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

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

Pursuant to Utah Code Ann. § 63G-4-102(4)(b) and Department of Commerce Administrative Procedures Act Rule ("Utah Admin. Code") R151-4-302, Respondents Purdue Pharma L.P., Purdue Pharma Inc., and The Purdue Frederick Company Inc. (collectively, "Purdue"), through counsel, hereby submit this *Motion to Dismiss the Division's Administrative Citation and Notice of Agency Action* ("Agency Action") issued by the Division of Consumer

Protection ("Division") on March 8, 2019 against Purdue and Drs. Richard and Kathe Sackler (together, "Individual Respondents").

SUMMARY

This unprecedented and improper Division Agency Action violates the constitutional protections afforded citizens in Utah and the United States, exceeds the limitations of the Utah Consumer Sales Practices Act ("UCSPA"), and fails to state a claim against Purdue.

This dispute between the State and Purdue began in May 2018, when the State filed a highly publicized civil lawsuit (the "Civil Action") that sought to hold Purdue alone liable for an opioid abuse crisis in Utah. The State blamed this complex public health crisis on Purdue's marketing of opioid medications that the federal Food and Drug Administration ("FDA") approved as safe and effective to treat chronic non-cancer pain.

Rather than pursue the Civil Action in a forum suited to the complexities of the issues presented by the State's claims, the State changed course and dismissed the Civil Action in January 2019. On the same day, the Division issued its Administrative Citation (the "Citation") with virtually ***identical*** allegations, and initiated the present administrative proceeding ("Agency Action"). The Citation, like the Civil Action, alleged that Purdue's marketing violates the UCSPA. Notably, Purdue stopped marketing its opioid medications to healthcare professionals in February 2018—months before the Division issued the Citation. Purdue also discontinued the specific promotional and medical education statements referenced in the Citation—in most cases, this happened years ago.

The Agency Action and Citation should be dismissed for three reasons. ***First***, this administrative proceeding violates due process and the Division is seeking an unconstitutionally excessive fine. ***Second***, the Citation ignores the limitations of the UCSPA and conflicts with the FDA's federal regulatory scheme. ***Third***, the Citation, as pleaded, fails to state a claim, most

notably because the Division does not even attempt to plead facts to show that any alleged deception caused harm.

I. This Administrative Proceeding Violates Due Process and the Division is Attempting to Seek an Unconstitutionally Excessive Fine.

The Division filed this administrative proceeding not because it is a better way to determine the truth or to administer justice, but rather to rush to judgment and threaten Purdue with massive statutory penalties—likely reaching hundreds of millions of dollars according to the Division's interpretation of the UCSPA—without adequate process. This is not a typical enforcement action, where the Division might seek an expedited administrative proceeding to get a cease and desist order that would curb deceptive practices. A complex dispute of this magnitude demands constitutionally sound procedural protections that are commensurate with the action's scope and complexity. The rules that govern this administrative proceeding—a proceeding that must conclude within six to eight months—cannot provide the critical procedural safeguards needed to ensure due process. Indeed, if the Division were to succeed on the merits in this abbreviated proceeding—which it should not for the reasons set forth herein—it surely would result in a violation of Purdue's due process rights and improperly permit the Division to seek an unconstitutionally excessive fine as well.

The Division urges this breakneck pace in an improper effort to gain leverage and force Purdue to settle this dispute. It is telling that the State abandoned the Civil Action in favor of this proceeding only after the State retained private counsel who are also lead plaintiffs' counsel in the national Opioid MDL pending in Cleveland, Ohio. The State's private counsel are using this administrative proceeding as the latest in a series of actions across the country designed to exert maximum settlement pressure on Purdue. The State acknowledges this is the true reason for its about-face. As the State announced: it "felt like it would take far too long to get to a judgment" in

traditional litigation, whereas the administrative procedure would allow it to short-circuit the judicial process, "expedite legal proceedings against Purdue," and, most egregious of all, "to put new 'pressure' on defendants to be 'more reasonable.'"

The Division requests statutory penalties likely to reach hundreds of millions of dollars. If successful (which it should not be), such an award would be an independent violation of Purdue's constitutional rights. Given the scope of the allegations, and the Division's inability to show causation, a penalty of the size pursued by the Division cannot possibly satisfy the State and federal constitutional requirements that fines be proportional to Purdue's own individual conduct and the harm (if any) caused by that conduct.

II. The UCSPA and Federal Law Foreclose This Agency Action.

Apart from these due process and excessive fine violations, the Division's claims also impermissibly conflict with the specific and comprehensive expert regulatory schemes through which Purdue's medications have been approved for the exact uses the Division now challenges. Because the FDA "specifically permitted" the conduct challenged by the Division—marketing an FDA-approved product for FDA-approved uses—the "safe harbor" provision of the UCSPA bars the Division's claims. And federal law preempts any state-law claim premised on the theory that Purdue could or should stop selling opioids for their FDA-approved and permitted uses. Further, it would be improper to use the blunt tool of the UCSPA when there are other more specific and direct statutory and regulatory enforcement mechanisms available to the State, the FDA, the federal Drug Enforcement Agency ("DEA"), and the Department of Justice. In any event, the UCSPA does not permit enforcement actions as broad as this Agency Action because: (1) the version of the UCSPA in effect at the time Purdue was marketing its opioids permitted administrative actions only for present or ongoing violations—of which there are none here; (2) the Division cannot bring "unconscionability" claims in an administrative action; and (3) the

UCSPA's enforcement reach does not extend to omissions.

III. The Division Fails to State a Claim.

The Division does not state a claim for four reasons. First, because the alleged deceptions relate to medications that are available only by prescription, and were allegedly received by prescribing healthcare professionals rather than consumers, they were not the "subject of a consumer transaction." Second, the Division does not plead facts to show that these alleged deceptions caused harm. Third, although the Division relies on a number of alleged misrepresentations made by third parties, the Division has not pleaded facts to establish that these third parties were Purdue's agents. Finally, the Division has not pleaded its claims with the requisite particularity.

For all of these reasons, explained in more detail below, the Agency Action should be dismissed in its entirety.

BACKGROUND

1. On May 31, 2018, the Utah Attorney General's Office brought the Civil Action against Purdue in the Carbon County District Court, Case No. 180700055,[1] alleging, *inter alia*, violations of the UCSPA, and demanding a jury trial.

2. The State took no steps to litigate the Civil Action for months, until the district court—on its own accord—served a notice of intent to dismiss the Civil Action for the State's failure to prosecute. (Dkt. Entry "Notice of Intent" (Nov. 14, 2018), attached as **Exhibit A**.)

3. The State urged the district court not to dismiss the case, explaining that the Civil Action "is one piece of a mosaic of litigation involving Purdue, other opioid manufacturers, opioid

[1] The Presiding Officer "may take judicial notice of public records and may thus consider them on a motion to dismiss." *BMBT, LLC v. Miller*, 2014 UT App 64, ¶ 6, 322 P.3d 1172 (internal quotation marks omitted).

distributors, and other individuals and entities." (State's Resp. to Notice of Intent to Dismiss at 2 (Nov. 26, 2018), attached as **Exhibit B**.) The State assured the district court that the "State and Purdue are actively engaged in the process of gathering information, evaluating claims, and pursuing resolution of the dispute underlying this lawsuit," and cited its ongoing efforts to retain outside counsel (six months after initiating its suit), the potential that the State might amend its complaint, and the potential consolidation of the case with other related cases. (*Id.*)

4. On January 30, 2019, however, the State abruptly filed a notice of voluntary dismissal, and issued its Citation against Purdue, repeating verbatim almost all the allegations asserted in the Civil Action, including violations of the UCSPA. Attorney General Sean Reyes publicly announced the issuance of the Citation in a press release, asserting for the first time that the State's claims had to be "expedit[ed]."[2] In a news conference, the Attorney General admitted that the State preferred the administrative proceeding to traditional legal process because "[w]e felt like it would take far too long to get to a judgment,"[3] and that the expedited proceedings are an effort "to put new 'pressure' on defendants to be 'more reasonable.'"[4]

5. In accordance with an order of the Presiding Officer, the Division filed a Notice of Agency Action ("NOAA") on March 8, 2019, followed by a renewed motion seeking to convert

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[2] Press Release, *Utah Office of the Attorney General, Utah Escalates Legal Action Against Purdue by Naming Executives and Expediting State's Claims* (Jan. 30, 2019), *available at* https://attorneygeneral.utah.gov/utah-escalates-legal-strategy-against-purdue-pharma/, attached as **Exhibit C**.

[3] Ben Winslow, *Utah Attorney General Drops Lawsuit, Files Administrative Action Against Purdue over Opioid Crisis*, FOX13 NEWS (Jan. 30, 2019), https://fox13now.com/2019/01/30/utah-attorney-general-drops-opioid-lawsuit-files-administrative-action-against-purdue-over-opioid-crisis/, attached hereto as **Exhibit D**.

[4] Katie McKellar, *Utah 'Streamlines' Legal Fight Against OxyContin Maker, Names Family in Filing*, DESERET NEWS (Jan. 30, 2019) (quoting Attorney General Reyes), https://www.deseretnews.com/article/900053214/utah-streamlines-legal-fight-against-oxycontin-maker-names-family-in-filing.html, attached hereto as **Exhibit E**.

from an informal to formal proceeding on March 21, 2019. Purdue and the Individual Respondents filed an Opposition to the Motion to Convert on April 1, 2019.

LEGAL STANDARD

To survive a motion to dismiss, the Citation "must allege facts sufficient to satisfy each element of a claim." *Harvey v. Ute Indian Tribe of Uintah & Ouray Reservation*, 2017 UT 75, ¶60, 416 P.3d 401. Pursuant to Utah Rule of Civil Procedure 9(c), "[i]n alleging fraud or mistake, a party must state with particularity the circumstances constituting fraud or mistake." UTAH R. CIV. P. 9(c). Because UCSPA claims must be pleaded with particularity, *Jackson v. Philip Morris Inc.*, 46 F. Supp. 2d 1217, 1222 (D. Utah 1998),[5] the Division must "not only allege facts to establish the elements of a fraud claim but also recite [t]he relevant surrounding facts, such as the identity of the person who made the alleged misrepresentation[ ] and the time and location at which it was uttered." *Webster v. JP Morgan Chase Bank, NA*, 2012 UT App 321, ¶ 19, 290 P.3d 930 (internal quotation marks omitted) (alterations in original). Finally, the Due Process Clauses of the U.S. and Utah Constitutions require "'the opportunity to be heard at a meaningful time and in a meaningful manner.'" *V-1 Oil Co. v. Dep't of Envtl. Quality, Div. of Solid & Hazardous Waste*, 939 P.2d 1192, 1197 (Utah 1997) (quoting *Mathews v. Eldridge*, 424 U.S. 319, 333 (1976)).

ARGUMENT

I. LITIGATING A CASE OF THIS SCALE AND COMPLEXITY IN AN ADMINISTRATIVE PROCEEDING VIOLATES PURDUE'S CONSTITUTIONAL RIGHTS AND THE DIVISION IS SEEKING AN UNCONSTITUTIONALLY EXCESSIVE FINE.

This is a complex case that, if allowed to proceed, will require mountains of documentary evidence and scores of lay and expert witnesses. The Division seeks potentially massive fines

[5] *Accord Hines v. Overstock.com, Inc.*, No. 09 CV 991 SJ, 2013 WL 4495667, at *8 (E.D.N.Y. Aug. 19, 2013); *Goodwin v. Hole No. 4*, No. 2:06-CV-00679, 2006 WL 3327990, at *7 (D. Utah Nov. 15, 2006).

against Purdue. Yet, in a case of this complexity, this administrative proceeding lacks critical procedural safeguards needed to protect Purdue's state and federal constitutional rights. The Division cannot use this administrative proceeding as an end run around Purdue's due process rights merely because the Division and the State believe protecting those rights would take "too long." Accordingly, the Citation should be dismissed.

"The U.S. and Utah Constitutions mandate that when life, liberty, or property is placed in jeopardy by reason of state action, due process must be accorded the individual affected by such action." *In re Baby Girl T.*, 2012 UT 78, ¶ 16, 298 P.3d 1251 (citing U.S. CONST. amend. XIV; UTAH CONST. art. 1, § 7). "These rights attach . . . whenever a citizen is threatened with deprivation of 'life, liberty or property,' . . . even when the deprivation occurs as a result of administrative action." *In re Worthen*, 926 P.2d 853, 876 (Utah 1996). "The most fundamental requirement in this context is 'the opportunity to be heard at a meaningful time and in a meaningful manner.'" *V-1 Oil Co. v. Dep't of Envtl. Quality, Div. of Solid & Hazardous Waste*, 939 P.2d 1192, 1197 (Utah 1997) (quoting *Mathews* 424 U.S. at 333).

Although Purdue separately and independently invokes the protections of both the federal and state Due Process Clauses, the analysis runs in tandem. *See In re Worthen*, 926 P.2d 853, 876 (Utah 1996); *lc. Utah Cty. v. Ivie*, 2006 UT 33, ¶ 21, 137 P.3d 797 (recognizing that Utah Supreme Court has ruled the state Due Process Clause provides ***more*** protection than its federal counterpart). Under both the federal and Utah Constitutions, courts apply a three-factor analysis to determine "the process due in any given instance." *Hamdi v. Rumsfeld*, 542 U.S. 507, 529 (2004); *accord In re Baby Girl T.*, 2012 UT 78, ¶ 17. Courts must balance: (1) "the private interest that will be affected by the official action"; (2) "the risk of an erroneous deprivation of such interest through the procedures used, and the probable value, if any, of additional or substitute procedural

safeguards"; and (3) "the Government's interest, including the function involved and the fiscal and administrative burdens that the additional or substitute procedural requirement would entail." *Mathews*, 424 U.S. at 355; *City Club, Inc. v. Dep't of Alcoholic Beverage Control*, 2014 UT App 110, ¶ 15, 327 P.3d 32. Given the nature and scope of the Division's allegations against Purdue and the substantial fines sought by the Division, the procedural limitations inherent in this proceeding will deprive Purdue of a meaningful opportunity to be heard.

A. Purdue's Interest Is Significant.

The Division seeks a separate fine for every alleged misrepresentation—and possibly even alleged omission—Purdue (and numerous third parties) made in Utah over a ten-year period regarding Purdue's prescription opioid medications, including through websites, promotional materials, conferences, dinner programs, doctors' guidelines, and personal visits. The Division plainly hopes to impose massive fines in this action. Purdue has a significant interest in defending against these unsupported allegations, and an equally strong interest in avoiding unwarranted and excessive fines. *See Business Commc'ns, Inc. v. U.S. Dep't of Educ.*, 739 F.3d 374, 379 (8th Cir. 2013) (recognizing a due process interest in avoiding monetary losses).

B. These Expedited Proceedings Create an Enormous Risk of an Erroneous Decision that Violates Due Process.

The truncated and expedited procedures established by the Division for an administrative proceeding—whether formal or informal—deprive Purdue of a meaningful opportunity to be heard and create a substantial risk of an erroneous decision.

"Because of the broad spectrum of concerns to which the term ['process'] must apply, . . . the quantum and quality of the process due in a particular situation depend upon the need to serve the purpose of minimizing the risk of error." *Greenholtz v. Inmates of Nebraska Penal & Corr. Complex*, 442 U.S. 1, 13 (1979). The Utah Supreme Court has cautioned that "as the private

interest at stake becomes more and more important, so too does the cost of an erroneous decision." *Bivens v. Salt Lake City Corp.*, 2017 UT 67, ¶ 49, 416 P.3d 338. Accordingly, any "deprivation of life, liberty or property by adjudication [must] be preceded by notice and opportunity for hearing ***appropriate to the nature of the case***." *Mullane v. Cent. Hanover Bank & Tr. Co.*, 339 U.S. 306, 313 (1950) (emphasis added); *accord McBride v. Utah State Bar*, 2010 UT 60, ¶ 16, 242 P.3d 769.

The Division's administrative procedures were never intended to be used, and have never before been used, for a dispute of this nature or magnitude. An analysis of the 450 actions disclosed on the Division's public online database[6] establishes that this Agency Action is unprecedented. Of these prior administrative actions, none has alleged violations related to the manufacture or sale of highly regulated prescription medications. To the contrary, the actions involve run-of-the-mill business operations, with nearly half involving "common problems" related to telemarketing, pawnshops, prize notices, or charitable solicitations.[7] None of these "common problems" that the Division regularly addresses is remotely close to the scope of the present action, which implicates both complicated, disputed scientific principles, and multiple regulatory decisions by expert federal authorities.

Indeed, the largest fine the Division has imposed since 2015 was $745,000, in a case in which the "facts [were] mostly not in dispute" and for which the presiding officer needed little more than a single page to recite the findings of fact and a mere five pages for the conclusions of

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[6] *Legal Actions Search*, CONSUMERPROTECTION.UTAH.GOV, https://consumerprotection.utah.gov/actions/index.html (last visited Apr. 7, 2019). Purdue has submitted a GRAMA request for all records of prior adjudications before the Division, and is awaiting a response.

[7] The Division has identified the "common problems" it addresses: scam calls, sweepstakes/lotteries, home improvement, car purchases and repair, credit reports and repair, identity theft, advance fee loans, telemarketing, work-at-home schemes, child protection registry, and internet service provider content filtering. *Education*, CONSUMERPROTECTION.UTAH.GOV, https://consumerprotection.utah.gov/edu/index.html (last visited Apr. 7, 2019).

law.[8] *In re Next-Gen, Inc. dba Award Notification Commission*, Case No. DCP 84688. Moreover, Purdue could locate only thirteen actions in which the Division imposed fines over $100,000.[9] The average fine was less than $20,000, with more than 75% of actions involving fines of $10,000 or less.

