one minute. Even more preferably, substantially all of the buprenorphine or said pharmaceutically acceptable salt thereof will be released within less than thirty seconds, twenty seconds, ten seconds or even within less than five seconds after oral, preferably sublingual, application of the dosage form. In one of the preferred embodiments these oral dosage forms will comprise between approximately 0.1 mg and approximately 16 mg buprenorphine or the equivalent amounts of a pharmaceutically acceptable salt thereof.

In a further preferred embodiment these oral pharmaceutical dosage forms will achieve an average C_{max} of between 1.5 ng/ml and approximately 2.25 ng/ml in the case of a dose of 0.4 mg buprenorphine hydrochloride being administered.

In the case of a dose of 8 mg buprenorphine HCl being administered, the C_{max} will typically be between approximately 2.5 and 3.5 ng/ml and if a dose of 16 mg buprenorphine hydrochloride is administered the C_{max} will preferably be between 5.5 to 6.5 ng/ml.

Yet another preferred embodiment of the invention relates to oral pharmaceutical dosage forms which may provide for the above-mentioned characteristics and/or an average Tmax of from approximately 45 to approximately 90 minutes.

In a particularly preferred embodiment the dosage forms will additionally comprise an opioid antagonist, preferably naloxone or a pharmaceutically acceptable salt thereof.

In yet a further preferred embodiment, the pharmaceutical dosage form will comprise buprenorphine and the opioid antagonist, which preferably is naloxone, in a weight ratio of from approximately 1:1 to approximately 10:1.

One embodiment of the present invention also relates to oral pharmaceutical dosage forms, which may have some or all of the aforementioned characteristics and wherein the dosage form has a film-like or wafer-like shape.

Another embodiment relates to a method of manufacturing the afore-mentioned described dosage forms.

Embodiments of the present invention also relate to the use of the afore-described oral, preferably sublingual, pharmaceutical dosage forms in the manufacture of a medicament for treating pain in a human or animal and/or for drug substitution therapy in drug-dependent human subjects.

One aspect of the invention also relates to a method of drug substitution therapy in drug-dependent human subjects wherein the aforementioned oral pharmaceutical dosage forms are administered to a drug-dependent subject in need thereof.

DETAILED DESCRIPTION OF THE INVENTION

From the prior art, sublingual tablets are known under the trade names Subutex® or Suboxone® both of which comprise the active agent buprenorphine hydrochloride for drug substitution therapy.

The suitability of particularly buprenorphine for drug substitution therapy had been recognised early on in view of buprenorphine's very long elimination half-life (reported as approximately 20 to 37 hours), which allows a reduced frequency of administration. As a consequence drug addicts who participate in drug substitution therapy have to report less frequently to the medical agency or healthcare professional supervising the substitution programme.

Furthermore, the sublingual absorption of buprenorphine has the advantage that an abuse by swallowing tablets of buprenorphine is less likely to occur. The tablets that are currently on the market in the form of Subutex® and Suboxone® preparations are both for sublingual administration and typically disintegrate over a time period of five to ten minutes. However, within that time period the drug addict may be able to divert the tablet before subsequently either selling the tablets on the street or isolating the active agents therefrom.

In order to reduce of eliminate these problems, the present invention provides oral pharmaceutical dosage forms which comprise the active agent buprenorphine and which release buprenorphine instantly after oral, preferably sublingual, administration of the drug.

It is understood that if reference is made in the context of this invention to the term "buprenorphine" this refers to the free base as well as to any pharmaceutically acceptable salt thereof such as the hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate, succinate salts and the like.

A particularly preferred pharmaceutically acceptable salt of buprenorphine is buprenorphine hydrochloride.

The provision of a pharmaceutical dosage form comprising buprenorphine or a pharmaceutically acceptable salt thereof in e.g. film-like or wafer-like shapes which allows for instant release of the active agent upon oral, preferably sublingual, administration of the dosage form should prevent the type of abuse resulting from illicit diversion of the tablets by drug addicts participating in drug substitution therapy programmes.

In the context of the present invention instant release means that substantially the whole amount of the buprenorphine or the respective pharmaceutically acceptable salt thereof will be released in less than five minutes. Preferably, substantially all of the buprenorphine or its pharmaceutically acceptable salt thereof will be released within less than four, within less than three, within less than two and more preferably within less than one minute.

In a particularly preferred embodiment, instant release refers to the situation that substantially all of the buprenorphine or the respective pharmaceutically acceptable salt thereof will be released within less than thirty seconds, within less than twenty seconds, or within less than ten seconds. In an even more preferred embodiment, the term "instant release" means that substantially all of the buprenorphine will be released from the dosage form within less than five seconds or within less than three seconds.

The term "substantially all" means that approximately 95% of the drug will have been released.

The term "approximately" in the context of the present invention describes a deviation from the indicated value of 10% and preferably of 5%.

Such efficient release of the drug is hard to achieve with a sublingual tablet which generally requires a greater amount of time to melt or to disintegrate.

Fast-dissolving or rapidly disintegrating dosage forms for other pharmaceutically active compounds are known which disintegrate within seconds upon contact with the mucosal saliva of the mouth and particularly the sublingual mucosa.

These pharmaceutical dosage forms and formulation principles are well known to the person skilled in the art and will be described in more detail below.

As regards the dosage amount, the pharmaceutical compositions in accordance with the present invention will typically comprise between approximately 0.1 mg and approximately 16 mg of buprenorphine or a pharmaceutically acceptable salt thereof such as buprenorphine hydrochloride. Preferred dosage amounts will be in the range of between approximately 0.4 mg and approximately 12 mg or between approximately 2 mg and approximately 8 mg buprenorphine or a pharmaceutically acceptable salt thereof.

The oral pharmaceutical dosage forms in accordance with the invention may have the further characteristic of providing a C_{max} of approximately 1.5 to 2.5 ng/ml in the case of a dose of 4 mg buprenorphine hydrochloride being administered. A preferred C_{max} in the case of a dose of 4 mg of buprenorphine hydrochloride being administered may be approximately between 1.7 ng/ml to 2 ng/ml.

In the case of a dose of 8 mg buprenorphine hydrochloride being administered, the C_{max} may be approximately between 2.5 and 3.5 ng/ml. In a preferred embodiment the C_{max} may be approximately between 2.75 ng/ml and 3.25 ng/ml in the case of a dose of 8 mg buprenorphine hydrochloride being administered.

In case of a dose of 16 mg buprenorphine hydrochloride being administered, the C_{max} may preferably be in the range of approximately 5 to 7 ng/ml. In a preferred embodiment the C_{max} may be between 5.5 and 6.5 ng/ml if 16 mg of buprenorphine hydrochloride are administered.

