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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
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Petition For Stay Of Action

Dear Sir/Madam:

The undersigned respectfully submit this petition requesting that the Commissioner of Food and Drugs stay the effective date of NDA 20-932, held by Roxane Laboratories, Inc. ("Roxane"), for the reasons set forth below, and in a Citizen Petition filed contemporaneously with this Petition and incorporated herein by reference. This petition is submitted under Section 505 of the Federal Food, Drug and Cosmetic Act and Section 10.35 of FDA's regulations on behalf of Purdue Pharma L.P. ("Purdue"), holder of approved New Drug Application 20-553 for OxyContin® (oxycodone hydrochloride) Controlled-Release Tablets, 10 mg, 20 mg, 40 mg, and 80 mg ("OxyContin®").

A. Decision Involved

The decision which is the subject of this Petition for Stay of Action is the purported October 26, 1998 approval of New Drug Application 20-932 covering Roxicodone™ (oxycodone HCl) Sustained Release Tablets, 10 mg and 30 mg ("Roxicodone™"), submitted and held by Roxane.¹ This Petition also involves any contemplated approvals of supplements

¹ This Petition for Stay should be filed by the Commissioner and considered as timely for the purposes stated herein despite the fact that it is being submitted more than 30 days after the purported effective date of the Roxicodone™ NDA. (21 C.F.R. §10.35(g)) Petitioner's ability to identify the grounds upon which this Petition and the contemporaneously filed Citizen Petition rest

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or amendments and any separate applications submitted by or on behalf of Roxane, or any other applicant other than Purdue, for any dosage strengths of extended or sustained release oxycodone tablets.

B. Action Requested

Petitioner requests that the Commissioner stay the effective date of the above-referenced NDA approvals and pending approvals until the Commissioner has fully evaluated and ruled on Petitioner's contemporaneously filed Citizen Petition.

C. Statement of Grounds

FDA regulations provide that a stay shall be granted if all of the following criteria are met:

- (1) The petitioner will otherwise suffer irreparable injury.
- (2) The petitioner's case is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
- (4) The delay resulting from the stay is not outweighed by public health or other public interests.

21 C.F.R. §10.35(e). Each of these criteria is met.

was entirely dependent upon the FDA's release of Summary Basis for Approval information under the Freedom of Information Act in December 1998, its review by qualified experts and the recognition by legal counsel of the apparent §505(b)(2) status of the Roxicodone™ application. The CDER ombudsman and FDA chief counsel's office were notified by the undersigned, by telephone, of the issues raised in these Petitions during the week of April 5, 1999, approximately two weeks after the issues were first identified. Although Roxane has been engaged in promotional activities regarding its product, it appears that it has not yet introduced the product to the marketplace. Thus, for the reasons elaborated upon in this Petition, consideration of the Petition and granting of the relief requested is both legally required and very much in the public interest.

1. **Petitioner Faces Imminent, Substantial and Irreparable Injury in the Absence of a Stay**

Purdue holds the original NDA approval for extended release oxycodone tablets, which it has manufactured and sold for over three years. By virtue of Purdue's pioneering work in this area, it was the first to successfully develop such a product and it holds several patents covering the product. Purdue's efforts are described by Mr. Michael Friedman, Vice President of Purdue, in a Declaration that accompanies this Petition as Exhibit A.

Under the 1984 amendments to the FDCA, the incentives for pioneer manufacturers such as Purdue to devote the substantial resources required to develop pioneer products are preserved by carefully crafted protections against "me too" approvals (i.e., abbreviated NDAs and "paper" NDAs) for directly competing versions of the pioneer products. These protections include patent certification procedures that ensure pioneer manufacturers the right to challenge potential infringement prior to effective approval of competing products. They also include periods of non-patent exclusivity during which FDA is similarly precluded from issuing effective approvals of "me too" products.

These protections have been violated by the Roxicodone™ approval, as outlined in detail in the accompanying Citizen Petition and the Exhibits attached thereto. As a consequence, the apparently imminent launch of the Roxicodone™ products pursuant to their invalid October 26, 1998 approval threatens to immediately and irreparably erode Purdue's legally appropriate, exclusive sales position prior to its competitors' compliance with the requisite legal safeguards. The nature of this injury is substantial and irreparable.

The accompanying Declaration of Amanda B. Jones and Affidavit of Craig Hasslinger (Exhibits B and C respectively) report on marketing efforts now being made by Roxane in apparent anticipation of the imminent launch of its Roxicodone™ product. These include statements by the Roxane sales force to potential prescribers that Roxane will soon have an extended release oxycodone product which is "the same product as OxyContin, only cheaper" and "less expensive than OxyContin." By engaging in these pre-sales promotional activities, Roxane is putting itself in a position to quickly jeopardize Purdue's exclusive position in the market as soon as Roxane decides to make its product commercially available.

The accompanying Declaration of Michael Friedman outlines the significant and irreparable types of harm that are expected to result from Roxane's imminent launch of its Roxicodone™ product. These include, among numerous others, 1) immediate and substantial lost sales of OxyContin® and the revenue therefrom, 2) a swift and irrecoverable erosion in the price of OxyContin® as Purdue is forced to compete with Roxane's price and 3) immediate and substantial disruption of the important educational and promotional

functions of Purdue's sales force as they are forced to turn their efforts to unjustified competitive issues.

Much of the substantial harm that would be caused to Purdue is not easily quantifiable. Moreover, Purdue's recovery of any resulting damages in the event that Roxane is not enjoined or otherwise precluded from marketing its product would most likely be contingent on a successful after-the-fact suit for patent infringement. Significantly, however, Purdue is legally entitled to protection from these damages regardless of whether it is ultimately able to successfully prosecute an after-the-fact patent infringement suit. Under the 1984 amendments to the FFDCFA, and FDA's implementing regulations, Purdue is entitled to advance notice of Roxane's purported grounds for believing that either the Roxicodone™ product does not infringe Purdue's patents or the Purdue patents are invalid. If Purdue then initiates an infringement action within the statutory 45 day timeframe, Roxane is not entitled to market its product for 30 months or until a final court decision that the Purdue patents are invalid or not infringed. Launch of the Roxane product in violation of these statutory protections would permanently and irreparably deny Purdue the substantial economic benefits of the protections afforded by statute.²

2. Petitioner's Case Is Strong, Simple and Compelling, Is Not Frivolous, and Is Being Pursued In Good Faith

In the contemporaneously filed Citizen Petition, Petitioner has raised serious and substantial questions regarding the legal propriety of FDA's October 26, 1998 purported approval of NDA 20-932 of Roxicodone™. That Petition, based largely on FDA-released documentation concerning that NDA, provides a compelling basis for concluding that the Roxicodone™ application is an application subject to §505(b)(2) of the FFDCFA due to the explicit and implicit reliance by both Roxane and FDA on data from studies that were not conducted by or for the applicant and to which the applicant does not possess a right of reference. The factual grounds for this conclusion include 1) explicit references in the Roxane application to a Purdue-sponsored placebo-controlled clinical study of Purdue's OxyContin® tablets, 2) reliance by Roxane and FDA on "pivotal" studies of Roxicodone™ that were premised upon third-party data establishing the effectiveness of "active" treatment

² Simultaneous with the filing of this Petition for Stay and the accompanying Citizen Petition, Purdue is also filing an action in federal court requesting judgment that the Roxicodone™ SR products will or do infringe a number of Purdue patents. While that action is consistent in all respects with the position taken in these Petitions, it is based on entirely different legal grounds, namely the threatened or actual infringement of Purdue's patents, and therefore neither moots nor reduces the significance of the issues raised in these Petitions or the immediate need for the relief sought herein.

controls; 3) explicit reliance by FDA, documented in the Roxicodone™ summary basis of approval documents, on preclinical toxicology studies that FDA required Purdue to conduct in order to obtain approval of Purdue's OxyContin® NDA; and 4) reliance by the FDA on "studies conducted previously" in patients with renal impairment and hepatic impairment – an apparent reference to Purdue data generated to satisfy explicit FDA approval requirements, and other data not generated by or for Roxane. Despite these facts, the Roxicodone™ NDA appears to have been processed by FDA as a §505(b)(1) application not subject to the restrictions imposed by §505(b)(2).