The UCSPA's legislative history also supports the conclusion that neither the Utah Legislature nor the Department of Commerce intended administrative proceedings as the forum for claims of this magnitude. In 1992, the Legislature amended Utah Code section 13-2-8, which provides that, with few exceptions not relevant here, all administrative fines or settlement money recovered by the Division "shall be deposited into the" Consumer Protection Education and Training Fund. UTAH CODE ANN. § 13-2-8. Before the amendment, the provision required the transfer of any balance exceeding $100,000 into the general fund at the end of the fiscal year. The 1992 amendment lowered the maximum amount to $75,000. When questioned about the reason for the change, the bill's sponsor explained it was a concession on the part of the Department of Commerce: "[the Department] currently ha[s] the ability to accumulate up to $100,000. They don't see any way they will ever be in danger of even getting to $75,000."[10] Under the current statute, the maximum permitted balance for the fund is only ***$500,000***. UTAH CODE ANN. § 13-2-8(4).

By contrast, in its seventy-page Citation, the Division pleads expansive allegations related to a complex public health crisis and a nation-wide "marketing campaign" spanning more than a

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[8] In addition, the citation itself was a mere ***three*** pages long, *id.*, compared to the seventy-page Citation the Division issued in the present matter.

[9] Even then, seven matters involved orders by default in which the respondent had not even participated, and in another seven matters, the Division agreed to collect 20% or less of the fine imposed, and suspended the remainder pending compliance with a cease and desist order.

[10] Senate Discussion, 1992, SB0082, at 1:37:01–1:45, *available at* http://utahlegislature.granicus.com/MediaPlayer.php?clip_id=15631&meta_id=480054.

decade. The Division asserts that each "material" misrepresentation or omission "constitutes a separate violation of the CSPA," (Citation ¶ 174); according to the Division's unprecedented and multiplicative damages theory, ***each*** material misrepresentation is subject to a separate statutory penalty of up to $2,500. The Division therefore has the burden to prove that each statement meets all elements of a violation of a specific provision of Utah law. This will require the Division to offer scientific and other technical evidence to establish the alleged falsity/deceptiveness and materiality of the statements, through both competent expert and lay testimony. (*See, e.g.*, *id.* ¶¶ 10–15, 18–28, 33–38, 41–105). There also will need to be a detailed examination of the precise nature of the relationships and interactions between Purdue, the medical professional groups and "key opinion leaders" alleged to have conveyed misstatements on Purdue's behalf, and thousands of Utah healthcare professionals.

It thus is clear that the Division's administrative procedures have never been, and were not intended to be, used to address matters of the nature, scope, or complexity of the instant action, which challenges the marketing of a prescription pharmaceutical that has been, and ***remains***, approved and continually scrutinized by the FDA for more than two decades. Indeed, Purdue will have to defend against each alleged deception—an immense undertaking that, for the following five reasons, cannot possibly be accomplished in this expedited administrative proceeding.

1. The Division's rules do not allow enough time for the parties to complete the fact discovery and investigation required for a proceeding of this magnitude.

The extraordinarily expedited and streamlined nature of the Agency Action "forecloses any meaningful opportunity for [Purdue] to protect its rights." In re Adoption of J.S., 2014 UT 51, ¶ 22, 358 P.3d 1009. Pursuant to the Division's Rules, the hearing must conclude within 180 days after the Division initiates the proceeding, UTAH ADMIN. CODE R151-4-108, or within 240 days on a showing of good cause. *Id.* R151-4-109(2). Here, the hearing must take place by

September 4, 2019, or at the latest by November 3, 2019. By contrast, in traditional litigation, case management is in the sound discretion of the judge and deadlines are tailored to the needs of each case. *See A.K. & R. Whipple Plumbing & Heating v. Aspen Const.*, 1999 UT App 87, ¶ 11, 977 P.2d 518. Similarly, absent an extension, the parties must complete any permitted fact discovery within 120 days after the filing of the Agency Action. UTAH ADMIN. CODE R151-4-508(2)(a). This is true regardless of the scope of the allegations or the size of the fine sought by the Division. By contrast, when as little as $300,000 is at issue before a district court, litigants have—***at a minimum***—210 days to complete fact discovery, with the option to seek or stipulate to additional time. UTAH R. CIV. P. 26(a)(4), (c)(5)–(6); UTAH R. CIV. P. 29; UTAH R. CIV. P. 37(a).

Both Purdue and the Division will almost certainly require a tremendous amount of fact and expert discovery. *See Warenski v. Advanced RV Supply*, 2011 UT App 197, ¶ 11, 257 P.3d 1096 (recognizing that expert testimony is necessary when the factual foundation for required elements is "not in the common knowledge and experience of the average person"). The crux of the Division's allegations against Purdue depends on highly technical, ever-evolving scientific issues subject to legitimate debate, and conduct that is subject to comprehensive regulatory oversight by the State, the FDA, and the DEA. (*See, e.g.*, Citation ¶¶ 28–29, 37–38, 41, 62.) It will be impossible to fairly evaluate the truth and alleged effects of potentially thousands of marketing statements without a detailed understanding of the medical literature and the relevant federal and state regulatory regimes and actions. In opioid actions currently pending in courts in other states, parties on both sides have struggled to prepare for trial in periods far exceeding the discovery period here. The statutorily-imposed schedule here makes the discovery challenges even more insurmountable and prejudicial to Purdue.

Moreover, the current state of discovery heightens the scheduling challenges and due process problems. The State, through its private counsel, already has access to significant discovery completed in other opioid actions around the country. Even if the Division were willing to forego ***all*** further discovery and instead rest on the tens of millions of pages of previously produced documents and scores of depositions of Purdue and third-party witnesses already taken in the MDL, there would still be a major discovery imbalance. Purdue has ***no*** discovery from the State, and does not even have an accounting of the alleged misrepresentations for which the Division seeks to impose fines. To the contrary, it appears the Division intends to submit a calculation of the statutory penalty it seeks only after the Presiding Officer makes a "liability finding." That is fundamentally unfair to Purdue. Within the procedural constraints of this action, Purdue cannot get notice of the specific alleged misconduct, and then have time to develop evidence to respond and test whether each statement is in fact a material misrepresentation that warrants a fine. These administrative procedures deprive Purdue of any real opportunity to fairly rebut the allegations in this action, and that is precisely the State's intention.

Likewise, Purdue has no affirmative discovery from State healthcare agencies and officials, which is relevant to show the State's knowledge about the scientific issues relevant to the Division's claims, and the State's own role in permitting, encouraging, or specifically authorizing prescriptions of the opioids it now claims to have caused harm. And Purdue has no discovery relating to Utah healthcare professionals who allegedly heard or saw deceptive statements that caused them to ignore their own medical training and independent judgment when prescribing allegedly unnecessary opioids. Similarly, the Division must identify and produce evidence to support the potentially thousands of specific representations upon which it relies, and both parties must produce experts to testify about the scientific accuracy of those representations, whether

those representations had any effect on opioid prescribing in Utah, whether the degree of that effect is measurable, and, if so, what effect they had. With this voluminous amount of work yet to be done, there is no conceivable way the parties can finish the discovery required to fairly adjudicate these claims, much less actually adjudicate those claims, ***by November 3 of this year***. The result is a haphazard, slapdash action that depends on incomplete and insufficient discovery, and impermissible short cuts, to rush to a result that denies Purdue its due process rights.

2. The Division's rules do not give Purdue the opportunity to meaningfully discover and test the Division's expert opinions before the hearing.

Unlike in civil proceedings, Purdue is not permitted to depose the Division's experts. *Compare* UTAH R. CIV. P. 26(a)(4)(C)(i), *with* UTAH ADMIN. CODE R151-4-504(1)(a)(ii). Instead, Purdue will receive only an expert report, potentially just days before the hearing. UTAH ADMIN. CODE R151-4-504(1)(b). Given the wide-ranging allegations, which carry with them the risk of significant statutory penalties, expert depositions are essential to Purdue's ability to defend itself. They are indispensable to preparing its case on the disputed issues in this litigation—including the truth of the representations, causation, and damages—and ***frequently*** lead to additional fact gathering (which, of course, is why flexible discovery procedures have been necessary in the over 2,000 opioid actions pending in courts around the country). The need for expert discovery is even more pronounced here, where Purdue expects the Division may well build its case through experts who use novel, untested, and/or unscientific methodologies in an attempt to avoid the burden to identify and prove the deceptiveness and materiality of each alleged misrepresentation.

3. The Rules of Evidence do not apply, increasing the risk that extraneous, prejudicial, or unreliable evidence will infect these proceedings.

The Utah Rules of Evidence do not apply to these proceedings. *Peterson v. Provo City*, 2002 UT App 430. Accordingly, there are few limitations on the evidence allowed, even if it is unreliable or prejudicial. Indeed, "[h]earsay and other forms of evidence that might be inadmissible

in a court of law may be considered during an administrative hearing." *Id.*[11] Even if the Presiding Officer converts this action to a formal proceeding over the Respondents' objection, the Presiding Officer may consider hearsay, and need not exclude evidence that "is irrelevant, immaterial, or unduly repetitious." UTAH CODE ANN. § 63G-4-206(1)(b)(i), (iii). There are no established procedures for vetting expert opinions, and apparently no requirement that testimony be based on personal knowledge. There is no requirement to authenticate evidence, and the Presiding Officer can use his own experience or knowledge to evaluate the record. *Id.* § 63G-4-206(1)(b)(iv). Apparently, "[a]ll that is necessary is that admitted evidence have some probative weight and reliability." *Bunnell v. Indus. Comm'n of Utah*, 740 P.2d 1331, 1333 (Utah 1987). Because the Rules of Evidence (and the hearsay bar) exist in large part to ensure reliable fact-finding procedures, the absence of those Rules increases the risk of an erroneous decision. This is particularly true with regard to expert opinions, which will provide crucial evidence on the issues in this proceeding. Although more lenient evidentiary rules may be appropriate for actions involving only a few witnesses, relatively simple proof, and issues within the special expertise of the Presiding Officer, they cannot adequately assure reliable determinations of fact in this action, which involves millions of documents and testimony from dozens of witnesses about both decades-old conversations and scientific issues that are the subject of ongoing study and debate.

4. The ten-year statute of limitations unfairly allows the Division to revive claims that would be time-barred if brought in the State's prior Civil Action.

The statute of limitations is twice as long in administrative proceedings. Specifically, the Division's UCSPA claims are subject to a ten-year limitations period in administrative

[11] It is well recognized that the bar on hearsay is essential to ensure the reliability of evidence presented to a fact finder. *See* 5 WEINSTEIN'S FEDERAL EVIDENCE § 802.02 (2019) ("The rule against hearsay seeks to eliminate the danger that evidence will lack reliability because faults in the perception, memory, or narration of the declarant will not be exposed.").

proceedings, UTAH CODE ANN. § 13-2-6(6)(a), compared to only a five-year period in a judicial proceeding. *Id.* § 13-2-6(6)(b). "[T]he policy underlying all statutes of limitations [is] to promote justice by preventing surprises through the revival of claims that have been allowed to slumber until evidence has been lost, memories have faded, and witnesses have disappeared." *Russell Packard Dev., Inc. v. Carson*, 2005 UT 14, ¶ 28, 108 P.3d 741 (internal quotation marks omitted). But that is precisely what Purdue faces here: it must confront a case woven from a speculative theory of "fraud in the air," based largely on the decade-old statements and decisions of doctors, employees, and other third parties. Indeed, with one extraordinary exception completely unrelated to this case, UTAH CODE ANN. § 78B-2-308(3)(a), Purdue is not aware of any Utah civil cause of action with a limitations period of ten years or longer. It perverts fundamental fairness and due process to permit the Division to use this administrative action to revive claims that were time-barred when the State filed its Civil Action in 2018.

5. This Agency Action unilaterally takes away the jury trial right that Purdue had when the State filed its Civil Action.

The State's decision to dismiss the Civil Action and initiate an administrative proceeding denies Purdue's right to a jury. In the original Civil Action, Purdue was entitled to a jury trial on the UCSPA claims. Indeed, the State initially demanded a jury in the Civil Action. Now, although the Division asserts the same allegations and seeks to enforce the same provisions of the UCSPA through this administrative proceeding, there is no jury and the Presiding Officer is the fact finder. *See* UTAH CODE ANN. §§ 63G-4-203(1)(i), -208.

Article I, section 10 of the Utah Constitution guarantees the right to a jury trial in civil cases. *See Int'l Harvester Credit Corp. v. Pioneer Tractor & Implement, Inc.*, 626 P.2d 418, 421 (Utah 1981). Utah has repeatedly recognized the importance of this crucial right:

> The jury historically has been an integral part of the Anglo-American legal system. It would require the clearest language to sustain the conclusion that there was an

> intention to abolish an institution so deeply rooted in our basic democratic traditions and so important in the administration of justice, not only as a buffer between the state and the sovereign citizens of the state, but also as a means for rendering justice between citizens.

Id. at 420. The jury serves an important function: "[a]s a fact-finding body, they provide an important and useful alternative to a single individual's resolving disputed issues of fact. In this regard ***the accumulated experience and the combined cognitive powers of jurors may produce more accurate fact finding than a single person, no matter how learned in the law.***" *Id.* (emphasis added). For this reason, the Utah Supreme Court has cautioned "that the right of trial by jury should be scrupulously safeguarded." *Abdulkadir v. W. Pac. R. Co.*, 318 P.2d 339, 341 (Utah 1957). But Purdue has lost its jury trial right as a result of the State's unilateral decision to transform its civil lawsuit into an administrative proceeding.

In sum, in an extremely short time, the parties must complete a tremendous amount of discovery regarding alleged representations spanning a decade. Because the Division (through its private attorneys) has a big head start on that discovery—while Purdue has nothing from the State, its relevant agencies and officers, or the healthcare professionals the Division claims were "duped" by the "marketing campaign"—that discovery burden is exceedingly one-sided. Moreover, despite facing potentially massive fines, Purdue will not be permitted to depose the Division's experts before the hearing, and the discovery materials and testimony may be considered by a single Presiding Officer without regard to the Rules of Evidence or "the combined cognitive powers of jurors." *Int'l Harvester Credit Corp.*, 626 P.2d at 420. These procedures exponentially increase the risk of an erroneous decision and do not safeguard Purdue's fundamental due process rights.

C. The State's Interest in These Truncated Proceedings Is Minimal.

Under these circumstances, affording Purdue its full procedural protections will not impact the Division's interest in protecting consumers, nor will it increase administrative burdens.

The Division's interest, as expressed by the UCSPA itself, is "to protect consumers from suppliers who commit deceptive and unconscionable sales practices." UTAH CODE ANN. § 13-11-2(2). Because Purdue stopped marketing opioid medications over a year ago, and Purdue does not market its opioid medications directly to patients, this proceeding cannot possibly protect consumers from ongoing marketing or sales practices. Instead, the Division's only interest here is in collecting fines for past conduct. But the Division can seek that same relief from a court and a jury, as the State initially intended to do when it filed its Civil Action. *See id.* § 13-11-17.

The Division has no protected interest in using expedited proceedings improperly to pressure Purdue to settle. *See Palmer v. St. George City Council*, 2018 UT App 94, ¶ 14 n.5, 427 P.3d 423, *cert. denied*, 432 P.3d 1231 (Utah 2018) ("[D]espite the flexibility of administrative hearings, there remains the necessity of preserving fundamental requirements of procedural fairness in administrative hearings . . . ." (internal quotation marks omitted)). Indeed, "[a]s always, the government's interest here is in the efficient ***and fair*** administration of the law." *Lander v. Indus. Comm'n of Utah*, 894 P.2d 552, 556 (Utah Ct. App. 1995) (emphasis added).

This is not a case where the Division has a strong interest in having its claims adjudicated by a presiding officer expert in consumer protection. *Cf. United State v. Mead Corp.*, 533 U.S. 218, 228 (2001) (noting that agencies sometimes have greater "relative expertise" in the interpreting statutes they are charged with enforcing). Consumer protection experience is of limited use here because Purdue's opioid medications and statements to healthcare professionals are heavily regulated by the FDA, which has unique scientific and regulatory expertise. The core issues raised in the Citation—the medical and scientific veracity of statements made by Purdue to physicians—are best suited for an agency with training and expertise in pharmacology, epidemiology, medicine, addiction risks, and the regulation of controlled substances.

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In sum, due process demands relief "when the appearance of unfairness is so plain that we are left with the abiding impression that a reasonable person would find the hearing unfair." *Bunnell v. Indus. Comm'n of Utah*, 740 P.2d 1331, 1333 n.1 (Utah 1987). In these circumstances, a reasonable person would find that subjecting Purdue to the possibility of millions of dollars in excessive fines with virtually no procedural protections is unfair. This proceeding should be dismissed.

D. The Statutory Penalties Sought by the Division Would Violate the Excessive Fines Clauses of the United States and Utah Constitutions.

The State's announced reasons for selecting this forum so that it could reach an expedited resolution, and its demand for statutory penalties, make clear that the State's objective is to threaten Purdue with enormous fines so that it can exert maximum pressure on Purdue to resolve this matter on favorable terms for the State.

The Division argues that it is entitled to a separate fine of up to $2,500 for "each instance where" Purdue allegedly "promote[d], directly and indirectly, deceptive marketing messages . . . [about] the dangers of opioid usage in Utah." (Citation ¶¶ 161, 174.) Given the way the Division has framed its requested relief, the constitutionally impermissible procedures through which it seeks to obtain that relief are likely to result in an aggregate penalty that is unconstitutionally excessive under the Eighth Amendment to the U.S. Constitution and Article 1, section 9 of the Utah Constitution.

The Eighth Amendment's Excessive Fines Clause "limits the government's power to extract payments, whether in cash or in kind, as punishment for some offense." *Phillips v. Dep't of Commerce, Div. of Sec.*, 2017 UT App 84, ¶ 41, 397 P.3d 863 (quoting *United States v. Bajakajian*, 524 U.S. 321, 328 (1998)); *accord Timbs v. Indiana*, 139 S. Ct. 682, 686–87 (2019)

(holding that "the protection against excessive fines guards against abuses of government's punitive or criminal-law-enforcement authority," and is "incorporated by the Due Process Clause of the Fourteenth Amendment" (quoting *McDonald v. Chicago*, 561 U.S. 742 (2010))). "[T]he Eighth Amendment unquestionably places upper limits on the [Division's] power to impose a fine on [Purdue] or any other violator of the Act." *Phillips*, 2017 UT App 84, ¶ 42. "The touchstone of the constitutional inquiry under the Excessive Fines Clause is the principal of proportionality." *Id.* (quoting *Bajakajian*, 524 U.S. at 334). The Utah Supreme Court has likewise applied a "proportionality standard" to Utah's counterpart provision. *State v. Houston*, 2015 UT 40, ¶ 65, 353 P.3d 55; *see also id.* ¶ 159 (Lee, J., concurring) ("[T]he prohibition of excessive bail or fines is an express invocation of a principle of proportionality."); *State ex rel. Utah Air Quality Bd. v. Truman Mortensen Family Tr.*, 2000 UT 67, ¶ 31, 8 P.3d 266 (recognizing the state and federal provisions are "nearly identical").