The AUC_{0-48} (i.e. the Area under the Curve for 48 hours after administration) may in the case of administration of 4 mg of buprenorphine hydrochloride be in the range of approximately 10 to 15 hours×ng/ml. In a preferred embodiment the AUC_{0-48} may be approximately 12 to 13 hours× ng/ml. In the case of 8 mg buprenorphine hydrochloride being administered the AUC_{0-48} may be approximately in the range of 15 to 25 hours×ng/ml. In a preferred embodiment the AUC_{0-48} in this case may be between approximately 20 to 22 hours×ng/ml. In the case of 16 mg buprenorphine hydrochloride being administered, the AUC_{0-48} may be in the range of 25 to 40 hours×ng/ml. In a preferred embodiment the AUC_{0-48} in this case may be in the range of approximately 30 to 35 hours×ng/ml.

The average T_{max} values for such preparations will preferably be from approximately 45 to approximately 90 minutes.

It is understood that the aforementioned pharmacokinetic parameters C_{max} and AUC_{0-48} are average values that are obtained by measuring the blood plasma levels in a group of eight to approximately twenty-four patients. These patients will be selected according to inclusion and exclusion criteria, as they are common for drug substitution programmes. It is understood that such patients typically will be of average weight and Caucasian origin.

The pharmaceutical dosage form in accordance with the invention will be administered such that the maximal dosage per day is 32 mg of buprenorphine. Once a patient is enrolled in substitution therapy, the initial dosage will be typically between 2 mg to 4 mg of buprenorphine. The formulations may be administered once a day, every two days, preferably every three days or even less fequently.

In a preferred embodiment, the oral dosage forms of the invention will additionally comprise an opioid antagonist. Such antagonists may be selected from the group comprising naltrexone, naloxone, nalmefene, nalorphine, nalbuphine, naloxoneazinen, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6-β-naloxol and 6-β-naltrexol or the pharmaceutically acceptable salts thereof.

Especially preferred antagonists comprise naltrexone, nalmefene and naloxone. Specifically preferred as an antagonist is naloxone and its hydrochloride salt.

It is understood, that if in the context of the present invention reference is made to an opioid antagonist, this also not only refers to the free base but also to pharmaceutically acceptable salts thereof such as those mentioned for buprenorphine.

A particularly preferred antagonist is naloxone. Of the naloxone salts, naloxone hydrochloride dihydrate may be particularly preferable in combination with buprenorphine hydrochloride.

The pharmaceutical dosage forms in accordance with the invention will comprise buprenorphine and the antagonist, which preferably is naloxone, in a weight ratio of from 1:1 to 10:1. A weight ratio of from 2:1 to 8:1 may be preferred, with a weight ratio of 4:1 being particularly preferred.

Thus, if an oral dosage form in accordance with the present invention for example comprises 2 mg buprenorphine hydrochloride it will comprise approximately 0.5 mg naloxone. If the dosage form comprises 0.4 mg buprenorphine hydrochloride, it will comprise 0.1 mg naloxone and if the dosage form comprises 8 mg buprenorphine hydrochloride it will comprise e.g. 2 mg naloxone hydrochloride.

A particularly preferred embodiment thus relates to an oral dosage form comprising buprenorphine, preferably buprenorphine hydrochloride, and naloxone, preferably naloxone hydrochloride, wherein the dosage form releases said active agents within less than one minute, preferably within less than thirty seconds and more preferably within less than ten seconds after sublingual application of the dosage form. In addition, the dosage forms may provide the preferred values of the aforementioned pharmacokinetic parameters C_{max}, and AUC_{0-48}.

Thus, the person skilled in the art will have to ensure that indeed an oral dosage form is used which is able to allow for incorporation of sufficient amounts of buprenorphine and preferably also of naloxone and which at the same time disintegrates rapidly enough to release the active agents instantly.

In one embodiment one may use non-gelatin film materials, e.g. films of modified cellulose materials as dosage forms. In this case, buprenorphine and optionally opioid antagonists such as naloxone are incorporated into the film matrix and films thus prepared may be administered orally.

In accordance with this aspect of the invention, the active ingredients may be dissolved in a hydrophilic, organic system to form a homogenous solution or dispersion. The solution or dispersion can then be applied to one or more surfaces of a non-gelatin polymeric film, e.g. a dry cellulose ether film, resulting in the active ingredient(s) and/or liquid carrier phase being transported through the surface of the "dry" film resulting in a new film composition.

The film substrate may remain completely intact or relatively physically unchanged immediately following the incorporation process. It can, however, be converted to any size or shape of unit dosage form. Alternatively, the film substrate may liquefy or dissolve partly or fully during the incorporation process, but nevertheless finally forming a single discrete film, after curing. Films according to this aspect of the invention are typically made up of one or more soluble polymer or polymers which will otherwise degrade at the intended site of release after administration in the mouth, e.g. sublingual administration, in order to provide the instant release of the active agents. Suitable cellulose ether film bases include e.g. hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC), methylcellulose (MC), carboxymethylcellulose (CMC) and salts and derivates of all of the aforesaid materials. A particularly suitable cellulose ether for forming the film is HPMC.

Optional ingredients may be added including colorants, emulsifiers, humectants, and anti-blocking agents.

Once one has a film being based on a cellulose ether available, in a next step the active ingredient(s) will be applied in the form of a liquid to the film. Appropriate means of liquid application onto the film substrate include extrusion, roller application, pouring, spraying, brush painting or whipping. Further details of the preparation of such films can be taken e.g. from WO 2005/079750 A2 which is incorporated by reference herewith.

Another possible technology in order to provide the afore-described pharmaceutical dosage forms of buprenorphine and preferably naloxone is described in WO 03/030883. In this latter embodiment of the present invention, a thin film drug delivery composition includes (i) a flowable water-soluble film-forming matrix and (ii) the active agent(s) uniformly stationed therein. Optionally a

taste-masking agent may be coated or intimately associate with the active agent(s) to provide taste masking of the active agent(s). The flowable water-soluble film-forming matrix together with the active agent(s) is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

The matrix may be a cellulosic material, a gum, a protein, a starch, a glucan and combinations thereof. For example one may use the already aforementioned methylcellulose, HMC, HEC, HC, HPC, HPMC, HMPC, gum Arabic, xanthan gum etc. The films are prepared according to standard technology and the active agents are displaced thereon and therein as described in WO 03/030883.

Yet another interesting technology relates to immediate release drug delivery forms as described in WO 99/17744, which is also incorporated by reference herein as far as it describes fast releasing oral dosage forms. The person skilled in the art will understand that the processes and dosage forms in WO 99/17744 may be used to obtain the aforementioned described pharmaceutical dosage forms of buprenorphine and preferably also naloxone.