As the Citizen Petition explains in detail, the processing of the Roxicodone™ application as a §505(b)(1) application and the purported approval thereof on October 26, 1998, render that purported approval null and void and of no effect because, as of that date, FDA was devoid of authority to approve the application by virtue of Purdue's three-year, non-patent exclusivity for extended-release oxycodone tablets under §505(c)(3)(D)(iii) – which exclusivity did not expire until December 12, 1998. In addition, as the Citizen Petition fully details, FDA regulations implementing the 1984 amendments to the FFDCA set bioavailability and bioequivalence standards for products submitted under §505(b)(2), which standards FDA did not require Roxane to meet because of FDA's failure to recognize the §505(b)(2) status of its application. Finally, by virtue of FDA's erroneous acceptance and processing of the Roxane application under §505(b)(1), and Roxane's apparent movement toward the marketplace, Purdue has been denied the benefit of its statutorily guaranteed right to notification and an opportunity to bring suit against Roxane for infringement of Purdue's patents in advance of the effective approval of the Roxane application.

For these reasons, the standard set forth in the FDA regulations – "petitioner's case is not frivolous and is being pursued in good faith" – is readily met.

3. **Sound Public Policy Requires That the Requested Stay be Granted**

Both the third and the fourth criteria set out in the FDA regulations governing the granting of the requested stay invoke public policy considerations that are addressed together in this section.

The incentives for innovation embodied in the 1984 amendments to the FFDCA would be meaningless if not enforced – and of cold comfort if they are somehow "enforced" only after competition inappropriately begins. The nature and extent of those incentives have been resolved entirely by Congress and have been long recognized by FDA. In this very context, FDA has advised:

“. . . an applicant seeking to submit a so-called 'full NDA' and thereby avoid any exclusivity or patent rights attaching to a pioneer drug must

conduct or sponsor the adequate and well-controlled investigations necessary to establish the effectiveness of the drug, or, if the applicant relies on literature for these studies, must obtain rights of reference to the data. The applicant must conduct, sponsor, or obtain rights of reference to these studies even if the pioneer applicant relied on literature citations. Similarly, the applicant must conduct, sponsor, or obtain a right of reference to all the safety tests without which the application could not be approved. In general, such tests will include animal carcinogenicity and reproduction studies, certain animal toxicity studies and some clinical investigations.” (54 Fed. Reg. at 28891.)

“This interpretation is consistent with Congress’ intent to encourage the pharmaceutical industry to develop and seek approval of significant new therapies by conferring periods of exclusive marketing. If exclusivity could easily be avoided by an application containing only minimal data generated or purchased by the applicant, the incentive created by the availability of such exclusivity would decrease considerably.” (Id.)

These statements set forth precisely what is at stake here. FDA has recognized that applicants in Roxane’s position have two choices – comply with the restrictions on ANDAs and §505(b)(2) NDAs or submit a truly “full” NDA that does not rely on anyone else’s data without consent. A muddy “middle ground” was rejected both by Congress and by FDA as creating a potential loophole that could be too easily used to thwart the incentives to innovation essential to the continued development of new drug products at private expense. The line was drawn clearly and brightly:

“FDA . . . believes that it would be inconsistent with the policies of the 1984 Amendments to allow these applications to rely on the approval of a listed drug unless they were subject to the listed drug applicant’s patent rights and exclusivity. Therefore, an application that relies in part on the approval of a listed drug is, for this purpose, considered an application described in section 505(b)(2) and must make a certification as to any relevant patents that claim the listed drug. In addition, the date of submission and effective approval of these applications may, under section 505(c)(3), be delayed to give effect to any patent or period of exclusivity accorded the listed drug.” (54 Fed. Reg. at 28892-3.)

In addition, FDA has itself recognized the public interest in restricting the marketing approval of products that would evade bioequivalence requirements by seeking approvals under §505(b)(2). It was for these reasons that FDA adopted regulations restricting such approvals when the applicant has not shown its product to be properly comparable to

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previously approved drugs and even forbids such approvals when they would (but for exclusivity restrictions) be eligible for processing as ANDAs. These restrictions not only protect the public health by assuring proper consideration of bioequivalence issues but also protect FDA resources that would otherwise be wasted on more extensive and costly, but unnecessary, §505(b)(2) reviews of bio-inequivalent products.

In the case of Roxicodone™, as described in the Citizen Petition, on October 26, 1998, FDA purported to “approve” two strengths of Roxicodone™, neither of which had been demonstrated to have comparable effects to the corresponding strengths of Purdue’s pioneer drug OxyContin®. Yet, as could readily be expected, Roxane is already suggesting that it will soon be selling “the same product as OxyContin®”. (See Exhibits B and C.) As FDA has long recognized:

“To allow [a less bioavailable] drug to be approved under section 505(b)(2) would thwart Congress’ clear intention to require that a duplicate of a listed drug be shown to be bioequivalent to that listed drug.” (54 Fed. Reg. at 28892.)

The relief requested in this Petition for Stay and in the accompanying Citizen Petition affords the only way to secure all of the important public and private interests embodied in the 1984 amendments and its implementing regulations.³

4. Conclusion

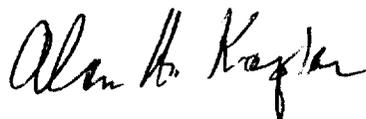
For the foregoing reasons, Petitioner respectfully requests that the requested stay be promptly issued. Because of the apparently imminent launch of the Roxicodone™ product, and the harm that will immediately flow from that action, we request action on this Petition for Stay by Wednesday, May 26, 1999. Since appropriate agency officials are familiar with the issues raised in this Petition and have previously been informed by Petitioner of the specific factual circumstances that are involved (see footnote 1, above), we believe that this is adequate time for the agency to make an appropriate response. In the event a response is

³ We are not aware of the extent to which Roxane may have disclosed, or FDA reviewers may have independently understood, the legal and regulatory necessity that a 505(b)(1) application must stand entirely on its own and not rely, in the absence of an appropriate right of reference, upon another party’s data before it may be approved without complying with the safeguards applicable to §505(b)(2) applications. Regardless, however, the importance of the interests at stake in preserving the incentives to innovation and the public health protections embodied in the restrictions on approvals of §505(b)(2) applications clearly outweigh any concern that the parties involved may have innocently but erroneously believed they were complying with the applicable standards.

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not received by that date, however, we intend to seek immediate relief, including issuance of the requested stay, in an appropriate federal court, having exhausted, to the extent possible and practicable, our administrative remedies.

Respectfully submitted,



Alan H. Kaplan



Richard S. Morey



Peter R. Mathers

A

DECLARATION OF MICHAEL FRIEDMAN

1. I am an officer of Purdue Pharma L.P. ("Purdue Pharma") and of The Purdue Frederick Company ("Purdue Frederick").

2. I joined Purdue Frederick in 1985 as a Vice President responsible for licensing and acquisitions. Since 1988, I have been a Group Vice President of Purdue Frederick.