The Division apparently seeks fines not only for "marketing messages" that allegedly include affirmative misrepresentations, but also for truthful messages that "fail to include material facts about[] the dangers of opioid usage," (Citation ¶ 161; *see also* Part II.E, *infra*), as well as messages made and distributed by third parties, whether or not Purdue controlled the content of these messages, the number of copies produced, or to whom those messages were distributed. (*See* Part III.C, *infra*.) In these circumstances, imposing a separate sanction for each message would necessarily be grossly disproportionate because it is not based on Purdue's own conduct, which (as alleged) was typically limited to providing funds for publications. Because it is impossible to determine the degree of harm, if any, attributable to Purdue's alleged conduct (*see* Part II.B. *infra*), the penalties the Division seeks violate the Excessive Fines clauses of the United States and Utah Constitutions and should be dismissed.

II. THE DIVISION'S CLAIMS ARE NOT COGNIZABLE.

The Division also ignores the limitations imposed by state and federal law on its authority to bring UCSPA claims.

A. The Division's Claims Are Barred by the UCSPA's Safe Harbor Provision and Preempted by Federal Law.

The Division's claims are barred because the UCSPA "does not apply to . . . an act or practice required or specifically permitted by or under federal law, or by or under state law." UTAH CODE ANN. § 13-11-22(1); *accord Miller v. Corinthian Colleges, Inc.*, 769 F. Supp. 2d 1336, 1342–43 (D. Utah 2011). The gravamen of the Division's claims is that Purdue misleadingly marketed opioids for long-term treatment of chronic non-cancer pain. Yet, many of the statements that the Division claims were improper are permitted by, or consistent with, OxyContin's FDA-approved product labeling, and therefore fall within the express language of the UCSPA's safe-harbor provision.

The FDA imposes exhaustive restrictions on prescription labeling and advertising. *See* 21 C.F.R. §§ 201.56, 201.57, 202.1(l). A manufacturer may sell a medication only after the FDA has approved it as "safe and effective." The FDA makes the decision to approve a medication for a particular use (or "indication") after reviewing clinical data that establishes the medication's safety and effectiveness. 21 U.S.C. § 355. The FDA also approves the "labeling," a lengthy technical document intended to inform healthcare professionals of the medication's benefits, risks, approved uses, and instructions for use, among other information. *See* 21 C.F.R. §§ 201.56. The FDA can require a manufacturer to change a medication's labeling, and the manufacturer is limited in its ability to change labeling without FDA approval. A manufacturer may not change the approved indications unless instructed by the FDA, and may unilaterally add or strengthen warning information or dosage and administration instructions only when those changes are based on

"newly acquired information." *See lc Id.* § 314.70(c)(6)(iii) ("Changes Being Effected" ("CBE") regulation); *id.* § 314.3(b) (defining "newly acquired information").

In addition to labeling, the FDA's regulatory authority extends to prescription medication promotional activity. Indeed, FDA regulations define "labeling" expansively to include "virtually all communication with medical professionals" about a medication. *Del Valle v. PLIVA, Inc.*, 2011 WL 7168620, at *4 (S.D. Tex. Dec. 21, 2011), *R. & R. adopted sub nom. Del Valle v. Qualitest Pharm. Inc.*, 2012 WL 2899406 (S.D. Tex. June 22, 2012), *aff'd sub nom. Lashley v. Pfizer, Inc.*, 750 F.3d 470 (5th Cir. 2014). Most significantly, a manufacturer must submit specimens of each "branded" advertisement for FDA review at the time of initial publication of the advertisement. 21 C.F.R. § 314.81(b)(3)(i). In this context, "branded" means an advertisement that mentions a specific product—such as OxyContin—by name. Although Purdue never marketed OxyContin directly to patients ("direct-to-consumer" or "DTC" ads), the FDA also would have required Purdue to submit any branded advertisement for review before dissemination to the public. And if a manufacturer deviates from the FDA-approved labeling without permission, or markets its products in a way that is not consistent with the FDA-approved labeling, the FDA has a wide range of enforcement tools at its disposal, including legal actions to declare the product "misbranded," to remove the product from the market or require corrective statements, or to recover fines.

In this case, it is undisputed that at all relevant times, Purdue's FDA-approved opioid medications were accompanied by FDA-approved labeling. When approving Purdue's opioids and their labeling, the FDA found "substantial evidence that the drug will have the effect it purports or is represented to have" and that the medication is safe and effective to treat chronic pain. 21 U.S.C. § 355(d); *see also In re Schering Plough Corp. Intron/Temodar Consumer Class Action*, 678 F.3d 235, 239 (3d Cir. 2012) ("To obtain FDA approval, drug companies generally must submit

evidence from clinical trials and other testing that evaluate the drug's risks and benefits and demonstrate that it is safe and effective for all of the indications 'prescribed, recommended, or suggested' on the drug's label." (quoting 21 U.S.C. § 355(d))).

Moreover, the FDA specifically approved Purdue's opioid medications as safe and effective for the long-term treatment of chronic non-cancer pain. *See* OxyContin Labeling, § 1 (*Indications and Usage*), attached as **Exhibit F**. At the same time, the FDA specifically approved the risk information in the labeling for these medications, including, most notably, a prominent "black box warning," the most serious type of warning that the FDA mandates. *See* 21 C.F.R. § 201.57(c)(1). This informs healthcare professionals:

Addiction, Abuse, and Misuse

> **OXYCONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.**

See OxyContin Labeling, **Exhibit F**. The labeling discloses in detail the risks of addiction, abuse, misuse, overdose, and death, and also emphasizes the need for prescribers to monitor and counsel patients on proper opioid use. The labeling also informs healthcare professionals of the FDA-mandated Risk Evaluation and Mitigation Strategy ("REMS"). The FDA requires this REMS "[t]o ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse." OxyContin Labeling § 5.2. The REMS requires Purdue to "make REMS-compliant education programs available to healthcare providers." *Id.*

The Division's claims rest on the premise that Purdue "over-promoted" its opioids by marketing them for the long-term treatment of chronic non-cancer pain, or that Purdue somehow hid the well-known risks of addiction and abuse, even though at all times the labeling specifically and prominently warned of those risks. The Division's claims also criticize promotional activity

consistent with the FDA-approved labeling and marketing pieces that were submitted to the FDA for review at the time of use. As explained above, however, the FDA "specifically permitted" this promotional activity, and the UCSPA therefore does not apply to that conduct. UTAH CODE ANN. § 13-11-22(1).

The Division's claims also must be dismissed because they impermissibly conflict with federal law. The Supremacy Clause of the United States Constitution establishes that federal law "shall be the supreme law of the land." U.S. CONST. art. VI, § 1, cl. 2. When it is impossible simultaneously to comply with federal-law and state-law obligations, federal law preempts the conflicting state law. *Arizona v. United States*, 567 U.S. 387, 399 (2012). Federal law therefore preempts any state-law claim that would require a pharmaceutical manufacturer to make statements about safety or efficacy that are inconsistent with what the FDA has required after it evaluated the available data. *See, e.g.*, *Cerveny v. Aventis, Inc.*, 855 F.3d 1091, 1105 (10th Cir. 2017).[12]

Here, the Division's central premise—that Purdue violated the UCSPA when it marketed and sold opioid medications for long-term treatment of chronic non-cancer pain—impermissibly conflicts with the FDA's approval of Purdue's opioids for precisely that use.[13] Indeed, the FDA specifically studied and ***rejected*** the same criticisms raised by the Division in this Agency Action.

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[12] *See also, e.g.*, *Guilbeau v. Pfizer, Inc.*, 880 F.3d 304, 317 (7th Cir. 2018); *Rheinfrank v. Abbott Labs., Inc.*, 680 F. App'x 369, 385 (6th Cir. 2017); *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 42-43 (1st Cir. 2015); *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 662-63 (S.D.N.Y. 2017); *Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1173-74 (S.D. Cal. 2016); *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1276-77 (W.D. Okla. 2011).

[13] It is no answer that Purdue could avoid the conflict if it stopped selling or marketing its products for FDA-approved uses. The United States Supreme Court rejected this "stop-selling" rationale as "no solution" because it "would render impossibility preemption a dead letter." *Mutual Pharma. Co., Inc., v. Bartlett*, 570 U.S. 472, 475 (2013).

The Division alleges that Purdue "disseminated misstatements through multiple channels, representing opioids as beneficial in treating chronic pain long-term," despite "the lack of evidence that OxyContin was safe and effective long-term." (Citation ¶¶ 16, 148.) ***The FDA did not agree***. In 2013, the FDA ***denied*** a request to modify the approved indication to exclude long-term use for chronic non-cancer pain. In response to a 2012 Citizen Petition filed by Physicians for Responsible Opioid Prescribing, the FDA concluded that the scientific evidence supports the use of extended release, long-acting opioids for the treatment of chronic non-cancer pain. *See Cerveny*, 855 F.3d at 1105 ("[T]he rejection of a citizen petition may constitute clear evidence that the FDA would have rejected a manufacturer-initiated change to a drug label.").[14] The FDA also did not require revision of the labeling to include additional risk information regarding a supposed lack of evidence in support of treating chronic pain with opioids. Instead, the FDA "determined that limiting the duration of use for opioid therapy to 90 days is not supportable."[15]

The Division cannot now use state law to second-guess or attack the FDA's determinations. Federal law preempts the Division's state-law claims, which are based on the marketing of Purdue's medications for their FDA-approved uses, including for the long-term treatment of chronic non-cancer pain.

B. The Division's Claims Fail Because More Specific Regulatory Schemes Govern the Alleged Conduct.

The Division's claims also cannot be brought under the UCSPA because more specific laws govern the alleged conduct. *See Berneike v. CitiMortgage, Inc.*, 708 F.3d 1141, 1150 (10th Cir. 2013) ("[A] UCSPA claim is barred when the complained-of conduct [is] governed by other, more specific law."); *accord Carlie v. Morgan*, 922 P.2d 1, 6 (Utah 1996). This is true whether

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[14] *See* September 2013 letter from FDA to Andrew Kolodny, MD, President of Physicians for Responsible Opioid Prescriptions at 10–11 (Sept. 10, 2013), attached as **Exhibit G**.

[15] *Id.* at 14.

the more specific statute is state or federal. *See, e.g.*, *West v. C.J. Prestman Co.*, No. 16-75, 2017WL 4621611, at *7 (D. Utah Oct. 13, 2017); *Burnett v. Mortg. Elec. Reg. Sys., Inc.*, No. 09-69, 2009 WL 3582294, at *4–5 (D. Utah Oct. 27, 2009). For example, in *Thomas v. Wells Fargo Bank, N.A.*, No. 13-686, 2014 WL 657394 (D. Utah Feb. 20, 2014), the plaintiff alleged that after her mother filed for bankruptcy, the defendant placed her mother's delinquent account in the plaintiff's name, and non-party credit reporting agencies then reported the delinquency on the plaintiff's credit report. *Thomas*, 2014 WL 657394, at *1. Because the Fair Credit Reporting Act ("FCRA") "places duties on furnishers of credit information," however, the court dismissed the UCSPA claims even though the FCRA does not provide a private cause of action against furnishers. *Id.* at *3.

Purdue's opioid medications are among the most heavily regulated prescription medications on the market. In fact, federal and state law comprehensively regulate the ***entire field*** of alleged conduct on which the Division's claims are based, including the manufacture, labeling, advertisement, physician education, distribution, prescription, and dispensation limitations related to opioid medications. *See, e.g.*, 21 C.F.R. §§ 201.56, 201.57, 202.1(l); UTAH CODE ANN. § 58-37-6(2)(a)(i).

As explained above, federal law imposes exhaustive restrictions on prescription labeling and advertising. *See* 21 C.F.R. §§ 201.56, 201.57, 202.1(l). Utah law requires that all prescription medications distributed within the state must comply with certain federal labeling requirements, UTAH CODE ANN. § 58-37-7(1), and must be accompanied by specific FDA-approved warnings of the risks of overdose and addiction, *id.* § 58-37-7(4). Utah law further requires manufacturers and distributors to register with the DEA. UTAH ADMIN. CODE R156-37-305, 156-37-502(9). Additionally, the federal Controlled Substances Act governs the legal distribution of Schedule II

controlled substances such as Purdue's opioid medications, and requires the United States Attorney General to consider, among other things, the "maintenance of effective controls against diversion of" controlled substances. 21 U.S.C. § 823(a)(1).

Utah also imposes restrictions on the distribution and dispensing of opioids. Specifically, Purdue's opioid medications can only be prescribed by a licensed healthcare practitioner, and practitioners must take educational courses on opioid medications. UTAH CODE ANN. § 58-37-6.5(6)(d). Prescribers have a legal duty to know the risks associated with medications they prescribe and are obligated to use their independent medical judgment, training, expertise, and evaluation of the specific patient before writing a prescription. *See Schaerrer v. Stewart's Plaza Pharm., Inc.*, 2003 UT 43, ¶¶ 20–22, 79 P.3d 922; *see also Downing v. Hyland Pharm.*, 2008 UT 65, ¶ 7, 194 P.3d 944. Utah regulations further prohibit a practitioner from "prescrib[ing] or administer[ing] a controlled substance without taking into account the drug's potential for abuse, the possibility the drug may lead to dependence, the possibility the patient will obtain the drug for a nontherapeutic use or to distribute to others, and the possibility of an illicit market for the drug." UTAH ADMIN. CODE R156-37-603(2). The Utah Department of Health instructs prescribers to undertake a "comprehensive evaluation . . . before initiating opioid treatment for chronic pain," including "screen[ing] for risk of abuse or addiction," in recognition of the fact that "[m]edicine is practiced one patient at a time and each patient is unique with individual needs and vulnerabilities."[16] Finally, a violation of these statutes and regulations can result in a host of specific remedies for the State, including criminal penalties, license revocation, and cease-and-desist letters. UTAH CODE ANN. §§ 58-1-401, 58-37-8; UTAH ADMIN. CODE R156-37-401.

[16] UTAH DEP'T OF HEALTH, UTAH CLINICAL GUIDELINES ON PRESCRIBING OPIOIDS FOR TREATING PAIN 2–3 (2010), *available at* http://www.health.utah.gov/prescription/pdf/guidelines/final.04.09opioidGuidlines.pdf.

In sum, because more specific state and federal laws "place duties on" manufacturers, distributors, dispensers, and prescribers regarding the supply, marketing, and dispensation of Purdue's medications, the Division's UCSPA claims are not cognizable and should be dismissed.

C. The Division Cannot Pursue Statutory Remedies For Past Conduct In This Action.

The Division cannot pursue claims for alleged past violations within an administrative proceeding. Prior to May 18, 2018, the Division could issue administrative citations only to those persons presently "engaged in violating" the UCSPA. UTAH CODE ANN. § 13-2-6(3) (2017). Accordingly, the Division's jurisdiction to issue a citation extended only to persons actively "violating [the USCPA]." *Id*. § 13-2-6(4)(a) (2017). It was not until May 2018 that the Utah Legislature amended § 13-2-6, authorizing the Division, for the first time, to issue a citation against a supplier who "***has violated*** or is violating" the USCPA. *Id*. § 13-2-6(3), (4) (2018) (emphasis added). Because Purdue stopped marketing its opioid medications by February 2018, however, Purdue's right not to be subjected to an administrative citation for past violations of the UCSPA vested before the amendment took effect in May 2018.

Moreover, the 2018 amendment cannot be applied retroactively. "A provision of the Utah Code is not retroactive, unless the provision is expressly declared to be retroactive." UTAH CODE ANN. § 68B-3-3; *accord Beaver Cty. v. Utah State Tax Comm'n*, 2010 UT 50, ¶ 10, 254 P.3d 158. In the absence of such an express retroactive effect, a statute cannot apply retroactively unless it "changes only procedural law by providing a different mode or form of procedure for enforcing substantive rights without enlarging or eliminating vested rights." *Evans & Sutherland Computer Corp. v. Utah State Tax Comm'n*, 953 P.2d 435, 437–38 (Utah 1997) (internal quotation marks omitted). An amendment "should not be applied in a retroactive manner to deprive a party of his rights or impose greater liability upon him." *Rocky Mountain Thrift Stores, Inc. v. Salt Lake City*

Corp., 784 P.2d 459, 461–62 (Utah 1989) (internal quotation marks omitted) (cited in *Gressman v. State*, 2013 UT 63, 323 P.3d 998).

Here, the 2018 amendment does not "provid[e] a different mode or form of procedure for enforcing substantive rights." *See Evans*, 953 P.2d at 438 (allowing for *de novo* review of Tax Commission decisions); *Due South, Inc. v. Department of Alcoholic Beverage Control*, 2008 UT 71, ¶¶ 12–14, 197 P.3d 982 (standard of review); *Heartwood Home Health & Hospice LLC v. Huber*, 2016 UT App 183, ¶ 10 n.3, 382 P.3d 1074 (time for appeal). Rather, applying the 2018 amendment retroactively would revive administrative claims against Purdue that were extinguished as of February 2018. *See Garfield Cty. v. United States*, 2017 UT 41, ¶ 72, 424 P.3d 46 ("[O]nce a party acquires a defense based upon an expired statute of limitations, that defense cannot be impaired or affected by subsequent legislation extending the limitation period." (internal quotation marks and alterations omitted)). Purdue's substantive right to be free of liability for past conduct in administrative proceedings—which, as described above, provide significantly fewer due process protections than a civil action—vested in February 2018. The claims related to past conduct therefore are not actionable, and the claims related to present or ongoing conduct are mooted by the fact that Purdue discontinued marketing its opioid medications more than a year ago. The Division's claims must be dismissed.