One may of course also use fast disintegrating tablets that disintegrate upon contacting the saliva, e.g. under the tongue, following oral administration. Such fast-disintegrating tablets are described e.g. in WO 99/44580 and are well known to the person skilled in the art.

A particularly interesting technology for fast-releasing dosage forms that may be used for the purpose of the present invention to provide an oral dosage form of buprenorphine and preferably an opioid antagonist such as naloxone can be taken from WO 96/26720.

Therein it is described how the active agent selegiline is formulated into a rapidly releasing dosage form that can be used e.g. for sublingual administration. WO 96/26720 describes in detail a "fast-dispersing dosage form" with the term encompassing all types of dosage forms being described in U.S. Pat. No. 5,120,549, U.S. Pat. No. 5,079,018, WO 93/12769, U.S. Pat. No. 5,298,261 and WO 91/04757.

As for WO 96/26720 in the case of the active agent selegiline, the present invention contemplates particularly using fast-dispersing dosage forms as described in UK patent number 1548022, that is, a solid fast-dispersing dosage form comprising a network of the active ingredient(s) and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

It is preferred that such a composition in accordance with the invention disintegrates within one to ten seconds, and particularly within two to eight seconds of being placed in the oral cavity and particularly sublingually.

The composition will preferably contain in addition to the active ingredient, matrix forming agents and secondary components.

Matrix forming agents suitable for use in this aspect of the present invention include materials derived from animal or vegetable proteins, such as gelatins, dextrins and soy, wheat and psyllium seed proteins, gums such as acacia, guar, agar, and xanthan, polysaccharides, alginates, carboxymethylcelluloses, carrageenans, dextrans, pectins, synthetic polymers such as polyvinylpyrrolidone, and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension.

Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring agents include red, black and yellow iron oxides. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame and thaumatin. Suitable taste-masking agents include sodium bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

Such fast-dispersing dosage forms containing buprenorphine and preferably an opioid antagonist such as naloxone may be similarly obtained as described in GB 1548022B or WO 96/26720, in particular Example 1 of the latter, which are incorporated herein in their entirety.

A particularly preferred embodiment of the present invention relates to dosage forms, which are produced along the lines described in WO 03/070227 A1.

This prior art reference describes taste-masked, film-type or wafer-type medicinal preparations. It is to be understood that the dosage forms in accordance with the present invention may preferably be such film-type or wafer-type medicinal preparations with the taste-masking being only an optional feature.

Flat active agent carriers that have a film-type or wafer-type structure provide for various advantages. As a consequence of the low thickness in comparison to the surface area, there is only a short diffusion pathway if such a dosage form is applied e.g. to the mucosa of the oral cavity. This typically leads to a very rapid release of the active agents which can then be quickly, efficiently and directly absorbed by the mucosa of the oral cavity and particularly sublingually if the active agent is absorbable at all via that route. Thus, in case of buprenorphine such very flat film-type or wafer-type dosage forms are highly desirable as they will allow for the provision of an instant release of active ingredient, thereby minimising the abuse problems encountered with the formulations of the prior art.

Flat active agent carriers have been developed for different purposes. One of the basic prior art references in this context is DE 27 46 414 in which active agent, binding agent and additional excipients are processed to yield a dosage form in the form of film-type strand.

One of the advantages of wafer-type pharmaceutical dosage forms as described in WO 03/070227 A1 is that there is a direct correlation between the amount of the active agent and the length of a certain part of the strand in view of the homogenous thickness, density and width. Thus, one can easily obtain a certain unit dosage by simply cutting the wafer-like dosage form in to appropriately sized pieces.

Such film-type or wafer-type dosage forms in accordance with the present invention are characterised in that they comprise a matrix which is formed from at least one matrix-forming polymer and in which buprenorphine and preferably an opioid antagonist such as naloxone are dissolved or homogenously dispersed.

The rapidly disintegrating matrix of the pharmaceutical dosage forms in accordance with the invention comprises as one of its basic substances water-soluble polymers or mixtures of such polymers. Preferably synthetic or partially synthetic polymers or naturally occurring biopolymers are used which can form films and are water-soluble. Particularly suitable for this purpose are polymers which may be selected from the group comprising cellulose derivatives, polyvinylalcohol, polyacrylates and polyvinylpyrrlidone.

Within the cellulose derivatives, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, and hydroxypropylmethylcellulose may be used. One may also use water-soluble polysaccharides being derived from plants or microbes. Preferred polysaccharides include pullulan, trantan, alginate, dextrin and pectins.

One may also use proteins and preferably gelatin or other gel-forming proteins. One may also use starch and starch derivatives, gelatin, polyvinylpyrrilidone, gum Arabic, pullulan, acrylates, polyethylene oxide with a particular focus on polyox 10, polyox 80, polyox 205, polyox 301, polyox 750 or copolymers of methylvinylether and maleic acid anhydride.

The person skilled in the art will appreciate that the extent to which buprenorphine and optionally an opioid antagonist such as naloxone are instantly released depends in part on the type of matrix-forming polymer chosen. For example, a dosage form using polyvinylalcohol as matrix-forming polymer may disintegrate faster than a dosage form using HPMC as matrix-forming polymer. The disintegration time may be adjusted by mixing a combination of different polymers in suitable amounts.

The person skilled in the art also knows disintegrating agents, which can "pull" water into the matrix which then pushes the dosage forms apart. Thus, such disintegrating agents may also be used for adjustment of the disintegration time.

In order to allow absorption of buprenorphine over the mucosa of the mouth, and particularly sublingually, in one embodiment the dosage forms may additionally use agents that enhance absorption of the active agent, i.e. so-called permeation enhancers.

Such permeation enhancers may be selected from the group comprising propandiol, dexpanthenol, and oleic acid. The permeation enhancers may also be selected from the group comprising saturated or unsaturated fatty acids, hydrocarbons, linear or branched fatty alcohols, dimethylsulfoxide, propylene glycol, decanol, dodecanol, 2-octyldodecanol, glycerine, ethanol or other alcohols.

According to a preferred embodiment the film-type or wafer-type oral dosage forms of the present invention in the presence of saliva can disintegrate within e.g. one second to three minutes or within five seconds to one minute or five seconds to thirty seconds.

The disintegration times of the oral dosage forms in accordance with the invention are measured according to the European pharmacopoeia, 4^{th} edition 2002.