3. I am also a Vice President of Purdue Pharma, a position I have held since that company was formed in 1991.

4. My current responsibilities include sales, marketing and business development for both Purdue Frederick and Purdue Pharma.

5. Purdue Frederick, Purdue Pharma and its related U.S. companies (collectively "Purdue") together are a mid-sized, privately-owned, research-based pharmaceutical company. Since 1973, Purdue's headquarters have been in Norwalk, Connecticut. Purdue also maintains a research and development facility in Ardsley, N.Y., a manufacturing facility in Totowa, N.J. and employs more than 1,700 people in the U.S.

6. I earned a B.A., with honors, from Brooklyn College in 1970. I earned an M.B.A. from the University of

Connecticut in 1976. I am currently working toward a doctorate in the field of business administration at Pace University.

7. This affidavit is offered in support of Purdue Pharma's Petition For Stay Of Action which seeks a stay of the effective date of the approval of New Drug Application 20-932, and any supplements or amendments to that application or any other pending applications for extended release oxycodone tablets other than those submitted by Purdue. I have been informed by counsel for Purdue that it is their opinion that the Food and Drug Administration ("FDA") approval of Roxane's NDA 20-932 was legally deficient and is void and invalid. While I have no qualifications to address this question, I do know that, whether it is correct or not, the effect of Roxane's entry to the market will be to cause irreparable injury to Purdue and its marketing of OxyContin®. Except as otherwise stated, this Declaration is based on my personal knowledge, and on information that was gathered for me at my request from Purdue's files.

OXYCONTIN® TABLETS

8. This affidavit concerns Purdue's commercially successful OxyContin® Tablets ("OxyContin®"), a controlled-release oxycodone analgesic which is the subject of NDA 20-553, first approved by the FDA on December 12, 1995, and the effects

on Purdue as a consequence of FDA permitting the marketing of competing controlled-release oxycodone analgesic tablets.

**PURDUE AND ITS RELATED
COMPANIES PIONEERED THE USE OF
CONTROLLED-RELEASE OPIOIDS TO TREAT PAIN**

9. One of Purdue's sister companies in the United Kingdom, Napp Pharmaceuticals Group, Ltd., began research on the treatment of moderate-to-severe pain in the 1970s. At that time, patients treated with opioids were limited to "immediate-release" forms. An immediate-release opioid, e.g., liquid or tablet, gets into the bloodstream in a relatively short period of time and usually provides pain relief for a limited period of time (e.g., 4-6 hours). As a result, immediate-release opioids need to be taken frequently (e.g., 4-6 times a day).

10. Immediate-release opioids suffer several disadvantages. First, because they require frequent dosing, immediate-release opioids are inconvenient. This inconvenience enhances the risk that the patient will fail to take the medication at the appropriate time or at all. This lack of patient compliance increases the likelihood that the patient will experience unnecessary pain. Habitual non-compliance can complicate the overall treatment process.

11. Because they provide only a few hours of pain relief, immediate-release opioids frequently do not permit the

patient to sleep through the night. The patient often has to (1) intentionally get up in the middle of the night to take the next dose, (2) run the risk that the recurrence of pain may cause awakening during the night, or (3) sleep through the night, but awaken in the morning in pain. None of these options is acceptable. Chronic fatigue and anxiety, which result from these shortcomings of immediate-release opioids, can amplify the patient's experience of pain.

12. To address these shortcomings, Napp Pharmaceutical Group, Ltd. developed an oral "controlled-release" delivery form for morphine. The morphine is combined with non-pharmacologically active ingredients that release the drug over time as the tablet passes through the patient's gastrointestinal tract.

13. In 1984, Purdue introduced MS Contin[®] Tablets ("MS Contin[®]"), the first controlled-release morphine product in the United States. In contrast to immediate-release opioids which are dosed every 4-6 hours, MS Contin[®] needs to be taken only once every 8-12 hours. MS Contin tablets have gone through the FDA approval process.

14. The benefits of MS Contin[®] over immediate-release morphine include (1) greater convenience to the patient (usually permitting the patient to take the medication once in the morning and once at night), (2) better pain management due to increased

compliance, and (3) the ability to sleep through the night and awaken without pain.

15. Purdue's MS Contin[®] product became the standard for cancer pain relief. MS Contin[®] accounted for over 70% of all oral controlled-release morphine prescriptions filled at retail pharmacies in the United States at year end 1998.¹

16. Despite the success of MS Contin[®] in controlling pain, Purdue believed that morphine products had disadvantages. One serious disadvantage is that many people appear to perceive morphine as an addictive narcotic drug used only as a last resort for terminally ill cancer patients. Because of this perception, Purdue felt that some doctors were reluctant to prescribe MS Contin[®] for moderate to severe non-cancer pain for fear of making the patient more anxious about his or her condition. In addition, a patient told that he or she was to receive morphine might believe that he or she had an incurable terminal condition.

17. To address the need for a better way to treat moderate-to-severe pain, Purdue began research to develop a controlled-release single-entity oxycodone product.

¹The source of this information is IMS International ("IMS"). IMS buys data from retail pharmacies throughout the United States regarding drugs purchased at those pharmacies. IMS then analyzes that data which it in turn sells to pharmaceutical companies and other buyers. IMS data is the leading company providing such independent data to the pharmaceutical industry.

18. That development program cost in excess of \$40 million and resulted in Purdue's OxyContin[®] product, which I understand is covered by a number of patents.

19. OxyContin[®] has been approved by the FDA for the management of moderate-to-severe pain where use of an opioid analgesic is appropriate for more than a few days. This approved indication encompasses both cancer pain and non-malignant pain such as arthritis pain, back pain and post-operative pain. OxyContin[®] provides the advantages of a controlled-release opioid product without the disadvantages of morphine. For example, OxyContin[®] is not morphine and does not suffer from the stigma attached to morphine. OxyContin[®] also provides the pharmacological benefits of oxycodone without the side effects and dosage limitations associated with "combination products" such as Endo Pharmaceuticals Inc.'s Percodan[®] and Percocet[®]. (See also Exhibit 1, the approved package insert for OxyContin[®].)

20. FDA approved and Purdue introduced OxyContin[®] in the United States in December 1995.

PURDUE'S OXYCONTIN[®] HAS BEEN COMMERCIALY SUCCESSFUL

21. During its first year on the market (1996), Purdue sold \$49 million of OxyContin[®] -- twice Purdue's initial forecast. Sales totaled \$145 million in 1997, and \$301 million

in 1998. (See Exhibit 2.) Purdue forecasts 1999 sales of approximately \$600-650 million.

22. OxyContin[®] accounted for half of Purdue's total sales in 1998.

23. In only three years on the market, OxyContin[®] has made substantial gains. In 1998, OxyContin[®] constituted approximately 37% of the dollar sales of non-injectable strong opioids sold in the U.S. at retail pharmacies. By contrast, Purdue's MS Contin[®] product, which has been on the market for 14 years, constituted approximately 19% of such products.²

24. Currently, over 54,000 prescriptions for OxyContin[®] are filled by retail pharmacies in the United States each week. This represents roughly 37% of the prescriptions for non-injectable strong opioids filled by retail pharmacies in the United States.³

25. OxyContin[®] has succeeded because it works. There is a growing body of clinical research and anecdotal reports that OxyContin[®] has dramatically improved the quality of life for people who had been debilitated by chronic pain.