D. The Division Cannot Bring "Unconscionability" Claims in this Administrative Proceeding.

Under the plain terms of the statute, a claim for unconscionable acts or practices cannot be brought in an administrative proceeding. UTAH CODE ANN. §13-11-5. The statute provides that the necessary determination of the "unconscionability of an act or practice is a question of law ***for the court***," *id.* §13-11-5(2) (emphasis added), and that "***the court***" shall consider certain specified circumstances in making such a determination. *Id.* §13-11-5(3) (emphasis added). Under the Utah

Administrative Procedures Act, an "adjudicative proceeding," like the present one, is "an agency action or proceeding." *Id.* §63G-4-103(1)(a). And an "agency" expressly "does not mean . . . the courts." *Id.* §63G-4-103(1)(b). The statute thus reserves to a court of law any decision about unconscionability. The Division's allegations that Purdue engaged in "unconscionable acts or practices" must be dismissed.

E. The UCSPA Does Not Permit Liability for Omissions.

The UCSPA imposes liability on a supplier if it "indicates" something false or deceptive related to a consumer transaction, not if it fails to indicate (or omits) something. *See* UTAH CODE ANN. §§ 13-11-4(2). This language imposes reasonable limitations on the scope of the UCSPA, which carries with it the specter of significant statutory penalties and attorneys' fees. Accordingly, the Division's claims should be dismissed insofar as they assert that fines should be imposed based on alleged "omissions."

III. THE DIVISION FAILS TO STATE A CLAIM FOR RELIEF.

Even if the Division's claims were procedurally proper and authorized by federal and state law, they nonetheless fail as a matter of law.

A. The Division's Claims Fail Because Prescription Medications Are Not "the Subject of a Consumer Transaction" as a Matter of Law.

The UCSPA imposes liability only for deceptive or unconscionable acts "by a supplier in connection with a consumer transaction." UTAH CODE ANN. §§ 13-11-4(1), 13-11-5(1). A "consumer transaction" is "a sale, lease . . . or other . . . disposition of goods, services, or other property, both tangible and intangible . . . to, or apparently to, a person for . . . primarily personal, family, or household purposes." *Id.* § 13-11-3(2)(a). Numerous courts interpreting substantially similar statutes have held, however, that prescription medications and medical devices are ***not*** sold for "primarily personal, family, or household purposes." *Latimer v. Medronic, Inc.*, No 2014-cv-

245871, 2015 WL 5222644, at *11 n.6 (Ga. Super. Ct. Sept. 4, 2015); *accord Aston v. Johnson & Johnson*, 248 F. Supp. 3d 43, 57 (D.D.C. 2017); *Kanter v. Warner-Lambert Co.*, 99 Cal. App. 4th 780, 797–98 (Cal. Ct. App. 2002).[17] This is because these products "are not directly available to the general public, but require a physician's prescription." *Latimer*, 2015 WL 5222644, at *11 n.6; *see also* UTAH CODE ANN. § 58-17b-617(2)(b) (controlled substances may be sold or provided in Utah "only . . . upon the issuance of an order or request by a person appropriately licensed under state and federal law to sell, prescribe, administer, or conduct research with prescription drugs"); 21 C.F.R. §§ 1306.11, 1306.03(a)(1). Similarly, Purdue never used branded prescription opioid marketing to patients; the claimed marketing misrepresentations went to ***doctors***, who are not the consumers the UCSPA was designed to protect.

Because Purdue's FDA-approved medications are not the subject of "consumer transactions," the Division's claims fail.

B. The Division Fails to Allege Causation.

The Division's claims under the UCSPA also fail because the Division does not even allege a causal link between the alleged misrepresentations and the harm alleged. The Division alleges that Purdue "helped cultivate a narrative that . . . paved the way for increased prescribing of opioids for chronic pain." (Citation ¶ 16.) The Division then describes a parade of harms—including increased opioid prescription and hospitalization rates, and burgeoning healthcare costs—that the Division alleges, in a conclusory fashion, were caused by Purdue's conduct. (*Id.* ¶ 28.)

[17] *See also, e.g.*, *Jasper v. MusclePharm Corp.*, No. 14-2881, 2015 WL 2375945, at *5–6 (D. Colo. May 15, 2015); *Reeves v. PharmaJet, Inc.*, 846 F. Supp. 2d 791, 798 n.2 (N.D. Ohio 2012); *In re Minn. Breast Implant Litig.*, 36 F. Supp. 2d 863, 876 (D. Minn. 1998); *Goldsmith v. Mentor Corp.*, 913 F. Supp. 56, 63 (D.N.H. 1995); *Kemp v. Pfizer Inc.*, 835 F. Supp. 1015, 1024–25 (E.D. Mich. 1993); *Cashen v. Johnson & Johnson*, No. MIS-L-002442-18, 2018 WL 6809093, at *9 (N.J. Super. Ct. L. Div. Dec. 24, 2018); *cf. Bhatia v. 3M Co.*, 323 F. Supp. 3d 1082, 1103 (D. Minn. 2018).

The Division itself concedes that it can recover civil penalties only if it shows that alleged misrepresentations caused harm. (*Id.* ¶ 29.) Moreover, as discussed above, a UCSPA claim depends on a showing that a supplier made a misrepresentation "in connection with" a consumer transaction. UTAH CODE ANN. § 13-11-4. Accordingly, even if the sale of a prescription medication were a "consumer transaction" (which it is not, *see* Part III.A, *supra*), the Division cannot recover statutory penalties for the simple marketing of a product untethered to some specific, identifiable transaction with a consumer of Purdue's product. In short, the Division must allege—and will have to prove—that Purdue made a misrepresentation directed at some particular consumer's transaction or, at the very least, that Purdue's representations actually materially affected a particular consumer transaction—*i.e.*, that a healthcare professional relied on Purdue's representations when she or he made a prescribing decision.

The Division has not alleged cause in fact. First, because only trained and licensed healthcare professionals may prescribe opioid medications to a patient, *see*, *e.g.*, 21 C.F.R. §§ 1306.11, 1306.03(a)(1), Purdue's "marketing campaign" could not have caused the injuries alleged unless it actually deceived a prescriber. Yet, the Division fails to identify any prescribers who actually received Purdue's purported misrepresentations or omissions.

Second, the Division fails to identify any Utah doctor who wrote a medically unnecessary prescription ***because*** of those alleged statements. Instead, the Division broadly contends that Purdue made misrepresentations in advertisements and through Purdue-sponsored speakers and publications. (*See*, *e.g.*, *id.* ¶¶ 33–72, 83, 85, 94–101.) But these allegations are not linked to any particular doctor or prescription, so the Division has failed to plead how the alleged misstatements, most of which were alleged to have occurred more than a decade ago, could have caused specific prescribing decisions to this day.

Third, the Division cannot state a claim simply by pointing to an aggregate increase in prescription rates for opioid medications. An overall increase in prescription rates during certain time periods does not mean that any false statements by Purdue caused those additional prescriptions. *See, e.g.*, *UFCW Loc. 1776 v. Eli Lilly & Co.*, 620 F.3d 121, 133 (2d Cir. 2010) (rejecting market causation theory and holding that "reliance on a misrepresentation made as part of a nationwide marketing strategy 'cannot be the subject of general proof'" (citation omitted)); *Kaufman v. i-Stat Corp*, 754 A.2d 1188, 1195 (N.J. 2000) (emphasizing that "[t]he actual receipt and consideration of any misstatement remains central to the case of any plaintiff seeking to prove that he or she was deceived by the misstatement or omission").

The Division also has not alleged proximate cause—"'that cause which, in natural and continuous sequence, (unbroken by an efficient intervening cause), produces the injury and without which the result would not have occurred.'" *Mitchell v. Pearson Enterprises*, 697 P.2d 240, 245-46 (Utah 1985) (quoting *State v. Lawson*, 688 P.2d 479, 482 & n.3 (Utah 1984)). "When the proximate cause of an injury is left to speculation, the claim fails as a matter of law." *Staheli v. Farmers' Co-Op of Southern Utah*, 655 P.2d 680, 684 (Utah 1982); *see also Ashley Cnty, Ark. v. Pfizer, Inc.*, 552 F.3d 659, 671–72 (8th Cir. 2009) ("Proximate cause seems an appropriate avenue for limiting liability in this context . . . particularly 'where an effect may be a proliferation of lawsuits not merely against these defendants but against other types of commercial enterprises—manufacturers, say, of liquor, anti-depressants, SUVs, or violent video games—in order to address a myriad of societal problems regardless of the distance between the 'causes' of the 'problems' and their alleged consequences.'" (quoting *Dist. of Columbia v. Beretta, U.S.A., Corp.*, 872 A.2d 633, 651 (D.C. 2005))).

Here, Purdue's alleged conduct is too remote from both the transactions and the alleged

harms to be actionable. As discussed above: (1) Purdue's alleged representations and omissions would have to deceive a doctor; (2) that deception would have to cause the doctor to prescribe opioids that she otherwise would not have prescribed; and (3) the doctor would have to ignore the black-box warning included with Purdue's prescription opioid products, which explicitly warn about the risks of abuse and addiction. Indeed, the Division's vague allegations about Purdue's purported influence over third-party doctors and medical professional groups with their own professional obligations, (Citation ¶¶ 33–72, 83, 85, 94–101), which in turn allegedly influenced prescribers' decisions, (*see, e.g.*, *id.* ¶¶ 113–24), add even more remote links to any causal chain.

The causal chain is also too remote for two additional, independent reasons. First, even if Purdue had failed to disclose these risks (which is not the case), that failure would not be "the proximate cause of a patient's injury if the prescribing physician had independent knowledge of the risk that the adequate warning should have communicated." *Ehlis v. Shire Richwood, Inc.*, 367 F.3d 1013, 1016 (8th Cir. 2004) (internal quotations and citation omitted).[18] Healthcare professionals rely on their independent medical judgment, training, experience, and evaluation of the particular patient when deciding whether to issue a prescription. Courts have dismissed claims where, as here, they would "have to delve into the specifics of each physician patient relationship to determine what damages were caused by [the] alleged fraudulent conduct, as opposed to what

[18] *See also Dist. 1199P Health & Welfare Plan v. Janssen, L.P.*, 784 F. Supp. 2d 508, 524 (D.N.J. 2011) ("'[It] is for the prescribing physician to use his own independent medical judgment, taking into account the data supplied to him from the drug manufacturer, other medical literature, and any other source available to him, and weighing that knowledge against the personal medical history of his patient, whether to prescribe a given drug.'"); *Foister v. Purdue Pharma, L.P.*, 295 F. Supp. 2d 693, 708 (E.D. Ky. 2003) ("Even if the patients did not read all of the inserts, their physicians had the ultimate responsibility to do so and to pass that information on to the patients when prescribing OxyContin."); *Koenig v. Purdue Pharma Co.*, 435 F. Supp. 2d 551, 555–56 (N.D. Tex. 2006); *Timmons v. Purdue Pharma Co.*, 2006 WL 263602, at *4 (M.D. Fla. Feb. 2, 2006).

damages were caused by the physician's independent medical judgment." *In re Yasmin & Yaz (Drospirenone) Mktg., Sales Pracs. & Prods. Liab. Litig.*, MDL No. 2100, 2010 WL 3119499, at *7 (S.D. Ill. Aug. 5, 2010).[19] Additionally, patients must decide whether and how to use the medicine, and each patient may respond differently to the medication. *See Labzda v. Purdue Pharma, L.P.*, 292 F. Supp. 2d 1346, 1355 (S.D. Fla. 2003) (the decedent's intentional and recreational misuse of OxyContin—simultaneously with alcohol and numerous other prescriptions and illicit substances—was the proximate cause of his death).

Second, to the extent the Division's request for statutory penalties results from alleged "harm to the State and its agencies," (Citation ¶ 28), the Division's causal chain relies on the intervening criminal acts of third parties, including opioid diversion and abuse of illegal drugs. (*See, e.g.*, *id.* ¶¶ 21–23, 32, 108, 110, 120, 123.) The Division's acknowledgment of the role diversion plays in the opioid abuse crisis renders its causal chain even more remote. *See City of Chicago v. Beretta U.S.A. Corp.*, 821 N.E.2d 1099, 1136 (Ill. 2004) ("[D]efendants' lawful commercial activity, having been followed by harm to person and property caused directly and principally by the criminal activity of intervening third parties, may not be considered a proximate cause of such harm." (quotation mark omitted)); *see also Your-tee v. Hubbard*, 474 S.E.2d 613, 620 (W. Va. 1996) ("[A] willful, malicious, or criminal act breaks the chain of causation."); *Young v. Tide Craft, Inc.*, 270 S.C. 453, 463 (1978) (an intervening criminal act generally "interrupts the foreseeable chain of events" and thus breaks the causal chain between the defendant's act and the

[19] *See also City of Chicago*, 2015 WL 2208423, at *14; *Travelers Indem. Co. v. Cephalon, Inc.*, 620 F. App'x 82, 87 (3d Cir. 2015); *Sidney Hillman Health Ctr. of Rochester v. Abbott Labs.*, 873 F.3d 574, 577 (7th Cir. 2017); *United Food & Commercial Workers Cent. Pa. & Reg'l Health & Welfare Fund v. Amgen, Inc.*, 400 Fed. App'x 255, 257 (9th Cir. 2010); *In re Yasmin & Yaz*, 2010 WL 3119499, at *7–9; *Ironworkers Local Union No. 68 v. AstraZeneca Pharm. LP*, 585 F. Supp. 2d 1339, 1344 (M.D. Fla. 2008).

plaintiff's injury). Furthermore, it would be virtually impossible for the Division to trace any alleged harm back to Purdue's medication, as opposed to other lawful or unlawful opioids, particularly in light of Purdue's small share of the overall market for lawful opioids (currently only 2%, and never more than 4%).

Because the Division has not alleged—and cannot prove—causation as required to succeed on its UCSPA claims, the claims must be dismissed.

C. The Division Has Not Pleaded Facts to Establish that Purdue Controlled the Representations of Third Parties.

Under Utah law, a defendant may only be liable for the conduct of a third party if the third party acts as the defendant's agent. *See Zeese v. Estate of Siegel*, 534 P.2d 85, 88 (Utah 1975). "The burden of establishing agency is upon the party asserting it." *Wardley Corp. v. Welsh*, 962 P.2d 86, 90 (Utah Ct. App. 1998) (quotation omitted). The essential feature of any agency relationship is ***control***—the principal must control both the result achieved by the agency relationship and "the ***manner*** in which the operations are to be carried out." *Sutton v. Miles*, 2014 UT App 197, ¶ 13, 333 P.3d 1279 (quotation mark omitted). Mere financial support of an individual or entity is not enough to establish the necessary control for an agency relationship to exist. *See Gen. Bldg. Contrs. Ass'n, Inc. v. Pennsylvania*, 458 U.S. 375, 395 (1982).[20]

The Division relies on years-old representations by the American Pain Foundation and other third parties in various publications, and by presenters at continuing medical education ("CME") programs. (Citation ¶¶ 33–72, 83, 85, 94–101.) Yet the Division does not allege that Purdue controlled the contents or dissemination of these materials. Rather, the Division claims that

[20] *See also Metro. Dade Cty. v. Glaser*, 732 So.2d 1124, 1125 (Fla. D. Ct. 1999) (per curiam) ("Plaintiffs presented evidence that the County provided OTAC's operating funds and oversaw OTAC's expenditures. However, that was the extent of the County's contact with OTAC. . . . [T]he County had no control or input into any of OTAC's operations or actions, and did not control the outcome of OTAC's activities nor the means used to achieve OTAC's goals." (citation omitted)).

Purdue should be liable because it gave these third parties financial support and "sponsored" some of these publications and CMEs. The Division even alleges that Purdue can be held liable for any "fact" that these third parties omitted—*i.e.*, any and all statements that the Division wishes the authors and presenters had included in their publications and presentations. In other words, the Division seeks to hold Purdue accountable not only for statements made by third parties over whom Purdue has no control, but also for statements those third parties did not make. Holding a supplier liable for the alleged ***omissions*** of third parties it did not control would lead to sprawling litigation that has no basis in the statute or case law. The Division's claims should be dismissed insofar as they rely on representations and omissions made by third parties.

D. The Division Fails to Plead Fraud with Particularity.

Finally, the Division's UCSPA claims must be dismissed for failure to plead with particularity. As explained above, by definition, the Division's claims "arise[] out of allegations of deception, false misrepresentations and omissions," and they "must therefore comply with the specific pleading requirements under Rule 9[(c)] of . . . the Utah Rules of Civil Procedure." *Jackson v. Philip Morris Inc.*, 46 F. Supp. 2d 1217, 1222 (D. Utah 1998). The Division's allegations are sweepingly general, however, and do not identify the particular facts of the allegedly fraudulent representations. (*See, e.g.*, Citation ¶¶ 47, 61, 63, 72, 73, 93.). For example, the Division alleges that Purdue "produced and provided directly to doctors and patients marketing materials that intentionally and fraudulently made similar misstatements," (*id.* ¶ 61), and "sponsored training sessions where doctors were given similar misleading information regarding the risks of opioid addiction." (*Id.* ¶ 63.) These allegations do not come close to meeting Rule 9(c)'s pleading requirements. *Webster*, 2012 UT App 321, ¶ 19.

The Division's failure to plead with particularity is especially problematic because it apparently seeks to impose a penalty for "each instance where Respondents have misrepresented

a material fact or suppressed, concealed, or omitted any material fact regarding the prescription opioids they manufactured or marketed," (Citation ¶174), but fails to identify "each instance" of fraud, let alone the surrounding facts, identity of the speaker, and time and location of the alleged utterance. *Webster*, 2012 UT App 321, ¶ 19. This is a critical omission, for Purdue is not on notice of the specific statements at issue, yet has only six to eight months to complete discovery and prepare a defense to these allegations. At a minimum, the Agency Action and Citation should be dismissed for failure to plead with the required particularity.