In the present case where the active agent buprenorphine is administered sublingually, the dosage forms in accordance with the invention may additionally comprise an excipient that mediates adhesion to the respective mucosa. Examples of such muco-adhesive substances are e.g. polyacrylic acid, carboxymethylcellulose, hydroxymethylcellulose, methylcellulose, alginic acid, gelatin and gum Arabic.

The thickness of the film-type or wafer-type dosage forms in accordance with the invention may typically be between 5 μm and 10 mm, 30 μm and 2 mm, or 0.1 mm and 1 mm. The dosage forms may be round, oval, elliptic, or may have a triangular, quadrangular, or multi-angular form. Typically the surface of the pharmaceutical dosage forms in accordance with the invention is flat.

As stated above, the film-type or wafer-type matrix of the dosage forms of this aspect of the invention comprises at least one matrix-forming polymer. The matrix-forming polymer(s) are an essential component of the matrix.

The polymer amount within the matrix may be between approximately 3% by weight and approximately 98% by weight and preferably between 7 and 80% by weight and even more preferably between 20 and 50% by weight, the weight percentages being based on the total weight of the dosage forms.

The mucoadhesive properties as well as the disintegrating properties are to a large extent determined by the type of matrix-forming polymer(s), as well as the relative amount of the polymer(s) used in the dosage forms.

Besides the matrix-forming polymers, buprenorphine and optionally an opioid antagonist, further excipients may be present within the matrix.

These additional excipients may be filling agents such as SiO_2, colorants and pigments (such as TiO_2) disintegrating agents particularly those which attract water (such Aerosil), emulsifying agents, plasticizers, sweeteners or conserving agents. Additionally, auxiliary excipients such as stabilising agents or antioxidants may be added.

If a taste-masking effect is to be obtained, the dosage form in accordance with this aspect of the invention may comprise additionally a carbon dioxide-forming agent that upon contact with the saliva develops carbon dioxide. Such carbonates are well known in the prior art from effervescent formulations and include e.g. sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate or potassium carbonate. In order to enhance CO_2 development, one may add acidic components such as e.g. sodium dihydrogen- or disodiumhydrogen phosphate, sodium tatrate, sodium ascorbate etc. One may of course also use citric acid, tartartic acid, adipinic acid, ascorbic acid, acetic acid, lactic acid etc.

Thus, one preferred embodiment of the invention relates to oral dosage forms of film-type or wafer-type film as described above which comprise buprenophine and optionally an opioid antagonist such as naloxone with the oral dosage form having the above-described characteristics as to the amount of buprenophine and the optional antagonist, the pharmacokinetic parameters C_{max} and AUC_{0-48} and the instant release of the active agents from the dosage form. The person skilled in the art will know how to produce such film-type or wafer-type dosage forms on the basis of the above-mentioned information. This may be achieved by common film-coating technologies, extrusion processes, spray drying etc. More details can be taken from WO 03/070227.

The person skilled in the art will also know other dosage forms, which allow an instant release of the active agent upon sublingual administration, so that such formulation technology may be applied to buprenorphine and optionally opioid antagonists preferably being naloxone.

In a further embodiment, the present invention relates to the use of any of the aforementioned described pharmaceu-

tical dosage forms comprising buprenorphine and optionally an opioid antagonist being preferably naloxone for the manufacture of a medicament for drug substitution therapy. The pharmaceutical dosage forms described above may, of course, also be used in the manufacture of a medicament for treating pain. Thus, the dosage forms may be used in opioid naïve patients or patients who are not dependent on opioids in order to provide fast pain relief by oral, preferably sublingual, administration of the preparations.

As far as drug substitution therapy is concerned, the effectiveness of the afore-described amounts and pharmacokinetic parameters of buprenorphine and optionally naloxone are known from the pharmaceutical preparations Subutex® and Suboxone®. Therefore it can be firmly assumed that the same efficacy will be observed in drug substitution therapy with the inventive preparations of the present invention.

One of the advantages of the preparations in accordance with the present invention is to be seen in the fact that in view of the instant release of buprenorphine, a drug addict will have a diminished chance of illicitly diverting the dosage form given that particularly the film-type and the wafer-type of dosage forms will disintegrate instantly upon contact with the saliva during sublingual administration. If an opioid antagonist such as naloxone is included in the dosage form it is additionally ensured that parenteral abuse of such dosage forms by dissolving the active agents out of the rapidly disintegrating dosage forms will be significantly diminished.

In yet a further embodiment, the present invention relates to a method of drug substitution therapy in drug addicts by administering a pharmaceutical formulation as described above which instantly releases buprenorphine and optionally an opioid antagonist being preferably naloxone upon oral, preferably sublingual, administration to a patient.

One embodiment of the present invention also relates to a method of treating pain by administering a pharmaceutical formulation as described above which instantly releases buprenorphine and optionally an opioid antagonist being preferably naloxone upon oral, preferably sublingual, administration to a patient.

The present invention has been described by reference to some of its preferred embodiments. This description is, however, in no way meant to limit the scope of the invention. Other embodiments that do not depart from the spirit of the invention should be similarly encompassed and addressed by the aforementioned description and the subsequent claims.

The invention claimed is:

1. A method of medication-assisted treatment for opioid addiction, the method comprising contacting a mucosal surface of the oral cavity of a patient in need thereof with a film dosage form comprising:

a) an amount of buprenorphine, or an equivalent amount of a pharmaceutically acceptable salt thereof, sufficient to provide an average buprenorphine C_{max} of less than about 7 ng/ml and an average buprenorphine AUC_{0-48} of less than 40 (hrs*ng)/ml;

b) naloxone or a pharmaceutically acceptable salt thereof; and

c) at least one non-gelatin polymeric film-forming material in which the buprenorphine or the equivalent amount of the pharmaceutically acceptable salt thereof and the naloxone or the pharmaceutically acceptable salt thereof, are dissolved or homogeneously dispersed;

the buprenorphine or the equivalent amount of the pharmaceutically acceptable salt thereof and the naloxone or the pharmaceutically acceptable salt thereof being present in the film dosage form in a weight ratio of from 1:1 to 10:1;

such that

within less than 5 minutes after contacting the mucosal surface of the oral cavity of the patient with the film dosage form, the buprenorphine or the pharmaceutically acceptable salt thereof and approximately substantially all of the naloxone or the pharmaceutically acceptable salt thereof contact the mucosal surface of the oral cavity.

2. The method of claim **1**, wherein the film dosage form further comprises a pH modifier.

3. The method of claim **2**, wherein the pH modifier is selected from the group consisting of citric acid, tartaric acid, phosphoric acid, hydrochloric acid, and maleic acid.