² Source of the data is IMS.

³ Source of the data is IMS.

**PURDUE HAS MADE A SUBSTANTIAL INVESTMENT
TO DEVELOP OXYCONTIN® AND TO EDUCATE DOCTORS
ABOUT ITS USE AND BENEFITS**

26. Purdue has spent substantial time and money to develop the market for OxyContin® and to educate doctors, patients and other caregivers about its potential to help people live with pain.

27. Like most prescription drugs, OxyContin® is marketed to doctors and hospitals by a sales force. Purdue spends substantial time and money to train its sales force, including a rigorous 26-week training and field sales development program. The first three weeks of the program is exclusively dedicated to teaching the new sales representative about the biology of pain, the nature of the conditions for which OxyContin® is appropriate, the characteristics of the known methods of treating pain (with and without drugs), and the laws relating to controlled substances.

28. Purdue's sales representatives are capable of discussing and reviewing with doctors, pharmacists and hospital personnel the proper and safe administration of OxyContin® and the treatment of side effects. Purdue's sales representatives' knowledge of their products has recently been recognized by long term care pharmacy executives, who identified Purdue as having one of the four most knowledgeable sales forces in the United States in 1998. (Exhibit 3).

29. In response to the success of OxyContin[®], Purdue dramatically increased the size of its sales force. In late 1995, when Purdue introduced OxyContin[®], Purdue's sales force numbered roughly 325. Currently, the sales force numbers roughly 625.

30. In furtherance of its commitment to education, Purdue sponsors continuing medical education programs and lectures given by eminent pain management specialists. These programs and lectures cover the principles and guidelines of pain management and are attended by physicians, pharmacists, nurses and other health care professionals throughout the United States. The cost of these educational programs is high. In 1998, Purdue spent over \$7 million on medical education; in 1999 the figure is expected to exceed \$12 million.

31. Purdue also sponsors a national program called Partners Against Pain[®] to increase public awareness of options for the treatment of pain. Partners Against Pain[®], which maintains a web site, makes literature and information available to caregivers, patients and their families.

32. Purdue additionally sponsors an Indigent Patient Assistance Program to make OxyContin[®] available to patients who might otherwise not be able to afford it.

33. In total, through the end of 1998, Purdue has spent over \$207 million related to the marketing and sales of OxyContin®.

34. Purdue is not the only company that has invested in the promotion of OxyContin®. Since 1996, OxyContin® has been sold as part of a co-promotion arrangement with Abbott Laboratories Hospital Products Division ("Abbott").

35. Under the Purdue-Abbott agreement, Purdue supplies the Abbott sales representatives with training materials and promotional materials. Abbott's personnel sell Purdue's OxyContin® product to hospitals as well as surgeons and anesthesiologists.

OXYCONTIN® FUELS PURDUE'S FUTURE GROWTH

36. As stated above, OxyContin® accounted for half of Purdue's revenues in 1998. The revenue stream OxyContin® generates presents many growth opportunities for Purdue.

37. Purdue plans to make OxyContin® increasingly available around the world through its related companies. This will require Purdue to make substantial investments of time and money to develop the necessary regulatory submissions, additional clinical trials, and appropriate educational and promotional materials.

38. Purdue uses, and plans to continue using, its profits from OxyContin® sales to fund and expand its research and development activities. The profits from OxyContin® have permitted Purdue to continue to research and develop innovative pain therapies and, for the first time, to research and develop new therapies for the treatment of underlying diseases such as cancer and diabetes. In addition, Purdue is using the profits from OxyContin® to fund research and development of new chemical entities and bio-pharmaceutical agents.

39. Purdue already has made substantial commitments in support of these goals. For instance, at year end 1995, when OxyContin® was introduced, Purdue employed 151 research and development personnel. By year end 1998, that number more than doubled to 409. One hundred fifty-one research employees joined Purdue in 1998 alone.

40. Purdue's expansion also includes acquisition of additional facilities. At year end 1995, when OxyContin® was launched, Purdue operated its research and development activities in 90,000 square feet of a facility in Yonkers, New York. Since then, Purdue has moved its research and development activities into two new laboratory buildings in Ardsley, New York totaling 135,000 square feet. The acquisition and renovation costs of the Ardsley buildings exceeded \$31 million. Purdue also intends to occupy one additional research building in Ardsley. That

building will provide an additional 40,000 square feet of space following acquisition and renovation at a cost expected to exceed \$10 million. In addition, a bio-pharmaceutical business in Princeton, New Jersey was recently acquired for \$3.9 million. Purdue expects an additional \$11.4 million to be spent on equipment and capital improvements at that site during 1999. The Princeton facility will provide 56,850 square feet of additional space for bio-pharmaceutical research.

41. The growth fueled by OxyContin® is not limited to research and development. Purdue's overall employee population has grown from 918 at year end 1995 to greater than 1700 today. As a result, Purdue has outgrown the five headquarters buildings it currently occupies in Norwalk, Connecticut. Next year, following a \$20-30 million renovation, Purdue will move its headquarters into a newly acquired \$77 million building in Stamford, Connecticut. That building, which formerly housed GTE's world headquarters, will provide over 500,000 square feet of office space.

42. Monies generated by sales of OxyContin® also support expansion of Purdue's manufacturing facilities. Construction of a new manufacturing facility in North Carolina is well underway. That facility will produce OxyContin® as well as other Purdue products.

43. In addition, Purdue uses its profits from OxyContin® to support its ongoing search for additional products that Purdue can "in-license" from others and further develop into marketable products.

44. All of these commitments and expenditures were made with the understanding that Purdue's patented OxyContin® product would continue unimpeded to generate a healthy stream of profits. That same understanding has led Purdue to position itself for continued growth fueled by OxyContin® products.

**PURDUE WILL SUFFER IRREPARABLE
HARM IF ROXANE IS
ALLOWED TO SELL THE ROXICODONE™ SR PRODUCT**

45. In my opinion, if OxyContin® is forced to compete with Roxane's Roxicodone™ SR product ("Roxicodone™ SR"), the damage will be great and irreparable.

46. To summarize what is discussed below in detail, if Roxicodone™ SR were to enter the market it will take sales that would otherwise be made by Purdue. Competition with Roxane will force Purdue to lower its prices, which will reduce Purdue's profits. Even if Roxicodone™ SR is subsequently removed from the market, Purdue will not be able to restore its prices to prior levels. This is so because once the industry becomes accustomed to lower prices, it will be difficult for Purdue to adjust its prices without incurring harsh criticism. The resulting

reduced profits will substantially disrupt Purdue's research and development activities, and will curtail Purdue's ability to fund educational activities relating to the improved treatment of pain. Furthermore, Purdue's sales force will have to direct its efforts toward defending against Roxicodone™ SR, reducing the time available to affirmatively promote OxyContin® and provide value and education for physicians. All of this works to tarnish Purdue's good name and goodwill.

**ROXICODONE™ SR WILL
TAKE OXYCONTIN®'S SALES**

47. As stated above, OxyContin® constituted approximately 37% of non-injectable strong opioids sold in the U.S. in 1998. OxyContin® is the only controlled-release oxycodone product now available. Purdue's OxyContin® will compete head-to-head with Roxicodone™ SR, which is also a controlled-release oxycodone product. OxyContin® is sold throughout the United States. For that reason, virtually every sale of Roxicodone™ SR will represent a lost sale of OxyContin®.