CONCLUSION

For the forgoing reasons, the Agency Action and Citation should be dismissed in its entirety.

Dated this 9th day of April, 2019.

SNELL & WILMER L.L.P.

/s/ Elisabeth M. McOmber
Elisabeth M. McOmber
Katherine R. Nichols
Annika L. Jones

Attorneys for Respondents Purdue LP, Purdue Inc., and the Purdue Frederick Company

CERTIFICATE OF SERVICE

I hereby certify that on this the 9th day of April, 2019, I served the foregoing on the parties of record in this proceeding set forth below by delivering a copy thereof by electronic means and U.S. Mail and/or as more specifically designated below, to:

Bruce L. Dibb, Presiding Officer
Administrative Law Judge
Heber M. Wells Building, 2nd Floor
160 East 300 South
Salt Lake City, Utah 84114
bdibb@utah.gov

Robert G. Wing, AAG
Kevin McLean, AAG
Assistant Attorneys General
Utah Attorney General's Office
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pjohnson@ck.law.com
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Attorneys for Respondents Richard Sackler, M.D. and Kathe Sackler, M.D.

Service via hand delivery upon:

Daniel R. S. O'Bannon – Director
Utah Division of Consumer Protection
160 East 300 South, 2nd Floor
Salt Lake City, Utah 84111

/s/ Elisabeth M. McOmber

4831-8472-0787

EXHIBIT A

7TH DISTRICT COURT PRICE
CARBON COUNTY, STATE OF UTAH

STATE OF UTAH vs. PURDUE PHARMA LP
CASE NUMBER 180700055 Miscellaneous

CURRENT ASSIGNED JUDGE
DOUGLAS B THOMAS

PARTIES
Plaintiff - STATE OF UTAH
Represented by: ROBERT G WING
Represented by: KEVIN M MCLEAN
Defendant - PURDUE PHARMA LP
Defendant - PURDUE PHARMA INC
Defendant - PURDUE FREDERICK COMPANY

ACCOUNT SUMMARY
TOTAL REVENUE Amount Due: 50.50
Amount Paid: 50.50
Credit: 0.00
Balance: 0.00
REVENUE DETAIL - TYPE: COMPLAINT - NO AMT S
Fee Waiver Status - Government
Original Amount Due: 360.00
Amended Amount Due: 0.00
Amount Paid: 0.00
Amount Credit: 0.00
Balance: 0.00
Account Adjustments

Date	Amount	Reason
May 31, 2018	-360.00	Government filer

REVENUE DETAIL - TYPE: JURY DEMAND - CIVIL
Fee Waiver Status - Government
Original Amount Due: 250.00
Amended Amount Due: 0.00
Amount Paid: 0.00
Amount Credit: 0.00
Balance: 0.00
Account Adjustments

Date	Amount	Reason
May 31, 2018	-250.00	Government filer

REVENUE DETAIL - TYPE: TELEPHONE/FAX/EMAIL

Amount Due:	28.00
Amount Paid:	28.00
Amount Credit:	0.00
Balance:	0.00

REVENUE DETAIL - TYPE: TELEPHONE/FAX/EMAIL

Amount Due:	22.50
Amount Paid:	22.50
Amount Credit:	0.00
Balance:	0.00

PROCEEDINGS

05-31-18 Filed: Complaint
05-31-18 Case filed
05-31-18 Fee Account created Total Due: 360.00
05-31-18 Fee Account created Total Due: 250.00
05-31-18 Judge DOUGLAS B THOMAS assigned.
05-31-18 Filed: Return of Electronic Notification
06-19-18 Filed return: Summons on Return Waiver of Service upon MARA GONZALEZ, ATTNY FOR DEFENDANT for
Party Served: PURDUE PHARMA LP
Service Type: Personal
Service Date: June 15, 2018
06-19-18 Filed return: Summons on Return upon MARA GONZALEZ, ATTNY FOR DEFENDANT for
Party Served: PURDUE PHARMA INC
Service Type: Personal
Service Date: June 15, 2018
06-19-18 Filed return: Summons on Return upon MARA GONZALEZ, ATTNY FOR DEFENDANT for
Party Served: PURDUE FREDERICK COMPANY
Service Type: Personal
Service Date: June 15, 2018
06-19-18 Filed: Return of Electronic Notification
07-31-18 Filed: Cross-Notice of Deposition of a Representative on Behalf of Defendants Purdue Pharma L.P., Purdue Pharma Inc., and The Purdue Frederick Company Inc.

07-31-18 Filed: Cross-Notice of Deposition of S. Seid as Fact Witness
for Defendants Purdue Pharma L.P., Purdue Pharma Inc., and The
Purdue Frederick Company
07-31-18 Filed: Return of Electronic Notification
10-30-18 Fee Account created Total Due: 28.00
10-30-18 TELEPHONE/FAX/EMAIL Payment Received: 28.00
10-30-18 Fee Account created Total Due: 22.50
10-30-18 TELEPHONE/FAX/EMAIL Payment Received: 22.50
11-14-18 Notice - Notice of Intent for Case 180700055
Notice is hereby given that, due to inactivity, the above entitled matter may be dismissed for lack of prosecution pursuant to Rule 4-103, Code of Judicial Administration. Unless a written statement is received by the court within 20 days of this notice showing good cause why this should not be dismissed, the court will dismiss without further notice.
11-26-18 Filed: Response to Notice of Intent to Dismiss
11-26-18 Filed: Return of Electronic Notification
11-26-18 Note: The case was taken off of OTSC hold
12-14-18 Filed order: Pre-Consolidation Case Management Order
Judge HELPDESK IT
Signed December 13, 2018
01-08-19 Filed order: Minute Entry Regarding Prior Professional
Associations (signed by Judge Mrazik)
Judge HELPDESK IT
Signed January 02, 2019
01-30-19 Filed: Notice of Dismissal
01-30-19 Filed: Return of Electronic Notification
01-30-19 Case Disposition is Dismsd w/o prejudice
Disposition Judge is DOUGLAS B THOMAS

EXHIBIT B

SEAN D. REYES (Bar No. 7969)
Utah Attorney General
SPENCER E. AUSTIN (Bar No. 150)
Chief Criminal Deputy, Utah Attorney General's Office
ROBERT G. WING (Bar No. 4445)
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Attorneys for the State of Utah

SEVENTH JUDICIAL DISTRICT COURT
CARBON COUNTY, UTAH

STATE OF UTAH, Plaintiff, v. **PURDUE PHARMA L.P.**, **PURDUE PHARMA INC.**, and **THE PURDUE FREDERICK COMPANY**, Defendants.	**RESPONSE TO NOTICE OF INTENT TO DISMISS** Case No. 180700055 Judge: Douglas B. Thomas

The State of Utah hereby responds to the Notice of Intent to Dismiss issued by the Court on November 14, 2018. Good cause exists for maintaining this action rather than dismissing it.

In this case, the State seeks relief from Purdue Pharma, L.P., et al., (jointly "Purdue Pharma") for the role Purdue Pharma played in the opioid crisis. This is a matter of substantial

public concern, which the State and Purdue Pharma take seriously. This case is one piece of a mosaic of litigation involving Purdue Pharma, other opioid manufacturers, opioid distributors, and other individuals and entities. Both the State and Purdue Pharma are actively engaged in the process of gathering information, evaluating claims, and pursuing resolution of the dispute underlying this lawsuit, though those activities are not yet evident in this case. The State anticipates this litigation will be vigorously contested. Two events must occur.

1. The process by which the State obtains outside counsel must be completed. Shortly after the State filed this action, it notified Purdue Pharma of two facts. First, the State was about to issue (and subsequently has issued) a Request for Proposals to engage outside counsel for this litigation. Second, once outside counsel was engaged, the State and counsel would determine whether to amend the Complaint. The State would not expect Purdue to answer or otherwise respond to the Complaint until after outside counsel was engaged and a decision about amendment reached. Purdue agreed to this approach.

The State received dozens of responses to its Request for Proposals, has evaluated them, and has interviewed candidates. It expects a contract with outside counsel to issue shortly.

2. On November 9, 2018, Purdue Pharma filed a Motion to Consolidate pursuant to Rule 42 of the Utah Rules of Civil Procedure. In that Motion, Purdue Pharma seeks to consolidate this case for purposes of discovery and pretrial procedures with cases filed by numerous counties and other political subdivisions. Purdue filed its motion jointly with several other entities which are not named in the State's complaint.

That Motion is pending in the Third Judicial District Court in Summit County, Utah and is currently being briefed. *See* Exhibit A, the State's Memorandum Opposing Manufacturer

Defendants' Joint Motion to Consolidate (filed three days ago on November 23, 2018). Once a determination about consolidation is made, the State anticipates this matter will move forward.

The State intends to pursue this matter vigorously and expects that Purdue will defend with equal vigor. Accordingly, the State asks that the matter be maintained and not be dismissed.

Dated this 26th day of November 2018.

SEAN D. REYES
UTAH ATTORNEY GENERAL

/s/ Robert G. Wing
ROBERT G. WING
ASSISTANT ATTORNEY GENERAL
UTAH ATTORNEY GENERAL'S OFFICE

Certificate of Service

I hereby certify that on this 26th day of November 2018 I caused a true and correct copy of the foregoing **Response to Notice of Intent to Dismiss** to be filed with the Court's electronic filing system, resulting in electronic delivery to counsel registered for automatic delivery, and that I sent the foregoing to the following, counsel for Purdue, by electronic mail:

Elisabeth M. McOmber
emcomber@swlaw.com
SNELL & WILMER LLP

Will W. Sachse
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Sheila L. Birnbaum
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DECHERT LLP

SEAN D. REYES
UTAH ATTORNEY GENERAL

/s/ Kevin McLean
Kevin McLean
Assistant Attorney General
UTAH ATTORNEY GENERAL'S OFFICE

EXHIBIT C

Utah Escalates Legal Action Against Purdue Pharma

FOR IMMEDIATE RELEASE
January 30, 2019

UTAH ESCALATES LEGAL ACTION AGAINST PURDUE PHARMA BY NAMING EXECUTIVES AND EXPEDITING STATE'S CLAIMS

State seeks administrative relief for misleading marketing practices by OxyContin producer

SALT LAKE CITY – Today, the Utah Attorney General's Office filed an administrative action against Purdue Pharma L.P., Purdue Pharma Inc., The Purdue Frederick Company, Richard Sackler, M.D., and Kathe Sackler, M.D., as part of the State's efforts to hold accountable the opioid companies and individuals that created and fueled the opioid epidemic throughout Utah.

In the filing, under Utah Code § 13-2-6, the Division of Consumer Protection of the Department of Commerce issued an administrative action, in the form of a citation, against the defendants alleging violations of the Utah Consumer Sales Practices Act. An administrative proceeding allows the State to seek to prove its claims and obtain a judgment, injunctive relief, and civil penalties more promptly than state district court proceedings.

Based on evidence that has emerged over the last year, this administrative action alleges that not only

Purdue, but two of its owners, Richard and Kathe Sackler, participated in Purdue's fraudulent conduct.

"We are committed to achieving the best results for the State of Utah and pursuing all legal avenues appropriate to hold the companies and individuals that created this crisis accountable," said Utah Attorney General Sean Reyes. "After seeing multiple media reports about Purdue retaining restructuring counsel, we decided that filing an administrative action is in the best interest of the people of Utah. This action allows us to expedite legal proceedings against Purdue and the named executives, who we allege incited and participated in the deceptive sales and marketing tactics that ultimately led to an epidemic of prescription opioid abuse in our state."

"The administrative process, which the Division of Consumer Protection regularly uses, will provide prompt and full consideration of the State's claims," added AG Reyes. "Our families, health care professionals, first responders, and law enforcement officers know the urgency of the opioid epidemic. As we recognized when we filed suit, and in the several months since then, we don't have more time to lose. Meanwhile, we are continuing to investigate other potential wrongdoers."

Concurrent with this action, the state dismissed without prejudice the civil litigation it filed against Purdue Pharma in Carbon County last May, which means the State may refile against Purdue Pharma for the same circumstance at a later day. This action will not preclude Utah from filing lawsuits in district court against other defendants.

In addition to today's actions, Utah continues to participate in investigations against other entities. Attorney General Reyes and a bipartisan group of more than 40 other state attorneys general have been aggressively investigating the extent to which entire opioid industry – manufacturers, distributors and pharmacies – engaged in unlawful practices. Purdue Pharma alone faces hundreds of lawsuits by government entities while other investigations remain ongoing. The State of Utah continues to investigate further lawsuits against additional defendants.

In Utah, non-fatal opioid costs to the state are approximately $524 million annually, according to research from the American Enterprise Institute. From 2013 to 2015, Utah ranked 7th highest in the nation for drug overdose deaths.

In May 2018, Attorney General Sean Reyes said, "Purdue Pharma manufactured one of the deadliest combinations in the history of our nation—OxyContin and lies. That lethal cocktail has led to a national public health crisis of epic proportions…. While Purdue's executives got rich, Utah was plunged into a national public health crisis."

# # #

NOTES:

1. A legal briefing on background concerning this matter will be held at 1:30pm and 2:30pm today in the Utah Attorney General's Office. Call Chief of Staff Ric Cantrell at 801-230-9890 for more information.

2. You can review a copy of the administrative action here. The large number of redactions in the document are information subject to a protective order in multi-district litigation which is ongoing in the United State District Court for the Northern District of Ohio. https://attorneygeneral.utah.gov/wp-content/uploads/2019/01/Utah-Admin-Citation-1-30-2019.pdf

3. These administrative claims are not dependent on other counties' or states' lawsuits and will proceed immediately while the district court claims have been stayed. Complex civil litigation takes years. The administrative claims should be adjudicated within 6 months.

Related

Utah Announces Lawsuit Against Purdue Pharma
May 31, 2018
In "Archived Posts"

Utah Opioid Litigation: RFP Findings and Contract
January 11, 2019
In "Recent Posts"

Utah Attorney General Announces Multistate Opioid Investigation
September 19, 2017
In "Recent Posts"

This entry was posted in Recent Posts and tagged Attorney General's Office, OxyContin, Purdue Pharma on January 30, 2019.

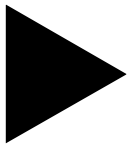
EXHIBIT D

Utah Attorney General drops lawsuit, files administrative action against Purdue over opioid crisis

POSTED 4:21 PM, JANUARY 30, 2019, BY BEN WINSLOW, *UPDATED AT 09:35PM, JANUARY 30, 2019*

FOX 13

Attorney General drops opioid lawsuit



SALT LAKE CITY -- Utah's Attorney General has dismissed a lawsuit filed against Purdue Pharma over the opioid crisis.

Instead, the state will pursue an administrative action against the pharmaceutical giant through Utah's Division of Consumer Protection.

"We believe it will give us the opportunity to streamline this case and get to a judgment much more rapidly than if we had stayed in state district court," Utah Attorney General Sean Reyes told reporters on Wednesday.

The administrative action was filed Wednesday against Purdue and two of its owners, Richard and Kathle Sackler. It seeks to hold them responsible for Utah's portion of the opioid crisis, accusing Purdue of overmarketing opoids and misstating the addiction risks.

RELATED STORY

Odds of dying from accidental opioid overdose in the US surpass those of dying in car accident

Reyes, who faced pressure to bring a lawsuit from Utah legislative leaders, defended his decision to drop the lawsuit and pursue administrative action.

"We felt like it would take far too long to get to a judgment, especially given some circumstances that have come to light more recently," he said.

The attorney general cited reports that Purdue was seeking to restructure itself and suggested it may be a way to avoid big payouts in any litigation that went against the pharmaceutical giant. Numerous counties have filed their own lawsuits against pharmaceutical companies, but Reyes said the manufacturers have sought to consolidate them into one.

Under an administrative action in Utah, the average case time is 180 days or less and Purdue could face as much as $2,500 per violation. But the litigation is also stripped down, meaning there wouldn't be the same volume of evidence or witnesses presented in a state courtroom.

In a statement to FOX 13, Purdue denied the accusations and said the state was trying to substitute its judgment for that of the FDA.

RELATED STORY

For the first time in a long time, there's good news on Utah's battle against the opioid epidemic

"We share the state's concerns about the opioid crisis. While Purdue Pharma's opioid medicines account for less than 2% of total prescriptions, we will continue to work collaboratively with the state toward bringing meaningful solutions forward to address this public health challenge," the company said.

Dr. Jennifer Plumb, who heads Utah Naloxone and advocates for those dealing with opioid addiction, said she supported the attorney general's decision.

"Ultimately what I want is not only for there to be resources for people desperately struggling and the state to help them, but I want accountability for wrongdoing," she said. "Just because you have millions and billions of dollars does not mean it's OK that you lied, you deceived and you convinced a whole lot of people along the way that you weren't doing that."

RELATED STORIES

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EXHIBIT E

Utah 'streamlines' legal fight against OxyContin maker, names family in filing

Utah attorneys allege Purdue Pharma lied about risk of addiction

By **Katie McKellar** **@KatieMcKellar1**
Published: January 30, 2019 3:27 pm
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SALT LAKE CITY — In an effort to "streamline" Utah's lawsuit against Purdue Pharma, the maker of OxyContin and other opioids, the Utah Attorney General's Office has a new strategy.

The office on Wednesday filed an administrative action in the form of a citation against Purdue — while also explicitly naming the companies' owners, Richard and Kathe Sackler — to expedite court proceedings in Utah's efforts to "hold accountable the opioid companies and individuals that created and fueled the opioid epidemic throughout Utah," the attorney general's office said in a statement.

The filing comes after evidence has emerged over the past year, leading Utah attorneys to allege that not only Purdue, but two of its owners participated in fraud.

Prosecutors allege that Purdue violated state consumer protection laws, misrepresented the risk of addiction, and falsely claimed doctors and patients could increase dosages without risk.

"We are committed to achieving the best results for the state of Utah and pursuing all legal avenues appropriate to hold the companies and individuals that created this crisis accountable," Attorney General Sean Reyes said.