4. The method of claim **1**, wherein the film dosage form is mucoadhesive.

5. The method of claim **1**, wherein the non-gelatin polymeric film-forming material is a modified cellulose material.

6. The method of claim **5**, wherein the modified cellulose material is a cellulose ether.

7. The method of claim **6**, wherein the cellulose ether is selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC), methylcellulose (MC), and carboxymethylcellulose (CMC).

8. The method of claim **1**, wherein the amount of buprenorphine is from 2 mg to 16 mg.

9. The method of claim **8**, wherein the amount of buprenorphine is 2 mg, 4 mg, 8 mg, or 16 mg.

10. The method of claim **1**, wherein the weight ratio is 2:1 to 8:1.

11. The method of claim **1**, wherein the film dosage form further comprises at least one of sodium dihydrogen or disodiumhydrogen phosphate, sodium tartrate, sodium ascorbate, citric acid, tartartic acid, adipinic acid, ascorbic acid, acetic acid, or lactic acid.

12. The method of claim **1**, wherein the film dosage form achieves a buprenorphine t_{max} from approximately 45 to approximately 90 minutes.

13. The method of claim **1**, wherein the film dosage form is administered once a day, every two days, every three days, or less frequently.

14. The method of claim **1**, wherein the film dosage form further comprises a flavoring agent.

15. The method of claim **14**, wherein the flavoring agent is selected from the group consisting of mint, raspberry, licorice, orange, lemon, grapefruit, caramel, vanilla, cherry, grape, and combinations thereof.

* * * * *

Exhibit 2

National Association of Attorneys General

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December 16, 2013

Margaret A. Hamburg, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg:

State Attorneys General have pursued a holistic approach to end our nation's prescription-drug abuse epidemic. This approach includes evidence-based prevention, robust law-enforcement operations targeting diverted pharmaceuticals, and the implementation of state-operated prescription-drug monitoring programs. This balanced attack, combined with the efforts of the Drug Enforcement Administration, has undoubtedly saved many lives by preventing prescription-drug overdoses.

The State Attorneys General want to thank you for your recent efforts to ensure branded opioid drugs have abuse-deterrent formulations. But we must go further. Ensuring that generic opioids, like their branded counterparts, have abuse-deterrent properties is a commonsense improvement that provides yet another important tool in the fight against our nation's prescription drug epidemic.

Accordingly, the undersigned State Attorneys General respectfully request that the FDA provide clear and fair regulatory standards for the incorporation of abuse-deterrent technologies into generic opioids. The FDA has been an excellent partner in fighting prescription drug abuse, and we look forward to continuing to work with you in ending this epidemic.

Sincerely,

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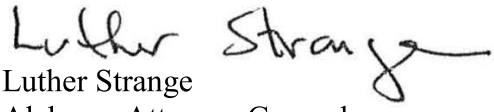

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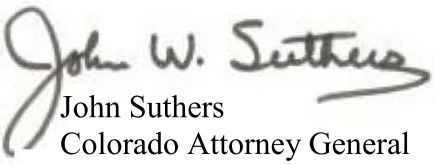

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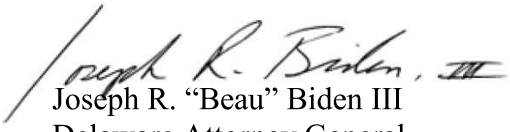

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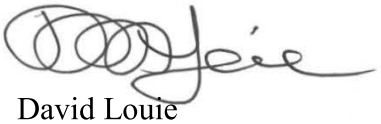

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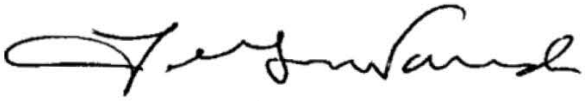

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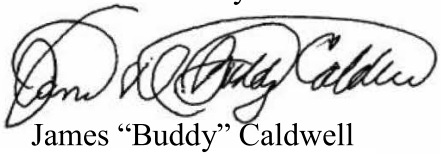

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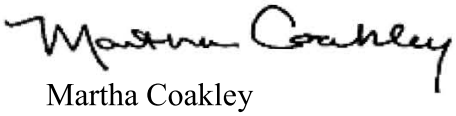

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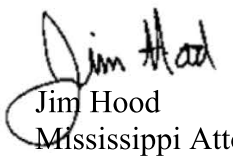

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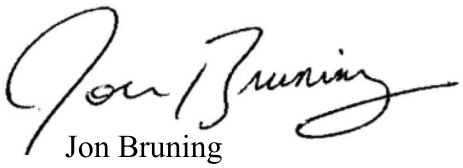

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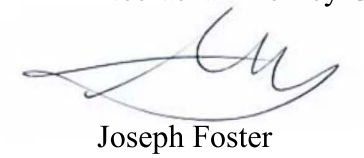

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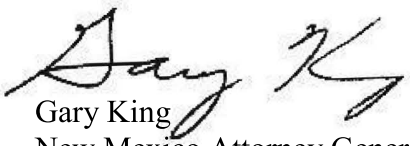

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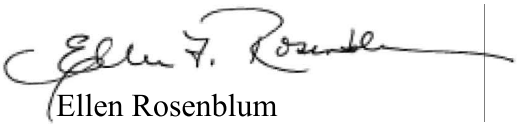

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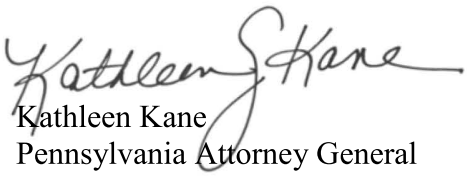

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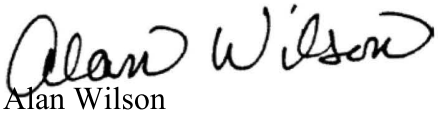

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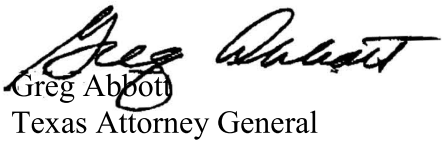

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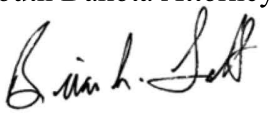

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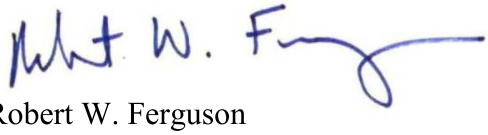

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Exhibit 3

OxyContin™ 10 mg Tablets
OxyContin™ 20 mg Tablets
OxyContin™ 40 mg Tablets

(Oxycodone Hydrochloride Controlled-Release)

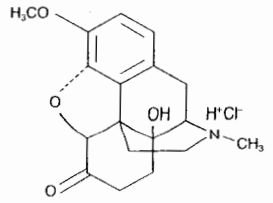
C II

WARNING: May Be Habit Forming

A4909-811

DESCRIPTION

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are an opioid analgesic supplied in 10 mg, 20 mg, and 40 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hydroxypropyl methylcellulose, lactose, magnesium stearate, povidone, red iron oxide (20 mg strength tablet only), stearyl alcohol, talc, titanium dioxide, triacetin, yellow iron oxide (40 mg strength tablet only), and other ingredients.