48. Roxicodone™ SR is to be marketed by Roxane. Roxane is an affiliate of Boehringer Germany. Boehringer Germany represents that it is the largest privately held pharmaceutical company in the world with 1997 sales totaling \$4.7 billion. In a letter distributed to healthcare providers, Roxane describes the substantial role to be played by Boehringer Germany in the

marketing of pain control products: "Through Roxane Laboratories, the company [Boehringer Germany] will continue to focus its development and marketing effort toward . . . pain management/palliative care . . . in the United States." (Exhibit 4). Roxane and its affiliated companies will be very strong competitors, based on their size and resources alone.

**ROXICODONE™ SR WILL CAUSE IRRECOVERABLE
EROSION OF THE PRICE OBTAINED ON OXYCONTIN®**

49. Purdue and Roxane each sell a controlled-release morphine product, Purdue's MS Contin® and Roxane's Oramorph SR® Tablets ("Oramorph SR®"). In the past Roxane has chosen to compete with Purdue in the controlled-release analgesic market by offering its product for a lower price. On Roxane's Internet website, Roxane makes a point of touting the price savings from Oramorph SR® in contrast to MS Contin®. (See Exhibit 5).

50. Today, the Boehringer defendants appear to be positioning Roxicodone™ SR as a lower cost alternative to OxyContin®. According to reports from Purdue's sales force, Roxane sales personnel are representing Roxicodone™ SR as, "the same product as OxyContin®, only cheaper." (See e.g., Affidavit of Craig Hasslinger and Declaration of Amanda B. Jones).

51. Based on this, Purdue has every reason to believe that Roxane will undercut Purdue's price on OxyContin® in order to position Roxicodone™ SR in the market. This is particularly

likely given that OxyContin[®] has already been on the market for over three years.

52. As a result, Purdue likely will have to substantially reduce its prices on OxyContin[®] in order to remain competitive. If Purdue is forced to reduce its price on OxyContin[®] in order to compete with Roxicodone[™] SR, Purdue will not be able to restore its original pricing structure if Roxicodone[™] SR is subsequently removed from the market. The market simply will not tolerate a substantial price increase after becoming accustomed to lower prices. Furthermore, after watching Purdue reduce its prices in order to compete with Roxicodone[™] SR, some may incorrectly view Purdue as a company whose products are priced unfairly. For this reason, the damage to Purdue will not end if Roxicodone[™] SR is removed from the market after a period of marketing, nor will it be easy to quantify the amount of damage moving forward into the future.

53. Because of this, I believe that the damage to Purdue that is likely to be caused by price erosion from competition between OxyContin[®] and Roxicodone[™] SR will be immediate and irreparable.

**ROXICODONE[™] SR WILL DISRUPT
PURDUE'S BUSINESS PLANS**

54. Competition with Roxane will disrupt the activities of Purdue's (and Abbott's) sales forces. Doctors and

hospital administrators have only limited time, if any, for each sales call. Instead of spending their limited time with doctors affirmatively promoting OxyContin[®] and providing education and training, the sales force will need to spend its time trying to persuade doctors and hospitals to prescribe Purdue's OxyContin[®] instead of Roxicodone[™] SR.

55. If Roxane takes Purdue's existing OxyContin[®] customers, Purdue will also lose the chance to develop or continue business relationships with those customers.

56. The loss of sales and profits will also keep Purdue from pursuing its plans to expand its business further. Our continuing research and development activities and our "in-licensing" of potential new products from other companies are funded from current income. If that income falls, then those projects will necessarily have to be curtailed.

57. If sales of OxyContin[®] and related products fall sufficiently, Purdue will also have to reduce the size of its sales force and research staff, thereby wasting the money and time that Purdue has spent to train those employees. Furthermore, morale and the affected individuals will suffer.

**MARKETING OF ROXICODONE[™] SR
WILL DAMAGE PURDUE'S GOODWILL**

58. Purdue has priced its products fairly, to recognize their value to doctors and patients and also to allow

Purdue to recoup the millions of dollars that it has spent developing OxyContin® and the market for it. As far as I am aware, Roxane has spent little or no money to develop a market for a controlled-release oxycodone product, and is now trying to take free advantage of Purdue's educational and marketing efforts with regard to such a product.

59. Nevertheless, if Roxane forces Purdue to lower its prices to compete, then Purdue, as discussed above, may be harshly and incorrectly criticized as a company whose products are overpriced. This would damage Purdue's reputation in the market for OxyContin®, and for other products, in ways that cannot be estimated.

**ROXICODONE™ SR'S PRESENCE MAY
EMBOLDEN OTHER POTENTIAL COMPETITORS
TO SEEK APPROVAL OF CONTROLLED-RELEASE OXYCODONE PRODUCTS**

60. The market for controlled-release oxycodone, pioneered by Purdue, has grown steadily from 1996 to date. If Roxane is allowed to market Roxicodone™ SR, other pharmaceutical manufacturers, seeing the success of OxyContin® and the approval of Roxicodone™ SR, may also try to market controlled release oxycodone products of their own. An influx of other competing products would cause further lost sales and lost profits.

**ROXICODONE[™] SR WILL ALSO HURT
SALES OF OTHER PURDUE PRODUCTS**

61. Patients treated with controlled-release opioids like OxyContin[®] sometimes experience pain known as "breakthrough pain." Breakthrough pain is pain that occurs because the dosage of controlled-release opioid is too low. Breakthrough pain for patients on OxyContin[®] may be treated using a "rescue dose" of an immediate-release analgesic.

62. For patients taking Purdue's OxyContin[®], breakthrough pain is commonly treated with Purdue's immediate-release oxycodone products, Oxy-IR[®] Tablets ("Oxy-IR[®]") or OxyFast[®] Solution ("OxyFast[®]"). In conjunction with OxyContin[®], Purdue's sales force promotes Purdue's Oxy-IR[®] and OxyFast[®] immediate-release products for treatment of breakthrough pain. Sales of Oxy-IR[®] have increased with sales of OxyContin[®], from \$451,000 in 1996 to \$3,578,000 in 1998, an overall increase of 693%.⁴ Purdue introduced OxyFast[®] in October 1998. Purdue expects that sales of OxyFast[®] will climb with sales of OxyContin[®]. Lost sales of OxyContin[®] will cause reduced sales of Oxy-IR[®] and OxyFast[®] as well.

⁴ In 1996, OxyContin[®] gross sales totaled \$48,930,000 and gross sales of Oxy-IR[®] totaled \$451,000. In 1997, OxyContin[®] gross sales climbed to \$144,827,000 (a 196% increase over 1996) and Oxy-IR[®] gross sales jumped to \$1,709,000 (a 279% increase over 1996). In 1998, gross sales of OxyContin[®] achieved \$301,236,000 (a 108% increase over 1997) and gross Oxy-IR[®] sales commensurately reached \$3,578,000 (a 109% increase over 1997).

63. In addition, patients who take opioids for pain relief frequently become constipated. As a result, physicians are encouraged to anticipate patients' constipation and to treat it with Purdue's Senokot® laxative. Sales of Purdue's Senokot® laxatives have grown in tandem with sales of OxyContin®, increasing from \$35,418,000 in 1996 to \$48,675,000 in 1998, an overall increase of 37.4%.⁵ Lost sales of OxyContin® will cause reduced sales of Senokot®.

**ROXANE AND ITS AFFILIATED COMPANIES WILL CONTINUE
IN THEIR OTHER CURRENT PROFITABLE BUSINESSES
EVEN IF ENJOINED IN THIS ACTION**

64. Roxicodone™ SR has not been commercially introduced as of this time. Accordingly, postponing the debut of Roxicodone™ SR is unlikely to meaningfully harm Roxane when compared to the harm that not postponing it would cause Purdue.