After seeing multiple media reports about Purdue retaining restructuring counsel — along with other indications the company could be considering bankruptcy — Utah Attorney General Sean Reyes said his team decided that filing an administrative action would be "in the best interest of the people of Utah."

An administrative filing allows the state to seek to prove its claims and obtain a judgment, injunctive relief and civil penalties more promptly than state district court proceedings, he said. The attorney general's office estimates the administrative filing could be adjudicated within 180 days, rather than years in the court.

"This action allows us to expedite legal proceedings against Purdue and the named executives, who we allege incited and participated in the deceptive sales and marketing tactics that ultimately led to an epidemic of prescription opioid abuse in our state," Reyes said.

Along with the new filing, the state dismissed without prejudice the civil lawsuit Utah filed against Purdue Pharma in Carbon County last May, meaning the state may refile against Purdue Pharma in the future, according to Reyes' office.

At the time of the lawsuit's filing, Reyes said Purdue Pharma "manufactured one of the deadliest combinations in the history of our nation — OxyContin and lies."

"That lethal cocktail has led to a national public health crisis of epic proportions," Reyes said. "While Purdue's executives got rich, Utah was plunged into a national public health crisis."

The previous complaint sought millions of dollars in damages and a court order stemming the flow of opioids into the state.

Reyes said his office is "confident" in the approach to put new "pressure" on defendants to be "more reasonable." He said the "door is still open" for a settlement, but his office isn't currently engaging in settlement discussions with Purdue or its owners.

Reyes said the aim is not just to get a "payout."

"We want to send a message and we want the practice and behaviors to stop," he said.

The administrative process, which the Division of Consumer Protection regularly uses, will provide "prompt and full consideration of the state's claims," Reyes said.

"Our families, health care professionals, first responders and law enforcement officers know the urgency of the opioid epidemic," he said. "As we recognized when we filed suit, and in the several months since then, we don’t have more time to lose."

Attorneys allege in court documents that Purdue and the Sackler family have "intentionally engaged, and continue to engage, in an aggressive marketing campaign to overstate the benefits and misstate and conceal the risks of treating chronic pain with opioids in order to increase their profits."

Purdue Pharma officials in a statement issued Wednesday said they "vigorously deny the allegations" in Utah's filing.

"We share the state's concerns about the opioid crisis," Purdue officials said in the statement. "While Purdue Pharma's opioid medicines account for less than 2 percent of total prescriptions, we will continue to work collaboratively with the state toward bringing meaningful solutions forward to address this public health challenge."

Purdue officials said Utah's filing "disregards basic facts" about Purdue's opioid medications, including that the Federal Drug Administration approved OxyContin and other Purdue medications as "safe and effective for their intended use." Additionally, the FDA approved a reformulated version of OxyContin, which Purdue developed in order to "deter abuse," the statement said.

Meanwhile, Reyes said his office is continuing to investigate other "potential wrongdoers."

Reyes and a group of more than 40 other state attorneys general have been investigating the extent to which the entire opioid industry — manufacturers, distributors and pharmacies — are accused of engaging in unlawful practices.

Purdue Pharma alone faces hundreds of lawsuits by government entities while other investigations remain ongoing.

The filing comes as legal pressure continues to mount on the Sackler family. Last week, a legal filing in Massachusetts accused the Sacklers and other executives of seeking to push prescriptions of the drug and downplay its risks, the Associated Press reported.

Members of the family are also defendants in a lawsuit brought by New York's Suffolk County. Few, if any, other governments have sued the family so far — but Utah's administrative filing Tuesday adds to the pressure.

Contributing: Ladd Egan

EXHIBIT F

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OXYCONTIN® safely and effectively. See full prescribing information for OXYCONTIN.

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)**
- **Accidental ingestion of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone. (5.3)**
- **Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	09/2018
Warnings and Precautions (5.2)	09/2018

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

OXYCONTIN is an opioid agonist indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

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

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow tablets intact and not to cut, break, chew, crush, or dissolve tablets (risk of potentially fatal dose). (2.1, 5.1)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in mouth. (2.1, 5.10)
- Do not abruptly discontinue OXYCONTIN in a physically dependent patient. (2.9)

Adults: For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.2, 2.3, 2.5)

Pediatric Patients 11 Years of Age and Older

- For use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OXYCONTIN. (2.4)
- See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.4, 2.5)

Geriatric Patients: In debilitated, opioid non-tolerant geriatric patients, initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.7, 8.5)

Patients with Hepatic Impairment: Initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.8, 8.6)

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

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. (3)

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

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

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

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OXYCONTIN in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OXYCONTIN in patients with impaired consciousness or coma. (5.10)
- Risk of Obstruction in Patients who have Difficulty Swallowing or have Underlying GI Disorders that may Predispose them to Obstruction: Consider use of an alternative analgesic. (5.11)

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

Most common adverse reactions (incidence >5%) were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- CNS Depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If co-administration is required and the decision to begin OXYCONTIN is made, start with 1/3 to 1/2 the recommended starting dosage, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.6, 5.6, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OXYCONTIN if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OXYCONTIN because they may reduce analgesic effect of OXYCONTIN or precipitate withdrawal symptoms. (5.14, 7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of morphine. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

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

Pregnancy: May cause fetal harm. (8.1)
Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OXYCONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of

neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

Cytochrome P450 3A4 Interaction
The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.5), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of OXYCONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

OXYCONTIN is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

- OXYCONTIN is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Adult patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OXYCONTIN and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

Instruct patients to swallow OXYCONTIN tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Instruct patients not to pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Warnings and Precautions (5.11)]*. Cutting, breaking, crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

OXYCONTIN is administered orally every 12 hours.

2.2 Initial Dosage in Adults who are not Opioid-Tolerant

The starting dosage for patients who are not opioid tolerant is OXYCONTIN 10 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.3)]*.

2.3 Conversion from Opioids to OXYCONTIN in Adults

Conversion from Other Oral Oxycodone Formulations to OXYCONTIN
If switching from other oral oxycodone formulations to OXYCONTIN, administer one half of the patient's total daily oral oxycodone dose as OXYCONTIN every 12 hours.

Conversion from Other Opioids to OXYCONTIN
Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There are no established conversion ratios for conversion from other opioids to OXYCONTIN defined by clinical trials. Initiate dosing using OXYCONTIN 10 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioids.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to OXYCONTIN.

Conversion from Methadone to OXYCONTIN
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to OXYCONTIN
Treatment with OXYCONTIN can be initiated after the transdermal fentanyl patch has been removed for at least 18 hours. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN, as there is limited documented experience with this conversion.

2.4 Initial Dosage in Pediatric Patients 11 Years and Older

The following dosing information is for use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least five consecutive days. For the two days immediately preceding dosing with OXYCONTIN, patients must be taking a minimum of 20 mg per day of oxycodone or its equivalent. OXYCONTIN is not appropriate for use in pediatric patients requiring less than a 20 mg total daily dose. Table 1, based on clinical trial experience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OXYCONTIN.

Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. Therefore, a conservative approach is advised when determining the total daily dosage of OXYCONTIN. It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to

overestimate the 24-hour oral oxycodone requirements and manage an adverse reaction due to an overdose.

Consider the following when using the information in Table 1.

- This is not a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion from one of the listed oral opioid analgesics to OXYCONTIN.
- The table cannot be used to convert from OXYCONTIN to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose.
- The formula for conversion from prior opioids, including oral oxycodone, to the daily dose of OXYCONTIN is mg per day of prior opioid x factor = mg per day of OXYCONTIN. Divide the calculated total daily dose by 2 to get the every-12-hour OXYCONTIN dose. If rounding is necessary, always round the dose down to the nearest OXYCONTIN tablet strength available.

Table 1: Conversion Factors When Switching Pediatric Patients 11 Years and Older to OXYCONTIN

Prior Opioid	Conversion Factor	
	Oral	Parenteral*
Oxycodone	1	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Morphine	0.5	3
Tramadol	0.17	0.2

*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.

Step #1: To calculate the estimated total OXYCONTIN daily dosage using Table 1:

- For pediatric patients taking a single opioid, sum the current total daily dosage of the opioid and then multiply the total daily dosage by the approximate conversion factor to calculate the approximate OXYCONTIN daily dosage.
- For pediatric patients on a regimen of more than one opioid, calculate the approximate oxycodone dose for each opioid and sum the totals to obtain the approximate OXYCONTIN daily dosage.

- For pediatric patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Step #2: If rounding is necessary, always round the dosage down to the nearest OXYCONTIN tablet strength available and initiate OXYCONTIN therapy with that dose. If the calculated OXYCONTIN total daily dosage is less than 20 mg, there is no safe strength for conversion and do not initiate OXYCONTIN.

Example conversion from a single opioid (e.g., hydrocodone) to OXYCONTIN: Using the conversion factor of 0.9 for oral hydrocodone in Table 1, a total daily hydrocodone dosage of 50 mg is converted to 45 mg of oxycodone per day or 22.5 mg of OXYCONTIN every 12 hours. After rounding down to the nearest strength available, the recommended OXYCONTIN starting dosage is 20 mg every 12 hours.

Step #3: Close observation and titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to OXYCONTIN. [*see Dosage and Administration (2.5)]* for important instructions on titration and maintenance of therapy.

There is limited experience with conversion from transdermal fentanyl to OXYCONTIN in pediatric patients 11 years and older. If switching from transdermal fentanyl patch to OXYCONTIN, ensure that the patch has been removed for at least 18 hours prior to starting OXYCONTIN. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN.

If using asymmetric dosing, instruct patients to take the higher dose in the morning and the lower dose in the evening.

2.5 Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older

Individually titrate OXYCONTIN to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OXYCONTIN to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and adverse reactions, as well as monitoring for the development of addiction, abuse and misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of OXYCONTIN or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain

before increasing the OXYCONTIN dosage. Because steady-state plasma concentrations are approximated in 1 day, OXYCONTIN dosage may be adjusted every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline for pediatric patients 11 years and older, the total aily oxycodone dosage usually can be increased by 25% of the current total daily dosage. As a guideline for adults, the total daily oxycodone dosage usually can be increased by 25% to 50% of the current total daily dosage, each time an increase is clinically indicated.

2.6 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin OXYCONTIN, start with one-third to one-half the recommended starting dosage of OXYCONTIN, consider using a lower dosage of the concomitant CNS depressant, and monitor patients for signs of respiratory depression, sedation, and hypotension *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

2.7 Dosage Modifications in Geriatric Patients who are Debilitated and not Opioid-Tolerant

For geriatric patients who are debilitated and not opioid tolerant, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage cautiously *[see Use in Specific Populations (8.5]*.

2.8 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage carefully. Monitor for signs of respiratory depression, sedation, and hypotension *[see Use in Specific Populations, (8.6), Clinical Pharmacology (12.3)]*.

2.9 Discontinuation of OXYCONTIN

When the patient no longer requires therapy with OXYCONTIN, taper the dosage gradually, by 25% to 50% every 2 to 4 days, while monitoring for signs and symptoms of withdrawal. If a patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OXYCONTIN *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.

- 10 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
- 15 mg film-coated extended-release tablets (round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other)
- 20 mg film-coated extended-release tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
- 30 mg film-coated extended-release tablets (round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other)
- 40 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
- 60 mg film-coated extended-release tablets (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
- 80 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

4 CONTRAINDICATIONS

OXYCONTIN is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OXYCONTIN contains oxycodone, a Schedule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OXYCONTIN, and monitor all patients receiving OXYCONTIN for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OXYCONTIN, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCONTIN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG .
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint .

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OXYCONTIN, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OXYCONTIN.

To reduce the risk of respiratory depression, proper dosing and titration of OXYCONTIN are essential *[see Dosage and Administration (2)]*. Overestimating the OXYCONTIN dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of OXYCONTIN with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.3)]*, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in OXYCONTIN-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using OXYCONTIN with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in OXYCONTIN-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of OXYCONTIN until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of OXYCONTIN with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using OXYCONTIN with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result if OXYCONTIN is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., non-benzodiazepines sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OXYCONTIN is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of OXYCONTIN in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: OXYCONTIN-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of OXYCONTIN *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating OXYCONTIN and when OXYCONTIN is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3, 5.6)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

OXYCONTIN may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of OXYCONTIN. In patients with circulatory shock, OXYCONTIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OXYCONTIN in patients with circulatory shock.

5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OXYCONTIN may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure.

Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OXYCONTIN.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OXYCONTIN in patients with impaired consciousness or coma.

5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick, or otherwise wet OXYCONTIN tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.12 Risks of Use in Patients with Gastrointestinal Conditions

OXYCONTIN is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxycodone in OXYCONTIN may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in OXYCONTIN may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during OXYCONTIN therapy.

5.14 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g.., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including OXYCONTIN. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing OXYCONTIN, gradually taper the dosage *[see Dosage and Administration (2.9)]*. Do not abruptly discontinue OXYCONTIN *[see Drug Abuse and Dependence (9.3)]*.

5.15 Risks of Driving and Operating Machinery

OXYCONTIN may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OXYCONTIN and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.16 Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions With Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11, 5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

Adult Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OXYCONTIN was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OXYCONTIN in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OXYCONTIN may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OXYCONTIN with placebo are shown in Table 2 below:

TABLE 2: Common Adverse Reactions (>5%)

Adverse Reaction	**OXYCONTIN (n=227) (%)**	**Placebo (n=45) (%)**
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OXYCONTIN with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis

General disorders and administration site conditions: chills, fever

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension

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

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypoesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

Clinical Trial Experience in Pediatric Patients 11 Years and Older

The safety of OXYCONTIN has been evaluated in one clinical trial with 140 patients 11 to 16 years of age. The median duration of treatment was approximately three weeks. The most frequently reported adverse events were vomiting, nausea, headache, pyrexia, and constipation.

Table 3 includes a summary of the incidence of treatment emergent adverse events reported in ≥5% of patients.

Table 3: Incidence of Adverse Reactions Reported in ≥ 5.0% Patients 11 to 16 Years

System Organ Class **Preferred Term**	**11 to 16 Years** **(N=140)** **n (%)**
Any Adverse Event >= 5%	71 (51)

GASTROINTESTINAL DISORDERS	56 (40)
Vomiting	30 (21)
Nausea	21 (15)
Constipation	13 (9)
Diarrhea	8 (6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (23)
Pyrexia	15 (11)
METABOLISM AND NUTRITION DISORDERS	9 (6)
Decreased appetite	7 (5)
NERVOUS SYSTEM DISORDERS	37 (26)
Headache	20 (14)
Dizziness	12 (9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	23 (16)
Pruritus	8 (6)

The following adverse reactions occurred in a clinical trial of OXYCONTIN in patients 11 to 16 years of age with an incidence between ≥1.0% and < 5.0%. Events are listed within each System/Organ Class.

Blood and lymphatic system disorders: febrile neutropenia, neutropenia

Cardiac disorders: tachycardia

Gastrointestinal disorders: abdominal pain, gastroesophageal reflux disease

General disorders and administration site conditions: fatigue, pain, chills, asthenia

Injury, poisoning, and procedural complications: procedural pain, seroma

Investigations: oxygen saturation decreased, alanine aminotransferase increased, hemoglobin decreased, platelet count decreased, neutrophil count decreased, red blood cell count decreased, weight decreased

Metabolic and nutrition disorders: hypochloremia, hyponatremia

Musculoskeletal and connective tissue disorders: pain in extremity, musculoskeletal pain

Nervous system disorders: somnolence, hypoesthesia, lethargy, paresthesia

Psychiatric disorders: insomnia, anxiety, depression, agitation

Renal and urinary disorders: dysuria, urinary retention

Respiratory, thoracic, and mediastinal disorders: oropharyngeal pain

Skin and subcutaneous tissue disorders: hyperhidrosis, rash

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of extended-release oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abuse, addiction, aggression, amenorrhea, cholestasis, completed suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OXYCONTIN.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with OXYCONTIN.

Table 4: Clinically Significant Drug Interactions with OXYCONTIN

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of OXYCONTIN and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of OXYCONTIN and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved *[see Warnings*

	and Precautions (5.5)]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of OXYCONTIN until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of OXYCONTIN and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.5)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider OXYCONTIN dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Dosage and Administration (2.6), Warnings and Precautions (5.6)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OXYCONTIN if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine

	reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	The use of OXYCONTIN is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of OXYCONTIN and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OXYCONTIN and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OXYCONTIN is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no available data with OXYCONTIN in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when

oxycodone hydrochloride was orally administered to rats and rabbits, during the period of organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 60 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. OXYCONTIN is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including OXYCONTIN, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with 0.5, 2, 4, and 8 mg/kg oxycodone hydrochloride (0.08, 0.3, 0.7, and 1.3 times the human daily dose of 60 mg/day, respectively based on a mg/m^2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 1.3 times the human dose of 60 mg/day. The high dose produced maternal toxicity characterized by excessive gnawing on forelimbs and decreased body weight gain.

Pregnant rabbits were treated with 1, 5, 25, and 125 mg/kg oxycodone hydrochloride (0.3, 2, 8, and 40 times the human daily dose of 60 mg/day, respectively, based on a mg/m^2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 40 times the human dose of 60 mg/day. The 25 mg/kg and 125 mg/kg doses high doses produced maternal toxicity characterized by decreased food consumption and body weight gain.

Pregnant rats were treated with 0.5, 2, and 6 mg/kg oxycodone hydrochloride (0.08, 0.32, and 1 times the human daily dose of 60 mg/kg, respective, based on a mg/m^2 basis, during the period of organogenesis through lactation. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 60 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3 times an adult human oral dose of 60 mg/day on a mg/m^2 basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m^2 basis).

8.2 Lactation

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended–release oxycodone, including OXYCONTIN, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with OXYCONTIN.

Clinical Considerations

Infants exposed to OXYCONTIN through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

8.4 Pediatric Use

The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 years. Use of OXYCONTIN is supported by evidence from adequate and well-controlled trials with OXYCONTIN in adults as well as an open-label study in pediatric patients ages 6 to 16 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.

The safety of OXYCONTIN in pediatric patients was evaluated in 155 patients previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OXYCONTIN. Patients were started on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose.