CLINICAL PHARMACOLOGY

Central Nervous System

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria and feelings of relaxation. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Efficacy Relationships (Pharmacodynamics)

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects. In normal volunteers these include pupillary constriction, sedation and overall "drug effect" and in patients, analgesia and feelings of "relaxation." In non-tolerant patients, analgesia is not usually seen at a plasma oxycodone concentration of less than 5–10 ng/mL.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or the development of tolerance.

Concentration—Adverse Experience Relationships

OxyContin™ tablets are associated with typical opioid-related adverse experiences similar to those seen with immediate-release oxycodone and all opioids. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is poorly understood.

As with all opioids, the dose must be individualized (see DOSAGE AND ADMINISTRATION), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

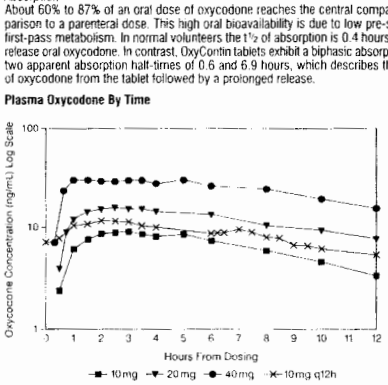
PHARMACOKINETICS AND METABOLISM

The activity of OxyContin™ (oxycodone hydrochloride controlled-release) tablets is primarily due to the parent drug oxycodone. OxyContin tablets are designed to provide controlled delivery of oxycodone over 12 hours. Oxycodone is well absorbed from OxyContin tablets with an oral bioavailability of from 60% to 87%. The relative oral bioavailability of OxyContin to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers, steady-state levels were achieved within 24-36 hours. Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of OxyContin was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers the $t_{1/2}$ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, OxyContin tablets exhibit a biphasic absorption pattern with two apparent absorption half-times of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone By Time



Dose proportionality has been established for the 10 mg, 20 mg and 40 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Given the short half-life of elimination of oxycodone from OxyContin, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin tablets. In a study comparing 10 mg of OxyContin every 12 hours to 5 mg of immediate-release oxycodone every 6 hours the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations. There was less fluctuation in plasma concentrations for the OxyContin tablets than for the immediate-release formulation.

Table 1

Mean [% coefficient variation]

Regimen/ Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose 10 mg OxyContin	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
20 mg OxyContin	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg OxyContin	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
Multiple Dose 10 mg OxyContin Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

†for single-dose AUC = $AUC_{0-\infty}$; for multiple-dose AUC = AUC_{0-t}

Food Effects

In contrast to immediate-release formulations, food has no significant effect on the absorption of oxycodone from OxyContin. Oxycodone release from OxyContin tablets is pH independent.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6L/kg. Oxycodone binding to plasma protein at 37C° and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen and brain. Oxycodone has been found in breast milk (see PRECAUTIONS).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone, but not noroxycodone, is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs (see Drug-Drug Interactions).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects. There were no differences in adverse event reporting between young and elderly subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Preliminary data from a study involving patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively and AUC values for oxycodone, noroxycodone and oxymorphone 60%, 50% and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in $t_{1/2}$ of elimination for oxycodone of only 1 hour (see PRECAUTIONS).

Hepatic Impairment

Preliminary data from a study involving patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The $t_{1/2}$ elimination for oxycodone increased by 2.3 hours (see PRECAUTIONS).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part via CYP2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination can be blocked by a variety of drugs (e.g., certain cardiovascular drugs and anti-depressants). Patients receiving such drugs concomitantly with OxyContin do not appear to present different therapeutic profiles than other patients.

CLINICAL TRIALS

OxyContin™ (oxycodone hydrochloride controlled-release) tablets were evaluated in studies involving 713 patients with either cancer or non-cancer pain. All patients receiving OxyContin were dosed q12h. Efficacy comparable to other forms of oral oxycodone was demonstrated in clinical studies using pharmacokinetic, pharmacodynamic and efficacy outcomes. The outcome of these trials indicated: (1) a positive relationship between dose and plasma oxycodone concentration, (2) a positive relationship between plasma oxycodone concentration and analgesia, and (3) an observed peak to trough variation in plasma concentration with OxyContin lying within the observed range established with qid dosing of immediate-release oxycodone in clinical populations at the same total daily dose.

In clinical trials, OxyContin tablets were substituted for a wide variety of analgesics, including acetaminophen (APAP), aspirin (ASA), other non-steroidal anti-inflammatory drugs (NSAIDs), opioid combination products and single-entity opioids, primarily morphine. In cancer patients receiving adequate opioid therapy at baseline, pain intensity scores and acceptability of therapy remained unchanged by transfer to OxyContin. For non-cancer pain patients who had moderate to severe pain at baseline on prn opioid therapy, pain control and acceptability of therapy improved with the introduction of fixed-interval therapy with OxyContin.

Use in Cancer Pain

OxyContin was studied in three double-blind, controlled clinical trials involving 341 cancer patients and several open-label trials with therapy durations of over 10 months.

Two, double-blind, controlled clinical studies indicated that OxyContin dosed q12h produced analgesic efficacy equivalent to immediate-release oxycodone dosed qid at the same total daily dose. Peak and trough plasma concentrations attained were similar to those attained with immediate-release oxycodone at equivalent total daily doses. With titration to analgesic effect and proper use of rescue medication, nearly every patient achieved adequate pain control with OxyContin.

In the third study, a double-blind, active-controlled, crossover trial, OxyContin dosed q12h was shown to be equivalent in efficacy and safety to immediate-release oxycodone dosed qid at the same total daily dose. Patients were able to be titrated to an acceptable analgesic effect with either OxyContin or immediate-release oxycodone with both treatments providing stable pain control within 2 days in most patients.

In patients with cancer pain, the total daily OxyContin doses tested ranged from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Studies in Non-Cancer Pain

A double-blind, placebo-controlled, fixed-dose, parallel group study was conducted in 133 patients with moderate to severe osteoarthritis pain, who were judged as having inadequate pain control with prn opioids and maximal non-steroidal anti-inflammatory therapy. In this study, 20 mg OxyContin q12h significantly decreased pain and improved quality of life, mood and sleep, relative to placebo. Both dose-concentration and concentration-effect relationships were noted with a minimum effective plasma oxycodone concentration of approximately 5–10 ng/mL.