65. Roxane's morphine-based, controlled-release product, Oramorph SR® accounted for only about 2-3% of sales of non-injectable strong opioids in the U.S. in 1998.⁶ Preventing

⁵For instance, in 1996, OxyContin® gross sales totaled \$48,930,000 and gross sales of Senokot® totaled \$35,418,000. In 1997, OxyContin® gross sales climbed to \$144,827,000 (a 196% increase over 1996) and Senokot® gross sales jumped to \$42,377,000 (a 19.6% increase over 1996). In 1998, gross sales of OxyContin® achieved \$301,236,000 (a 108% increase over 1997) and gross Senokot® sales commensurately reached \$48,675,000 (a 14.9% increase over 1997).

⁶ Source of data is IMS.

the marketing of Roxicodone™ SR will not affect Roxane's ability to sell Oramorph® SR.

66. Roxane and its affiliated companies are a multinational pharmaceutical company whose 1997 sales totaled \$4.7 billion. (Exhibit 4). These sales will not be significantly affected by preventing Roxane from selling Roxicodone™ SR.

**PREVENTING THE MARKETING OF ROXICODONE™ SR
IS IN THE PUBLIC INTEREST**

67. Purdue has been able to meet the growing demand for controlled-release oxycodone. Purdue anticipates that demand over the 5-year period 1999-2004 will continue to grow. Purdue anticipates no trouble meeting this expected future increased demand. If Roxane is not permitted to sell Roxicodone™ SR, the public will still be able to obtain from Purdue as much controlled-release oxycodone as it demands.

68. In addition, the public interest favors not permitting the marketing of Roxicodone™ SR at this time. If this product is permitted to be marketed and subsequently withdrawn from the market, this will create a disruption for doctors and patients, who will then have to find a new pain-treatment method, whether it is Purdue's OxyContin® or some other form of treatment. It is obviously undesirable to disrupt patients' pain

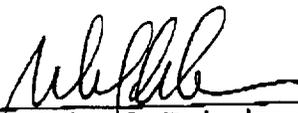
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therapies. The public interest lies in ensuring uninterrupted and effective treatment for people in pain.

I hereby declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

5/17/99
Date



Michael Friedman

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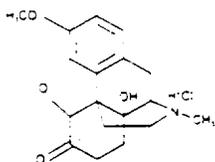
5/17/99
Date



Michael Friedman

DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, and 80 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), yellow iron oxide with FD&C blue No. 2 (80 mg strength tablet only), and other ingredients.

OxyContin® 80 mg Tablets ARE FOR USE IN OPIOID TOLERANT PATIENTS ONLY.

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

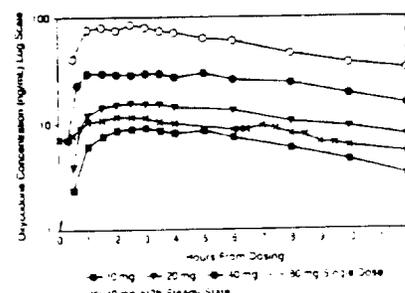
The activity of OxyContin® (oxycodone hydrochloride controlled-release) tablets is primarily due to the parent drug oxycodone. OxyContin tablets are designed to provide controlled delivery of oxycodone over 12 hours. Oxycodone is well absorbed from OxyContin tablets with an oral bioavailability of from 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, 40 mg, and 80 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, 40 mg, and 80 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.
80 mg OxyContin*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	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-∞}; for multiple-dose AUC = AUC_{0-T}

*data obtained while volunteers received naloxone which can enhance absorption.

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 (V_{ss}) for oxycodone was 2.6L/kg. Oxycodone binding to plasma protein at 37°C 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).

Rectal Administration

Rectal administration of OxyContin tablets is not recommended. Preliminary data from a study involving 21 normal volunteers, show OxyContin tablets administered per rectum resulted in an

AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth (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 pm 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 pm 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-naïve 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.

A cohort of patients have been treated with OxyContin 80 mg tablets. There were no differences in the efficacy or safety profiles than seen with the other tablet strengths.

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

Special precautions regarding OxyContin® 80 mg Tablets

OxyContin® 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescription of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences.

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, pm 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 (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, 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).

Post-Operative Use

Morphine and other opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

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 reinstatement 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/Carcinogenicity

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 μg , chromosomal aberration test in human lymphocytes (in the absence of metabolic activation and with activation after 48 hours of exposure) at doses of up to 1500 $\mu\text{g/ml}$, and in the in vivo bone marrow micronucleus assay in mice (at plasma levels of up to 48 $\mu\text{g/ml}$). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 $\mu\text{g/ml}$) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 $\mu\text{g/ml}$ or greater with metabolic activation and at 400 $\mu\text{g/ml}$ or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its carcinogenic 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/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 4 and 60 times a human dose of 120 mg/day (74 mg/m²), based on mg/kg of a 60 kg adult (0.7 and 19 times this human dose based upon mg/m²). 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-naïve 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.

Rectal Administration

OxyContin[®] Tablets are not recommended for administration per rectum. A study in normal volunteers showed a significantly greater AUC and

higher C_{max} during this route of administration (see PHARMACOKINETICS AND METABOLISM).

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)		Immediate-Release (n=225)		Placebo (n=45)	
	# Pts	(%)	# Pts	(%)	# 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, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tinnitus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

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 admin-

istered 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, 40, and 80 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	1.0	—
Codene	0.15	—
Fentanyl TTS	SEE BELOW	SEE BELOW
Hydrocodone	0.9	—
Hydromorphone	4.0	20.0
Levorphanol	7.5	15.0
Meprobamate	0.1	0.4
Methadone	1.5	3.0
Morphine	0.5	3.0

*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.

Special instructions for OxyContin® 80 mg Tablets
(For use in opioid tolerant patients only.)

OxyContin® 80 mg Tablets are for use only in opioid tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescription of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences.

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 pm 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)	pm Rescue Dose immediate-release oxycodone (mg)
10 (1x10 mg)	5
20 (2x10 mg)	5
30 (3x10 mg)	10
40 (2x20 mg)	10
60 (3x20 mg)	15
80 (2x40 mg)	20
120 (3x40 mg)	30
160 (2x80 mg)	40
240 (3x80 mg)	60

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

NDC 59011-100-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

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

NDC 59011-103-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

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

NDC 59011-105-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

OxyContin® (oxycodone hydrochloride controlled-release) 80 mg tablets are round, unscored, green-colored, convex tablets bearing the symbol OC on one side and 80 on the other. They are supplied as follows:

NDC 59011-107-10: child-resistant closure, opaque plastic bottles of 100

NDC 59011-107-25: unit dose packaging with 25 individually numbered tablets per card; one card per glue end carton

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

Dispense in tight, light-resistant container.

CAUTION

DEA Order Form Required.