The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)]*.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, a dosage reduction in debilitated, non-opioid-tolerant patients is recommended *[see Dosage and Administration (2.7)]*.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who are not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of OXYCONTIN slowly in these patients and monitor closely for signs of central nervous system and respiratory depression. *[see Warnings and Precautions (5.7)]*.

Oxycodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

A study of OXYCONTIN in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Therefore, a dosage reduction is recommended for these patients *[see Dosage and Administration (2.8)]*. Monitor closely for signs of respiratory depression, sedation, and hypotension.

8.7 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 *[see Clinical Pharmacology (12.3)]*. Follow a conservative approach to dose initiation and adjust according to the clinical situation.

8.8 Sex Differences

In pharmacokinetic studies with OXYCONTIN, 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.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OXYCONTIN contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

OXYCONTIN contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction 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 addiction.

OXYCONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of OXYCONTIN

OXYCONTIN is for oral use only. Abuse of OXYCONTIN poses a risk of overdose and death. The risk is increased with concurrent use of OXYCONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular

heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.

Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as "OXYCONTIN".

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies
In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 5.

Table 5: Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OXYCONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration

The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary
The *in vitro* data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is

subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. 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). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OXYCONTIN should not be abruptly discontinued *[see Dosage and Administration (2.9)]*. If OXYCONTIN is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and 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.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with OXYCONTIN can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression

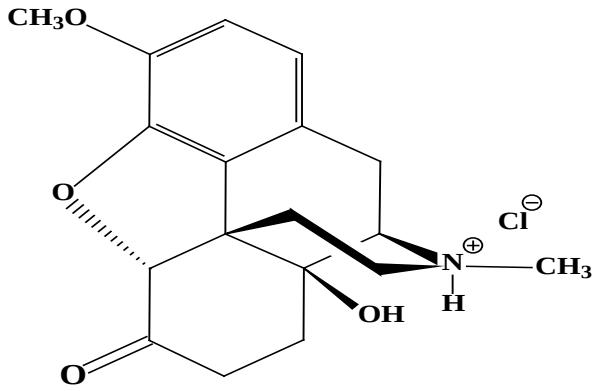
secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal is expected to be less than the duration of action of oxycodone in OXYCONTIN, carefully monitor the patient until spontaneous respiration is reliably reestablished. OXYCONTIN will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets is an opioid agonist supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets 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:



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

The chemical name is 4, 5α-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 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 15 mg tablets also contain black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain polysorbate 80 and red iron oxide.

The 30 mg tablets also contain polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain polysorbate 80, red iron oxide and black iron oxide.

The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

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 are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in CO_2 tension and electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Overdosage (10)]*.

Effects on the 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 biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration –Efficacy Relationships

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, such as pupillary constriction, sedation, overall subjective "drug effect", analgesia and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.5)]*.

Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.5)]*.

12.3 Pharmacokinetics

The activity of OXYCONTIN is primarily due to the parent drug oxycodone. OXYCONTIN is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OXYCONTIN impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OXYCONTIN is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OXYCONTIN to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OXYCONTIN in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life ($t_{½}$) 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.

Plasma Oxycodone Concentration over Time

Dose proportionality has been established for OXYCONTIN 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) *(see Table 6)*. Given the short elimination $t_{½}$ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OXYCONTIN. 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.

TABLE 6

Mean [% coefficient of variation]

Regimen	Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	T_{max} (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	15 mg	196 [28]	16.8 [29]	4.59 [19]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	30 mg	377 [24]	34.6 [21]	4.61 [19]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	60 mg	705 [22]	64.6 [24]	4.15 [26]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

* for single-dose AUC = $AUC_{0\text{-}inf}$

†data obtained while subjects received naltrexone, which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OXYCONTIN.

Distribution

Following intravenous administration, the steady-state volume of distribution (V_{ss}) for oxycodone was 2.6 L/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 Use in Specific Populations (8.4)]*.

Elimination

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated *N*-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated *O*-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7)]*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Age: Geriatric Population

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Age: Pediatric Population

In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

Sex

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown *[see Use in Specific Populations (8.9)]*.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy 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 mean elimination $t_{½}$ for oxycodone increased by 2.3 hours.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed 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 was 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 mean elimination $t_{½}$ for oxycodone of 1 hour.

Drug Interaction Studies

CYP3A4 Inhibitors

CYP3A4 is the major isoenzyme involved in noroxycodone formation. Co-administration of OXYCONTIN (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7)]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with OXYCONTIN *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone was genotoxic in the in vitro mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the in vitro chromosomal aberration assay, the in vitro bacterial reverse mutation assay (Ames test), and the in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg/day). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (up to 8 mg/kg/day), up to 1.3 times a human dose of 60 mg/day.

14 CLINICAL STUDIES

Adult Clinical Study

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OXYCONTIN 20 mg, but not 10 mg, was statistically significant in pain reduction compared with placebo.

Pediatric Clinical Study

OXYCONTIN has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg to 100 mg based on the patient's prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group.

16 HOW SUPPLIED/STORAGE AND HANDLING

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 10 mg are film-coated, round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-410-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-410-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 15 mg are film-coated, round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-415-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-415-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 20 mg are film-coated, round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-420-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-420-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 30 mg are film-coated, round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-430-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-430-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 40 mg are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-440-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-440-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 60 mg are film-coated, round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-460-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-460-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 80 mg are film-coated, round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-480-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-480-20**).

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

Dispense in tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse and Misuse

Inform patients that the use of OXYCONTIN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting OXYCONTIN or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

To guard against excessive exposure to OXYCONTIN by young children, advise caregivers to strictly adhere to recommended OXYCONTIN dosing.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*. Instruct patients to take steps to store OXYCONTIN securely and to dispose of unused OXYCONTIN by flushing the tablets down the toilet.

Interactions with Benzodiazepines or Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OXYCONTIN is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking OXYCONTIN while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking OXYCONTIN *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)]*.

Important Administration Instructions

Instruct patients how to properly take OXYCONTIN, including the following:

- OXYCONTIN is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN tablets can result in a fatal overdose *[see Dosage and Administration (2.1)]*.
- OXYCONTIN tablets should be taken one tablet at a time *[see Dosage and Administration (2.1)]*.
- Do not pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Dosage and Administration (2.1)]*.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Dosage and Administration (2.1)]*.
- Do not discontinue OXYCONTIN without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.9)]*.

Hypotension

Inform patients that OXYCONTIN may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.9)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in OXYCONTIN. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that OXYCONTIN can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation:

Advise patients that breastfeeding is not recommended during treatment with OXYCONTIN *[see Use in Specific Populations (8.2)]*

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that OXYCONTIN may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.15)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Disposal of Unused OXYCONTIN

Advise patients to flush the unused tablets down the toilet when OXYCONTIN is no longer needed.
Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers 6,488,963; 7,129,248; 8,309,060; 8,808,741; 8,821,929; 8,894,987; 8,894,988; 9,060,976; 9,073,933; 9,492,389, 9,492,391, 9,492,392, 9,492,393, and 9,522,919

Medication Guide
OXYCONTIN® (ox-e-KON-tin) (oxycodone hydrochloride) extended-release tablets, CII

OXYCONTIN is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.
- Not for use in children less than 11 years of age and who are not already using opioid pain medicines regularly to manage pain severe enough to require daily around-the-clock long-term treatment of pain with an opioid.

Important information about OXYCONTIN:

- **Get emergency help right away if you take too much OXYCONTIN (overdose).** When you first start taking OXYCONTIN, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking **OXYCONTIN** with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your OXYCONTIN. They could die from taking it. Store OXYCONTIN away from children and in a safe place to prevent stealing or abuse. Selling or giving away OXYCONTIN is against the law.

Do not take OXYCONTIN if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking OXYCONTIN, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OXYCONTIN during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with OXYCONTIN. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCONTIN with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCONTIN:

- Do not change your dose. Take OXYCONTIN exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OXYCONTIN whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCONTIN because this may cause you to overdose and die.
- OXYCONTIN should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCONTIN without talking to your healthcare provider.**
- After you stop taking OXYCONTIN, flush any unused tablets down the toilet.

While taking OXYCONTIN DO NOT:

- Drive or operate heavy machinery until you know how OXYCONTIN affects you. OXYCONTIN can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with OXYCONTIN may cause you to overdose and die.

The possible side effects of OXYCONTIN are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of OXYCONTIN. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, **www.purduepharma.com or call 1-888-726-7535**

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 12/2016

OXYCONTIN® (II)
(OXYCODONE HCl) EXTENDED-RELEASE TABLETS

EXHIBIT G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

SEP 10 2013

Andrew Kolodny, MD
President, Physicians for Responsible Opioid Prescribing
920 48th Street, Suite 1510
Brooklyn, NY 11219

Re: Docket No. FDA-2012-P-0818

Dear Dr. Kolodny:

This letter responds to the citizen petition submitted by Physicians for Responsible Opioid Prescribing (PROP), which was received by FDA on July 26, 2012 (Petition). The Petition describes PROP's concerns about the safety and efficacy of opioid analgesic drugs for long-term use in chronic non-cancer pain, and requests that the Food and Drug Administration (FDA or Agency): (1) "[s]trike the term 'moderate' from the indication [of opioid analgesics] for non-cancer pain"; (2) "[a]dd a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain"; and (3) "[a]dd a maximum duration of 90-days for continuous [daily] use" for non-cancer pain (Petition at 2).[1]

FDA has carefully reviewed PROP's Petition and the numerous comments submitted to the public dockets[2] by government entities, medical societies, healthcare providers, patients, and other members of the public. For the reasons described in detail in this response, the Petition is granted in part and denied in part.

Today, on the basis of the information discussed below, FDA has notified application holders for extended-release/long-acting (ER/LA) opioid analgesics that, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(o)(4)), important safety labeling changes are needed to the labeling of ER/LA opioid analgesics.[3] It is the agency's intent that these changes, which are described more fully below, will help more effectively communicate the serious risks of misuse, abuse, neonatal opioid withdrawal syndrome (NOWS), addiction, overdose, and death associated with the use of ER/LA opioids overall, and during pregnancy. FDA has also determined that more data are needed about the safety of long-term use of opioids. Pursuant to section 505(o)(3) of the FD&C Act, FDA is therefore requiring all new drug application (NDA) sponsors of ER/LA opioids to conduct postapproval studies and clinical trials

[1] The Petition requests pertain to analgesia products; therefore, this response is limited to opioids with indications for analgesia.

[2] FDA received comments on the PROP citizen petition in the above-captioned docket and comments relevant to the PROP citizen petition in the docket for a part 15 hearing the agency held in February 2013, titled Impact of Approved Drug Labeling on Chronic Opioid Therapy (Part 15 Hearing) (*see* Docket No. FDA-2012-N-1172).

[3] Pursuant to section 505(o)(4) of the FD&C Act, FDA is notifying holders of approved NDAs and holders of approved ANDAs that reference a NDA that is not currently marketed.

(post-marketing requirements, or PMRs) to assess certain known serious risks of ER/LA opioid use: misuse, abuse, hyperalgesia, addiction, overdose, and death.

I. BACKGROUND

A. Opioids

Opioids are a class of powerful pain-relieving agents that includes oxycodone, hydrocodone, and morphine, among others. When prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority.[4] Chronic pain is a serious and growing public health problem: it "affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence."[5] There is also evidence that pain is inadequately treated in many patients.[6] However, pain is a self-reported symptom that is difficult to quantify, and its treatment is complex.

Opioids also have grave risks, the most well-known of which include addiction, overdose, and even death. The labeling for these products contains prominent warnings about these risks. Moreover, the boxed warning states that all patients should be "routinely monitor[ed]...for signs of misuse, abuse, and addiction." Even proper use of opioids under medical supervision can result in life-threatening respiratory depression, coma, and death (see Boxed Warning and Section 5.3 of Warnings in current labeling). Indeed, a Centers for Disease Control and Prevention (CDC) analysis published in February 2013 documents an 11th straight year of increases in drug overdose deaths, with opioids being involved in 75% of pharmaceutical overdose deaths, either alone or in combination with other drugs.[7]

Most opioid-only drugs are controlled under Schedule II of the Controlled Substances Act.[8] By law, prescriptions for Schedule II drugs cannot be refilled; patients need a new prescription to obtain the drug beyond the initial number of doses prescribed.[9] There are also strict recordkeeping, reporting, and physical security requirements. This level of

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[4] *See* "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." Committee on Advancing Pain Research, Care, and Education; Institute of Medicine. 2011:1-364 (available at http://www.nap.edu/catalog.php?record_id=13172).

[5] *Id.* at p. 5.

[6] *Id.* at p. 1.

[7] Jones CM, Mack, KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013; 309(7): 657-9.

[8] *See* 21 U.S.C. 801 *et seq*; 21 CFR 1308.12. There are some opioids in Schedule III (*e.g.*, buprenorphine, *see* 21 CFR 1308.13(e)(2)(i)) and Schedule IV (*e.g.*, butorphanol and pentazocine, *see* 21 CFR 1308.14(f)). Tramadol, a synthetic opioid, is not currently scheduled under the Controlled Substances Act, *see* www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf.

[9] Although opioid drug labeling does not recommend a limit on the number of doses a patient should receive, the Schedule II status of most opioid drugs imposes certain restrictions on their availability. 21 CFR 1306.12(a). However, prescribers "may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a Schedule II controlled substance" as long as certain conditions are met. 21 CFR 1306.12(b)(1).

control reflects a finding that most opioid drugs have "high potential for abuse" and that "[a]buse of the drug . . . may lead to severe psychological or physical dependence."[10]

Opioid drugs have been approved for different conditions of use based on the data and information submitted by the sponsor of each drug product. Accordingly, product labeling may vary among approved opioid drugs, and such drugs may be prescribed to different patient populations.[11] The approved indications for ER/LA opioid analgesics are uniform, however. These drugs are currently indicated "for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[12] The current labeling for these drugs also contains a prominent statement that they are **not** for use:

- As an as-needed (prn) analgesic,
- For pain that is mild or not expected to persist for an extended period of time,
- For acute pain,
- In the immediate postoperative period, or
- For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.[13]

The labeling for some ER/LA opioid analgesics also states that they are for use (or for use at higher doses) only in opioid-tolerant patients.[14]

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[10] 21 U.S.C. 812(b)(2).

[11] For example, indications for which particular IR opioid products have been approved include "the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate" (Oxecta (oxycodone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/202080s001lbl.pdf); "the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate" (Codeine sulfate (NDA 022402) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022402s006lbl.pdf); and "the management of pain in patients where an opioid analgesic is appropriate" (Dilaudid (hydromorphone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2007/019892s015lbl.pdf).

[12] OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[13] Labeling for OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf (internal references omitted).

[14] *See, e.g.,* labeling for Exalgo (hydromorphone hydrochloride) (NDA 021217) and Duragesic (fentanyl) (NDA 019813). Further, certain opioid drugs also have limitations of use on the higher doses, with labeling stating that higher doses are for opioid-tolerant patients only. *See, e.g.,* labeling for Avinza (morphine sulfate) extended-release capsules (NDA 021260), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/021260s017lbl.pdf and OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

B. ER/LA Opioid Analgesic Risk Evaluation and Mitigation Strategy

FDA approved a shared-system Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics on July 9, 2012 (ER/LA Opioid Analgesic REMS).[15] The goal of the ER/LA Opioid Analgesic REMS is to "reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of [ER/LA opioids] while maintaining patient access to pain medications."[16] Under the REMS, "[a]dverse outcomes of concern include addiction, unintentional overdose, and death."[17] The REMS is currently limited to ER/LA opioid products because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids.[18]

Currently, more than 30 products are subject to the ER/LA Opioid Analgesic REMS.[19] The ER/LA Opioid Analgesic REMS contains requirements for distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids. Prescriber education training is considered ER/LA Opioid Analgesic REMS-compliant if, among other things, it includes the elements described in the "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (FDA Blueprint).[20] The FDA Blueprint provides guidance to prescribers to enable appropriate ER/LA opioid prescribing practices, as well as information prescribers can use in counseling patients about the risks and benefits of ER/LA opioid use.

C. Public Input

FDA has received a considerable amount of input from stakeholders and other commenters on issues pertaining to the benefits and risks of opioid use. For example, FDA participated in a two-day workshop in May 2012 hosted at the National Institutes of Health (NIH), called, "Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop."[21] Several stakeholders and other members of the public gave presentations

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[15] *See* www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf (most recently modified in April, 2013).

[16] *Id.* at p. 2.

[17] *Id.*

[18] *See* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q5; *see also, e.g.*, Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf) (providing data showing growing harm associated with ER/LA opioids).

[19] The list of drugs required to have a REMS, grouped by application holder, may be found at www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf.

[20] Available at http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf.

[21] *See* Docket No. FDA-2012-N-0067; *see also* http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm.

about issues relating to opioid treatment of chronic pain, and additional comments and subsequent input were posted to the public docket for that meeting.[22]

On February 7 and 8, 2013, FDA held a public hearing on chronic use of opioid drug products, titled, "Impact of Approved Drug Labeling on Chronic Opioid Therapy" (Part 15 Hearing).[23] FDA requested information, particularly scientific evidence, on issues pertaining to the use of opioid drugs in the treatment of chronic pain, including diagnosis and understanding of pain, understanding and adhering to the labeling of pain-treating products, and limiting opioid prescriptions and use.[24] The Agency received input from dozens of presenters, including patients, individuals who had lost loved ones due to opioids, clinicians, public health experts, professional associations, academicians, and others, including PROP. FDA also received over 600 comments to the Part 15 Hearing docket. The majority were from patients voicing concerns that labeling changes could make legitimate patient access to opioid analgesics more difficult.[25] The remainder reflected the same diversity of viewpoints and concerns presented during the hearing itself.