In a double-blind, active-controlled, crossover study involving 57 patients with low-back pain inadequately controlled with prn opioids and non-opioid therapy, OxyContin administered q12h provided analgesia equivalent to immediate-release oxycodone administered qid. Patients could be titrated to an acceptable analgesic effect with either OxyContin or immediate-release forms of oxycodone.

Single-Dose Comparison with Standard Therapy

A single-dose, double-blind, placebo-controlled, post-operative study of 182 patients was conducted utilizing graded doses of OxyContin (10, 20 and 30 mg). Twenty and 30 mg of OxyContin gave equivalent peak analgesic effect compared to two oxycodone 5 mg /acetaminophen 325 mg tablets and to 15 mg immediate-release oxycodone, while the 10 mg dose of OxyContin was intermediate between both the immediate-release and combination products and placebo. The onset of analgesic action with OxyContin occurred within 1 hour in most patients following oral administration.

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) because the safety or appropriateness of fixed-dose, long-acting opioids in this setting has not been established.

Other Clinical Trials

In open-label trials involving approximately 200 patients with cancer-related and non-cancer pain, dosed according to the package insert recommendations, appropriate analgesic effectiveness was noted without regard to age, gender, race, or disease state. There were no unusual drug interactions observed in patients receiving a wide range of medications common in these populations.

For opioid-naive patients, the average total daily dose of OxyContin was approximately 40 mg per day. There was no evidence of oxycodone and metabolite accumulation during 8 months of therapy. For cancer pain patients the average total daily dose was 105 mg (range 20 to 720 mg) per day. There was a significant decrease in acute opioid-related side effects, except for constipation, during the first several weeks of therapy. Development of significant tolerance to analgesia was uncommon.

INDICATIONS AND USAGE

OxyContin™ tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days. (See: CLINICAL PHARMACOLOGY; CLINICAL TRIALS).

CONTRAINDICATIONS

OxyContin™ is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

Respiratory Depression

Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin™, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. OxyContin may produce orthostatic hypotension in ambulatory patients. OxyContin, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are intended for use in patients who require oral pain therapy with an opioid agonist of more than a few days duration. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient (see DOSAGE AND ADMINISTRATION).

Selection of patients for treatment with OxyContin should be governed by the same principles that apply to the use of similar controlled-release opioid analgesics (see INDICATIONS AND USAGE). Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using non-opioid analgesics, prn opioids and/or combination products, and chronic opioid therapy with drugs such as OxyContin in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and the American Pain Society.

Use of OxyContin is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin, like all opioid analgesics, should be used with caution and started in a reduced dosage ($\frac{1}{3}$ to $\frac{1}{2}$ of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery

OxyContin is not recommended pre-operatively (preemptive analgesia) or for the management of pain in the immediate post-operative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Patients who are already receiving OxyContin tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given and the temporary changes in physiology caused by the surgical intervention (see PRECAUTIONS: Drug-Drug Interactions, and DOSAGE AND ADMINISTRATION).

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is the occurrence of withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

Significant tolerance should not occur in most of the patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of cancer patients will develop some degree of tolerance and require progressively higher dosages of OxyContin to maintain pain control during chronic treatment. Regardless of whether this occurs as a result of increased pain secondary to disease progression or pharmacological tolerance, dosages can usually be increased safely by adjusting the patient's dose to maintain an acceptable balance between pain relief and side effects. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effect of opioids is usually paralleled by tolerance to side effects, except for constipation.

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity (see OVERDOSAGE). If OxyContin is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. This is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate or heart rate.

If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of OxyContin combined with symptomatic support (see DOSAGE AND ADMINISTRATION: Cessation of Therapy).

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin (oxycodone hydrochloride controlled-release) tablets or their caregivers should be given the following information by the physician, nurse, pharmacist or caregiver:

1. Patients should be advised that OxyContin tablets were designed to work properly only if swallowed whole. They may release all their contents at once if broken, chewed or crushed, resulting in a risk of overdose.
2. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
3. Patients should be advised not to adjust the dose of OxyContin without consulting the prescribing professional.

4. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
5. Patients should not combine OxyContin with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
6. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
7. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
8. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
9. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids or illicit drugs which cause central nervous system depression.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers and alcohol because respiratory depression, hypotension and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Mutagenicity

Studies of oxycodone in animals to evaluate its carcinogenic and mutagenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy

Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m^2) and 125 mg/kg (1375 mg/m^2), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m^2), based on mg/kg of a 60 kg adult (0.7 and 19 times this human dose based upon mg/m^2). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects—Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery

OxyContin is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin since oxycodone may be excreted in the milk.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established with this dosage form of oxycodone. However, oxycodone has been used extensively in the pediatric population in other dosage forms, as have the excipients used in this formulation. No specific increased risk is expected from the use of this form of oxycodone in pediatric patients old enough to safely take tablets if dosing is adjusted for the patient's weight (see DOSAGE AND ADMINISTRATION). **It must be remembered that OxyContin tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen based on age, and the usual doses and dosing intervals are appropriate for the geriatric patient. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (< 60 mL/min.), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

Serious adverse reactions which may be associated with OxyContin™ (oxycodone hydrochloride controlled-release) tablet therapy in clinical use are those observed with other opioid analgesics, including: respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension or shock (see OVERDOSE).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

In clinical trials comparing OxyContin with immediate-release oxycodone and placebo, the most common adverse events (>5%) reported by patients (pts) at least once during therapy were:

Table 2

	OxyContin n=227 # pts (%)		Immediate-Release n=225 # pts (%)		Placebo n=45 # pts (%)	
Constipation	52	(23)	58	(26)	3	(7)
Nausea	52	(23)	60	(27)	5	(11)
Somnolence	52	(23)	55	(24)	2	(4)
Dizziness	29	(13)	35	(16)	4	(9)
Pruritus	29	(13)	28	(12)	1	(2)
Vomiting	27	(12)	31	(14)	3	(7)
Headache	17	(7)	19	(8)	3	(7)
Dry Mouth	13	(6)	15	(7)	1	(2)
Asthenia	13	(6)	16	(7)	—	—
Sweating	12	(5)	13	(6)	1	(2)

The following adverse experiences were reported in OxyContin treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, peripheral edema, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis

Special Senses: abnormal vision, taste perversion

Urogenital: dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

DRUG ABUSE AND DEPENDENCE (Addiction)

OxyContin™ is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone products are common targets for both drug abusers and drug addicts. Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of a drug.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medicinal purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Iatrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common to addicts. Tolerance and physical dependence in pain patients are *not* signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects.

Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Parenteral venous injection of the tablet constituents, especially talc, can be expected to result in local tissue necrosis and pulmonary granulomas.

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. They should be administered cautiously to persons who are known, or suspected to be, physically dependent on any opioid agonist including OxyContin™. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OxyContin™ (oxycodone hydrochloride controlled-release) TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF OXYCODONE.

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

OxyContin is intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic for more than a few days. The controlled-release nature of the formulation allows it to be effectively administered every 12 hours. (See CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM.) While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient

(2) the daily dose, potency and kind of the analgesic(s) the patient has been taking

(3) the reliability of the conversion estimate used to calculate the dose of oxycodone

(4) the patient's opioid exposure and opioid tolerance (if any)

(5) the balance between pain control and adverse experiences

Care should be taken to use low initial doses of OxyContin in patients who are not already opioid tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see PRECAUTIONS: Drug-Drug Interactions).

Patients Not Already Taking Opioids (opioid naive)

Clinical trials have shown that patients may initiate analgesic therapy with OxyContin. A reasonable starting dose for most patients who are opioid naive is 10 mg q12h. If a non-opioid analgesic [(aspirin (ASA), acetaminophen (APAP) or a non-steroidal anti-inflammatory (NSAID)] is being provided, it may be continued. If the current non-opioid is discontinued, early upward dose titration may be necessary.

Conversion from Fixed-Ratio Opioid/APAP, ASA, or NSAID Combination Drugs

Patients who are taking 1 to 5 tablets/capsules/caplets per day of a regular strength fixed-combination opioid/non-opioid should be started on 10 to 20 mg OxyContin q12h. For patients taking 6 to 9 tablets/capsules/ caplets, a starting dose of 20 to 30 mg q12h is suggested. For those taking 10 to 12 tablets, caplets or capsules a day, 30 to 40 mg q12h should be considered. The non-opioid may be continued as a separate drug. Alternatively, a different non-opioid analgesic may be selected. If the decision is made to discontinue the non-opioid analgesic, consideration should be given to early upward titration.

Patients Currently on Opioid Therapy

If a patient has been receiving opioid-containing medications prior to OxyContin therapy, the total daily (24-hour) dose of the other opioids should be determined.

1. Using standard conversion ratio estimates (see Table 3 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. Divide this 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of OxyContin.
3. Round down to a dose which is appropriate for the tablet strengths available (10, 20, and 40 mg tablets).
4. Discontinue all other around-the-clock opioid drugs when OxyContin therapy is initiated.

No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 3 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 3

*Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone**

(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	—
Codeine	0.15	—
Fentanyl TTS	SEE BELOW	SEE BELOW
Hydrocodone	0.9	—
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

*To be used only for conversion to oral oxycodone. For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia (see below) should be made available in the form of immediate-release oral oxycodone or another suitable short-acting analgesic.

OxyContin can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see PRECAUTIONS).

Conversion from Transdermal Fentanyl to OxyContin

Eighteen hours following the removal of the transdermal fentanyl patch, OxyContin treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of OxyContin, should be initially substituted for each 25 μg/hr fentanyl transdermal patch. The patient should be followed closely for early titration as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with anti-emetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Rescue medication should be available (see: Supplemental Analgesia). Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the health-care team, the patient and the caregiver/family.

Supplemental Analgesia

Most cancer patients given around-the-clock therapy with controlled-release opioids will need to have immediate-release medication available for "rescue" from breakthrough pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Rescue medication can be immediate-release oxycodone, either alone or in combination with acetaminophen, aspirin or other NSAIDs as a supplemental analgesic. The supplemental analgesic should be prescribed at 1/4 to 1/3 of the 12-hour OxyContin dose as shown in Table 4. The rescue medication is dosed as needed for breakthrough pain and administered one hour before anticipated incident pain. If more than two doses of rescue medication are needed within 24 hours, the dose of OxyContin should be titrated upward. Caregivers and patients using prn rescue analgesia in combination with around-the-clock opioids should be advised to report incidents of breakthrough pain to the physician managing the patient's analgesia (see Information for Patients/Caregivers).

Table 4

Table of Appropriate Supplemental Analgesia

OxyContin q12h Dose (mg)	prn Rescue Dose immediate-release oxycodone (mg)
10 (1×10 mg)	5
20 (2×10 mg)	5
30 (3×10 mg)	10
40 (2×20 mg)	10
60 (3×20 mg)	15
80 (2×40 mg)	20
120 (3×40 mg)	30

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with OxyContin tablets, patients receiving doses of 20–60 mg/day can usually have the therapy stopped abruptly without incident. However, higher doses should be tapered over several days to prevent signs and symptoms of withdrawal in the physically dependent patient. The daily dose should be reduced by approximately 50% for the first two days and then reduced by 25% every two days thereafter until the total dose reaches the dose recommended for opioid naive patients (10 or 20 mg q12h). Therapy can then be discontinued.

If signs of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each dose reduction.

Conversion from OxyContin to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed. Initiate treatment with about 50% of the estimated equianalgesic daily dose of parenteral opioid divided into suitable individual doses based on the appropriate dosing interval, and titrate based upon the patient's response.

SAFETY AND HANDLING

OxyContin™ (oxycodone hydrochloride controlled-release) tablets are solid dosage forms that pose no known health risk to health-care providers beyond that of any controlled substance. As with all such drugs, care should be taken to prevent diversion or abuse by proper handling.

HOW SUPPLIED

OxyContin™ (oxycodone hydrochloride controlled-release) 10 mg tablets are round, unscored, white-colored, convex tablets bearing the symbol OC on one side and 10 on the other. They are supplied as follows:

NDC 59011-100-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 20 mg tablets are round, unscored, pink-colored, convex tablets bearing the symbol OC on one side and 20 on the other. They are supplied as follows:

NDC 59011-103-10: child-resistant closure, opaque plastic bottles of 100

OxyContin (oxycodone hydrochloride controlled-release) 40 mg tablets are round, unscored, yellow-colored, convex tablets bearing the symbol OC on one side and 40 on the other. They are supplied as follows:

NDC 59011-105-10: child-resistant closure, opaque plastic bottles of 100

Store tablets at controlled room temperature 15–30°C (59–86°F).

Dispense in tight, light-resistant container.

CAUTION

DEA Order Form Required.

Federal law prohibits dispensing without prescription.

Manufactured by The PF Laboratories, Inc.
Totowa, N.J. 07512

Distributed by Purdue Pharma L.P.
Norwalk, CT 06850-3590

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