R_x Only

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

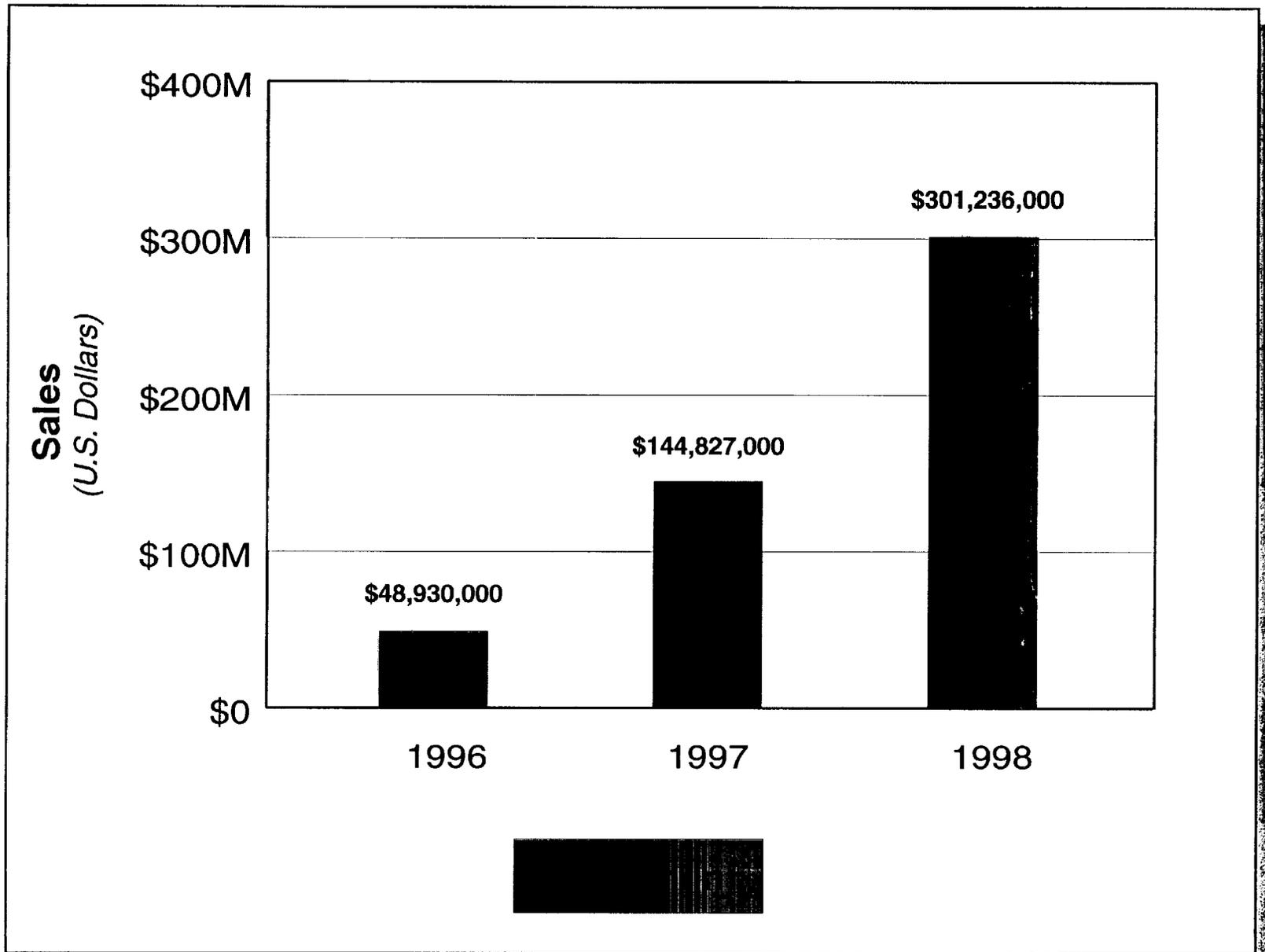
Distributed by Purdue Pharma L.P. Norwalk, CT 06850-3590

Copyright© 1995, 1998 Purdue Pharma L.P. U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295.

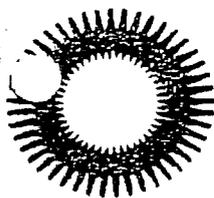
June 15, 1998

G4909-E 00P017

OxyContin Sales



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**SCOTT
LEVIN**

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Marketing

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Consulting,

Software,

Training and

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A division of
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/ 0000

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FOR IMMEDIATE RELEASE

Merck Tops Across the Board with Long-Term Care

Company	Overall	Contracts	Value-added Services	Knowledgeable Reps.	Rank by Volume of LTC Contacts
Merck & Co.	1	1	1	1	2
J&J	2	4	2	3	3
Bayer	3	2	2	7	6
Pfizer	3	3	2	2	1
Novartis	5	9	6	8	7
Purdue/Frederick	6	6	5	4	4
Abbott	7	9	8	5	5
Alpharma	8	9	9	12	25
Knoll	8	*	7	12	14
Boehringer-Ingelheim	10	33	13	35	17
Dey Labs	10	6	13	12	17

Source: Scott-Levin, *Nursing Home Pharmacy Provider/Consultant Promotional Audit*, Fall 1998

NEWTOWN, Pa. (January 25, 1999) -- LTC pharmacy executives rate Merck the best overall pharmaceutical company, according to Scott-Levin's Fall 1998 *Nursing Home Pharmacy Provider/Consultant Promotional Audit*.

Merck also placed first in three specific categories: best contracts, best value-added services, and most knowledgeable sales representatives.

Merck ranked second, behind Pfizer, in number of contacts with LTC executives recorded during the 8-week audit cycle.

Panelists appreciate Merck's efforts to support value-added programs in long-term care. Pharmacy providers feel, "Merck is taking some financial burden off us through continuing education programs, research, DSM [disease state management], studies, etc."

Other Merck accolades included: "Far superior in support; great contracts, disease state management programs and educational programs; understand our industry; ask us to help educate them and their staff"; and "Great understanding of LTC industry; evolution of market with regard to prospective payment, disease state management programs and application of therapeutic interchange."

Managed Care / Sales

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Other highlights of the audit:

Lilly Drops in Rank

Lilly cut promotional contacts to long-term care by 28% in fall 1998. In addition, Lilly decreased its promotion of value-added services. In fall 1998, 39% of Lilly's LTC contacts pertained to promotion of value-added programs, a substantial decrease from 63% in spring 1998.

This decline in activity may have influenced Lilly's ratings drop in this category. In spring 1998, pharmacy providers rated Lilly eighth in value-added performance, compared with 39th in fall 1998. Consequently, the company's overall rating fell to 15th from sixth in spring 1998. Many pharmacy providers felt Lilly was no longer offering support for their LTC needs.

New Player Makes Its Move

Contacts to long-term care by Johnson & Johnson increased 10% between the spring and fall 1998 audit cycles. The gain in promotional activity may be attributed to J&J's new LTC group, ElderCare, a division of J&J subsidiary Janssen. ElderCare focused its attention on promotion of Duragesic and Risperdal throughout the fall 1998 audit cycle.

J&J moved into the number two position for overall performance and tied for second in value-added performance with Pfizer and Bayer. Pharmacy providers note that J&J is, overall, "very supportive of educational needs" and chooses a "partnering relationship" with long-term care.

Abbott Sees Results

Abbott's new LTC involvement continued during the fall 1998 audit cycle. The company's young LTC sales force accounted for 43% of Abbott's total contacts to LTC. During this time, Abbott dramatically increased its promotion of value-added programs to pharmacy providers. In fall 1998, Abbott dedicated 67% of its promotional activity to value-added services, compared with 47% in spring 1998.

Abbott's ratings for both value-added services and overall performance significantly improved between the two audit cycles. The company moved into the top 10 in both categories. In spring 1998, Abbott ranked 34th in value-added performance and 19th overall. Abbott "made a push to be in the LTC market, [and its] presence is improving."

About the Audit

Scott-Levin's latest *Nursing Home Pharmacy Provider/Consultant Promotional Audit* was released Dec. 31. The audit is based on the responses of pharmacy providers and consultants who represent 63% of all nursing home beds in the United States. These influential executives reported promotional activity by pharmaceutical companies over an 8-week period during fall 1998. They also rated these companies on their ability to meet LTC's needs in four areas:

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contracts, value-added services, knowledgeable sales reps and overall quality of service.

For more information on this study, contact Robert Houghton, Peter Nieto or Steve Amend at (215) 860-0440; fax: (215) 860-5477; Or e-mail them at marketing@scottlevin.com.

About Scott-Levin

Scott-Levin, a division of PMSI/Scott-Levin Inc., provides consulting services used by more than 80 U.S. and international pharmaceutical clients. It offers the pharmaceutical industry a full complement of managed care services that monitor key areas such as product promotion, industry trends, retail pharmacy activity and market performance. Visit Scott-Levin on the World Wide Web at www.scottlevin.com.



Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

12/1/98

Roxane Logo Change

Dear Healthcare Provider:

Roxane Laboratories, Inc. will soon begin to change its look. Over the next 12 to 18 months a new logo will appear on business cards, stationary, advertising material, and product labels. Our products, however, and their NDC numbers will not change.

The reason for this new logo and look is to clearly identify the strong relationship that Roxane Laboratories, Inc. has as part of the Boehringer Ingelheim family of companies throughout the world—an association we have been proud to be part of since 1978.

Boehringer Ingelheim, the largest privately held pharmaceutical company in the world (US \$4.7 billion in 1997), was founded in 1885 in Ingelheim, Germany. Through its various subsidiaries, Boehringer Ingelheim develops, produces, and sells human pharmaceuticals, veterinary medicines and biologicals, and fine, specialty chemicals in more than 100 countries. Through Roxane Laboratories, the company will continue to focus its development and marketing effort toward the treatment of HIV/AIDS, pain management/palliative care, and respiratory pharmaceuticals in the United States.

The relationship that we have shared, with you in the past will continue to be the relationship we will share well into the future, with an expanded presence worldwide. Our quality, standards, and service remain unchanged. As always, thank you for your support and business.

Sincerely,

Werner Gerstenberg
President & COO

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

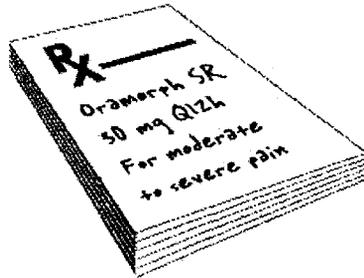
12-21-98



Proven, dependable pain relief
at a **lower cost**

Oramorph®SR (II)

(morphine sulfate sustained release tablets)
15 mg, 30 mg, 60 mg, 100 mg Tablets



- **Proven**, dependable pain relief for patients requiring opioid analgesics for more than a few days
- **Effective** in double-blind, multiple-dose, placebo-controlled studies of patients with moderate to severe chronic pain due to advanced cancer^{1,2}
 - **91%** (31/34) of patients elected to remain on sustained release morphine Q12h at study completion¹
 - Few patients experience **breakthrough pain¹**
- Convenient **12-hour** duration of action—dosage can be titrated up to manage increasing pain, or dosing interval can be shortened to no less than 8 hours
- **Flexible** dosing—15 mg, 30 mg, 60 mg, 100 mg tablets
- Up to **\$387 less** per year than MS Contin* on a typical prescription

The major hazards associated with morphine are respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

Oramorph SR tablets are to be taken whole and are not to be broken, chewed, or crushed.

Please see full Prescribing Information. Click [here](#) to view in PDF format. Click [here](#) for html version.

Click [here](#) if you need to download the Acrobat PDF viewer from Adobe.

* Based on Medi-Span, January 1998 wholesale acquisition cost comparison for bottle of 50 tablets, 30 mg, supplied over 1 year to a patient requiring one 30 mg

tablet Q12h, Oramorph SR vs. MS Contin. Retail pricing may vary from pharmacy to pharmacy and may affect cost savings to the patient. MS Contin is a registered trademark of The Purdue Frederick Company.

References:

1. Finn JW, Walsh TD, MacDonald N, et al. *J Clin Oncol.* 1993;11:967-972.
2. Walsh TD, MacDonald N, Bruera E, et al. *Am J Clin Oncol.* (CCT) 1992;15:268-272.

B

DECLARATION OF AMANDA B. JONES

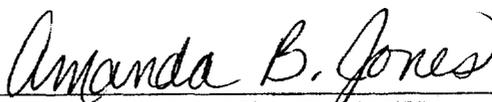
I, AMANDA B. JONES, declare that:

1. I am a sales representative for Purdue Pharma L.P. My title is Professional Sales Representative. My territory covers the Charleston– Myrtle Beach, South Carolina area.
2. On Thursday, May 6, 1999, I paid a regular sales call on Coastal Orthopedics, an orthopedic group located at 1400 Highway 544, Conway, South Carolina.
3. During my sales call, I spoke with Brian Forbes, a physician's assistant. Mr. Forbes stated that a sales representative from a competitive company had recently visited the office. He added, in words or substance, that the sales representative stated that her company would be coming out soon with a new sustained-release oxycodone product that would be less expensive than OxyContin® Tablets.
4. Mr. Forbes then showed me some promotional materials left by the sales representative. The sales representative's business card was attached to those materials. I attach as Exhibit A to this Declaration a copy of that business card that identifies the sales representative as:

"Julie Babin
Pallative Care Sales Representative
Certified Field Trainer

Boehringer Ingelheim
Roxane Laboratories"

I hereby declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.



AMANDA B. JONES

Executed this 13 day of May, 1999

Julie Babin
Palliative Care Sales Representative
Certified Field Trainer



Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216-6532
Telephone (800) 848-0120
Voice Mail Ext. 2522

10

moments later with some promotional literature and a business card. Joe showed me the business card which was that of a Roxane sales representative. I did not review the promotional pieces, but Joe described them to me as older Roxane literature that made no mention of a new product.

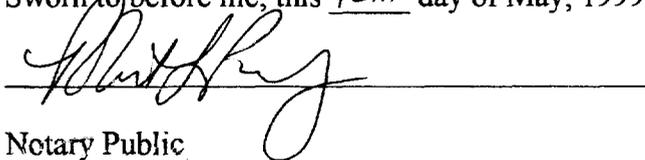
7. Ms. Harshman also mentioned that the Roxane representative had scheduled a lunch meeting with the doctors in the practice for late June. In the years I have called on Medical Neurology, I have come to understand that that the physicians in the practice are only willing to schedule a lunch meeting with a sales representative when the sales representative has to discuss a new product or a new indication for a product. I also understand that pharmaceutical sales representatives usually do not hold these "in-service" lunch meetings regarding a new drug until the drug is available to patients. For these reasons, I conclude that it appears highly likely that Roxane intends to launch their new sustained-release oxycodone product no later than mid- to late-June, if not sooner.

8. Before I left, I spoke briefly to Dr. Marc Raphaelson, one of the neurologists in the practice. Dr. Raphaelson stated that the Roxane representative called the new product something like "Roxicodone Long Acting".



CRAIG HASSLINGER

Sworn to before me, this 12th day of May, 1999.



Notary Public
My Commission Expires:

Embossed Hereon Is My
State of Maryland Notary Public Seal
My Commission Expires February 4, 2003
ROBERT L. PASSOW, JR.