FDA also received more than 1900 comments on the PROP Petition. Many public health agencies and organizations supported the requests in the Petition, citing concerns about increased opioid use and abuse.[26] However, the majority of comments opposed PROP's requests. Many professional societies (*e.g.*, the American Academy of Pain Medicine, the American Medical Association, the American Society of Anesthesiologists, the American Pain Society) did not support the Petition and stated that the data cited by PROP did not support PROP's requests (particularly those requests for limits on dose and duration of use of opioids). Professional societies also expressed concern that the labeling changes requested by PROP were not supported by scientific evidence, and that a "one-size-fits-all" approach to a maximum dose or duration of treatment would be problematic and inconsistent with the need for individualized treatment and the variability among patient responses to opioids.[27]

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[22] *See* Docket No. FDA-2012-N-0067.

[23] *See* Docket No. FDA-2012-N-1172.

[24] *See* www.gpo.gov/fdsys/pkg/FR-2012-12-19/pdf/2012-30516.pdf.

[25] However, for privacy reasons, many comments from individual patients are not publicly available on www.regulations.gov. They nevertheless are considered to be included in the public docket.

[26] *See, e.g.*, comments from the New York City Department of Health and Mental Hygiene (Docket No. FDA-2012-P-0818-0785); County of Los Angeles Public Health (Docket No. FDA-2012-P-0818-0336); Denver Public Health (Docket No. FDA-2012-P-0818-0677); and the National Center on Addiction and Substance Abuse at Columbia University (Docket No. FDA-2012-P-0818-0691).

[27] *See, e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165); the American Medical Association (Docket No. FDA-2012-P-0818-0783); the American Society of Anesthesiologists (Docket No. FDA-2012-P-0818-0246); the American Pain Society (Docket No. FDA-2012-P-0818-0187); the American Academy of Physical Medicine and Rehabilitation (Docket No. FDA-2012-P-0818-0658); the American Society of Regional Analgesia and Pain Medicine (Docket No. FDA-2012-P-0818-0276); the Texas Pain Society (Docket No. FDA-2012-P-0818-0331); and the Florida Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0333). Some commenters submitted critiques of PROP's cited studies that identified the studies' limitations. *See, e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165). For example, the Florida Academy of Pain Medicine states, "it appears that the petitioners are asking for changes to the indications for long-term

II. SAFETY LABELING CHANGES

After evaluating stakeholder and commenter input regarding opioid labeling, and based on FDA's review of relevant literature, FDA has determined that safety labeling changes to the labeling of ER/LA opioid analgesics are needed to more effectively communicate to prescribers the serious risks associated with these drugs, and to more clearly describe the population in whom these drugs should be used in light of these serious risks—thus encouraging better prescribing, monitoring, and patient counseling practices involving these drugs. FDA is therefore exercising its authority under section 505(o)(4) of the FD&C Act to notify application holders that modifications to ER/LA opioid analgesic labeling are needed.[28] It is the agency's intent that these changes will help reduce inappropriate prescribing[29] and help curb the increase in misuse, abuse, NOWS, addiction, overdose, and death associated with ER/LA opioid analgesic use.

These safety labeling changes apply only to ER/LA opioid analgesics, and, at present, FDA is not requesting or requiring that any labeling changes be made to IR opioids or opioid/non-opioid combination products (which include both an IR opioid and a non-opioid analgesic).[30] Much of the literature FDA reviewed assessed opioid use from all opioid sources, or did not necessarily separate data according to opioid formulation (*i.e.*, ER/LA versus IR or opioid/non-opioid combinations). However, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products; indeed, the recognition of

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high-dose opioid therapy (LTHDOT) for non-cancer pain, based on a small number of studies with significant methodological shortcomings and findings that are not conclusive. In short, they are basing their request for label changes on the same kind of evidence they themselves, criticize as being insufficient to support the safety and efficacy of LTHDOT for non-cancer pain" (Docket No. FDA-2012-P-0818-0333).

[28] Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FD&C Act, as codified in section 505(o)(4) of the FD&C Act, to authorize FDA to require holders of approved drug applications to make safety labeling changes (SLCs) if the agency becomes aware of "new safety information" that FDA determines should be included in the labeling of the drug. *New safety information* is information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug of which the Agency has become aware (that may be based on a new analysis of existing information) since the drug was approved, the REMS was approved, or since the last assessment of the approved REMS; or the effectiveness of the approved REMS for the drug obtained since the last assessment of such strategy. *See* section 505-1(b)(3) of the FD&C Act.

[29] Pain patients in the United States receive care from prescribers with different backgrounds and levels of experience and expertise in treating pain. IMS Health, Vector One®: National (VONA). Data Extracted September 2012. Weblink: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM337148.pdf. For example, some prescribers may not understand how to identify patients at risk for addiction, how to identify behaviors associated with misuse and abuse, and how to manage patients who are receiving opioids for chronic pain so as to reduce the risks of misuse, abuse, NOWS, addiction, overdose and death.

[30] Therefore, the agency denies PROP's Petition insofar as it requests labeling changes for IR opioids, or opioid/non-opioid combination products.

disproportionate safety concerns for ER/LA opioids informed FDA's decision to require the ER/LA Opioid Analgesic REMS. For example, data show that the risk for misuse and abuse is greater for ER/LA opioids.[31] Because they are intended to release the drug over a longer period of time, many ER/LA opioids contain higher doses of opioids compared to IR opioids or opioid/non-opioid combinations. This increases the risk of a fatal outcome in the event of an overdose, and may make ER/LA opioids more desirable in the eyes of opioid abusers and addicts. Furthermore, ER/LA opioids are often used in a chronic pain setting. Thus, in light of the risks posed by ER/LA opioids, and the totality of available data on both ER/LA opioids specifically and opioid drugs in general, the Agency has decided to make ER/LA opioid analgesics its current focus.

First, FDA is requiring changes to the boxed warning for ER/LA opioid analgesics to give greater emphasis and prominence to the risks of misuse, abuse, NOWS, addiction, overdose, and death. For example, the first sentence of the new boxed warning provides that ER/LA opioids "expose patients and other users to the risks of opioid addiction, abuse, and misuse which can lead to overdose and death." The new boxed warning also urges prescribers to "assess each patient's risk" before prescribing, and to "monitor all patients regularly for the development of these behaviors or conditions."

Second, FDA is requiring changes to the Indications and Usage section of the labeling. As noted above, ER/LA opioid analgesics currently are "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[32] The Agency has concluded that use of terminology predicated only on a categorical "severity scale" (e.g., mild, moderate, severe) to characterize the intensity of pain for which ER/LA opioids are indicated does not sufficiently focus prescribers' attention on their responsibility to make an individualized assessment of patient needs in light of the serious risks of ER/LA opioids. Given these serious risks, especially those of overdose and death, the Agency believes that clarity as to the appropriate use of such drugs is of the utmost importance. The new language clearly communicates to prescribers that ER/LA opioid analgesics should be used only when alternative treatments are inadequate because of the serious risks of these drugs. The new language also identifies specific examples of alternative treatment options, namely, "non-opioid analgesics or immediate-release opioids," and provides additional guidance on when such treatments may be deemed inadequate to provide sufficient management of pain.

Furthermore, the new labeling language underscores that patients in pain should be assessed not only by their rating on a categorical pain intensity scale, but also based on a

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[31] Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf).

[32] *See, e.g.*, OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

more thoughtful determination that their pain — however it may be defined — is *severe enough* to require daily, around-the-clock, long-term opioid treatment, *and* for which alternative treatment options are inadequate. This framework better enables prescribers to make decisions based on a patient's individual needs, given the serious risks associated with ER/LA opioids, against a backdrop of alternatives such as IR opioids and non-opioid analgesics. It allows prescribers to make an assessment of pain relative to a patient's ability to perform daily activities or enjoy a reasonable quality of life, not only on where a patient's pain falls on an intensity scale, and assess if ER/LA opioids are needed after determining whether (a) the pain is severe enough to require daily, around-the-clock, long-term opioid treatment, and (b) if alternatives to ER/LA opioids are inadequate to manage such pain, in light of the serious risks associated with ER/LA opioid analgesics.

The revised indication language reads as follows:

> **"[Tradename] is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.**
>
> **<u>Limitations of Use</u>**
> **• Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.**
> **• [Tradename] is not indicated as an as-needed (prn) analgesic."**

This new language is intended to prompt prescribers to more closely assess each individual patient's condition, and carefully evaluate whether alternative treatment options such as non-opioid analgesics or IR opioids are appropriate. The new language is intended to reflect that ER/LA opioid analgesics should be prescribed only when the prescriber determines that such alternatives are ineffective, not tolerated, or would otherwise be inadequate.

Third, FDA is notifying application holders of the need for changes to the Dosage and Administration, Warnings and Precautions, Drug Interactions, and Use in Specific Populations sections of ER/LA opioid analgesic labeling. These changes are specifically intended to urge prescribers to weigh carefully whether the benefits of an ER/LA opioid outweigh its serious risks on a patient-by-patient basis. If an ER/LA opioid analgesic is prescribed, the labeling changes emphasize that prescribers should monitor patients carefully for signs of abuse and addiction. FDA is also notifying application holders of the need for changes to the Patient Counseling Information and the product-specific Medication Guides to improve the communication of risks to patients.[33] The Agency

[33] Following the approval of the safety labeling changes, a REMS modification will be required to incorporate the approved safety labeling changes into the REMS materials, as applicable.

believes that the changes will improve communication of serious risks associated with the use of these products and help improve the safe use of ER/LA opioid analgesics overall.

FDA intends these changes to enable not only a more careful and thorough approach to determining whether ER/LA opioid analgesics should be prescribed for a particular patient, but also allows prescribers to better assess whether the serious risks associated with ER/LA opioids, including the risks of misuse, abuse, addiction, overdose and death associated with ER/LA formulations, are offset by the benefits ER/LA opioids may provide in managing pain for an individual patient.

Accordingly, PROP's request that FDA remove the term "moderate" from the indication for ER/LA opioid analgesic drugs is granted for the reasons explained above. As explained above, the changes to the labeling also reflect a departure from an indication based solely on a severity scale, and transitions to an indication that facilitates careful prescribing decisions based on an individualized assessment of a patient's situation (*i.e.*, whether an individual's pain is severe enough to require daily, around-the-clock, long-term opioid treatment) and a heightened recognition that, because of the serious risks associated with the use of these drugs, ER/LA opioids should be used only when alternative treatment options are inadequate.[34]

All of PROP's labeling change requests are limited to "non-cancer" pain, a distinction that is not made in current ER/LA opioid analgesic labeling. It is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer, and comments to the Petition docket reflect similar concerns.[35] FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling.[36]

In accordance with section 505(o)(4) of the FD&C Act, the ER/LA opioid analgesic application holders are required to submit by October 10, 2013, a supplement proposing changes to the approved labeling to reflect the new safety information, or else notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted.[37]

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[34] When other analgesics are contraindicated or ineffective, restricting the indication of opioid drugs to treatment of severe pain only could leave some patients with chronic pain with an impaired ability to carry out daily activities, resulting in a diminished quality of life. *See* National Pharmaceutical Council (2001): Pain: Current Understanding of Assessment, Management, and Treatments, http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_related_research/pub_quality_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf.

[35] *See, e.g.*, comments from National Hospice and Palliative Care Organization (Docket No. FDA-2012-P-0678); Purdue Pharma (Docket No. FDA-2012-P-0818-0707).

[36] FDA notes that some epidemiology studies make distinctions between cancer and non cancer pain. However, while such classifications may be standard in epidemiological research, FDA believes that they are not relevant to ER/LA opioid labeling.

[37] *See* section 505(o)(4)(B) of the FD&C Act.

If the ER/LA opioid application holders do not submit the requested safety labeling changes, or if FDA disagrees with alternative language that the companies propose, the FD&C Act provides timelines under section 505(o)(4) for discussions regarding the labeling changes.[38] At the conclusion of these discussions, section 505(o)(4)(E) authorizes FDA to issue an order directing labeling changes as appropriate.

III. POSTAPPROVAL SAFETY STUDIES AND CLINICAL TRIALS

ER/LA opioid drugs generally have been approved in part based on randomized, controlled clinical trials that lasted for a 12-week period. This is due, in part, to the fact that for chronic pain, it can be difficult to ensure subject participation in controlled trials beyond 12 weeks. Many commenters, including PROP, have voiced increasing concern about the lack of controlled clinical trial data evaluating opioid use longer than 12-weeks. FDA is not aware of adequate and well-controlled[39] studies of opioid use longer than 12 weeks.[40]

FDA has evaluated concerns pertaining to the serious risks of misuse, abuse, hyperalgesia,[41] addiction, overdose, and death associated with opioid use. The Agency acknowledges that the available data demonstrate an association—though not necessarily a causal relationship—between opioid dose and certain serious risks of opioid use. However, FDA also agrees that more data are needed regarding the relationship between opioid dose and adverse effects, and the relationship between opioid duration of use and adverse effects, before the Agency can determine whether additional action needs to be taken. More data are also needed on the point at which the risks of opioid use at escalating doses and longer durations of treatment may outweigh the benefits of opioid analgesic therapy.

Thus, FDA is exercising its authority under section 505(o)(3)(A) through (B) of the FD&C Act to require ER/LA opioid drug sponsors to conduct PMRs to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of opioid analgesics. FDA has established milestone dates for

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[38] *See* section 505(o)(4)(D) of the FD&C Act.

[39] In this setting, "well-controlled studies" exclude active-controlled trials because they lack assay sensitivity, and failure to detect a statistically significant difference is difficult to interpret—either both drugs had the desired effect or both drugs did not have the desired effect.

[40] There are numerous uncontrolled studies that have evaluated patients on opioids for as long as a year; although some patients drop out of the studies over this period of time, many remain on opioid therapy, which may suggest that they continue to experience benefits that would warrant the risks of opioid use.

[41] Hyperalgesia is a known serious risk associated with chronic opioid analgesic therapy in which the patient becomes more sensitive to certain painful stimuli over time. *See, e.g.*, Varney SM, Bebarta VS. Opioid-induced hyperalgesia--worsening pain in opioid-dependent patients . Am J Emerg Med. 2013 Feb;31(2):458.e5-6; Angst MS, Clark JD Opioid-induced Hyperalgesia A Qualitative Systematic Review. Anesthesiology 2006; 104:570–87. It also may lead to increased use of opioid analgesics. *See, e.g.*, Chapman CR, Davis J, Donaldson GW, Naylor J, Winchester D. Postoperative pain trajectories in chronic pain patients undergoing surgery: the effects of chronic opioid pharmacotherapy on acute pain. J Pain 2011;12:1240-6.

completion of these studies and clinical trials, and is encouraging ER/LA opioid application holders to work together on these studies and clinical trials to provide the best information possible. First, the sponsors will have the opportunity to discuss with the Agency the particulars of the design and conduct of these PMRs.[42] We expect that this process will be completed in time for sponsors to submit final protocols to FDA within one year (*i.e.*, no later than August 2014). Sponsors must periodically report on the status of the studies and clinical trials.[43] The milestones for completion vary by study, with some expected to be completed as early as August 2015 and others expected to be completed in 2018.

As with the safety labeling changes, FDA is requiring PMRs only of ER/LA opioid analgesic application holders. While a majority of the literature that FDA reviewed did not distinguish between opioid formulation and/or composition, such as ER/LA versus IR opioids, or single ingredient opioids versus opioid/non-opioid combination products, FDA has made the determination that PMRs should be required of ER/LA opioid analgesic application holders to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose and death. FDA is taking this approach for the same reasons the Agency has decided to require safety labeling changes for ER/LA opioid analgesics: as discussed in greater detail in section II, above, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products[44] and because ER/LA opioids are often used in a chronic pain setting. Thus, in light of the serious risks of ER/LA opioids, and the totality of available data, the Agency has decided to make ER/LA opioid analgesics its current focus for requiring PMRs.

IV. REQUESTS FOR MAXIMUM DOSE AND DURATION OF USE

The Agency declines to specify or recommend a maximum daily dose or duration of use for any opioid at this time, for the reason described below. However, FDA has determined that PMRs are necessary to assess the known, serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These studies will address, among other things, the effect of dose and duration of opioid use on these serious risks.

A. Maximum Daily Dose

PROP requests that FDA "add a maximum daily dose" of the equivalent of 100 milligrams (mg) of morphine (100 mg morphine equivalent dose (MED)) to opioids

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[42] *See* Guidance for Industry, *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011) at 12.

[43] Section 505(o)(3)(iii) of the FD&C Act.

[44] *See, e.g.*, Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf).

(Petition at 2). In support of PROP's request, the Petition asserts that high-dose chronic opioid therapy is associated with increased risk of overdose death,[45] increased risk of emergency room visits,[46] and increased risk of fractures in the elderly,[47] (Petition at 2). PROP also maintains that "three large observational studies published in 2010 and 2011 found dose-related overdose risk" in patients on chronic opioid therapy (Petition at 2).

FDA agrees that adverse events and substance abuse of opioids occur at high doses—but adverse events can also occur at doses less than 100 mg MED. FDA also acknowledges that the available data do suggest a relationship between increasing opioid dose and risk of certain adverse events. However, the available information does not demonstrate that the relationship is necessarily a causal one. FDA has reviewed the studies cited in support of PROP's request, as well as studies cited in comments to the Petition docket and other studies described in the literature. For the reasons discussed in further detail below, the scientific literature does not support establishing a maximum recommended daily dose of 100 mg MED. Further, creating a maximum dose of 100 mg MED, or another dose ceiling, could imply a superior opioid safety profile under that set threshold, when there are no data to support such a conclusion. The Agency therefore denies PROP's request that opioid labeling specify a maximum daily dose.

1. Cited Data Do Not Define a Relationship between Opioid Dose and Risk of Fractures in the Elderly

FDA agrees that the Saunders study[48] PROP cites suggests a positive trend between opioid dose and fractures in the elderly. However, the elderly population is at risk for falls and fractures in general, and has more co-morbidities and more rapid fluctuations in health status than the overall adult population. The Saunders study did not take into account any co-morbidities in the elderly patients that arose after the initial patient visit when pain was diagnosed and an opioid was prescribed and the absence of that information may have confounded the results. Without additional data and a replication of the study's apparent finding, it would be premature to conclude that the risks of high-dose opioids outweigh their benefits in this population. Additionally, the highest dose-level in the Saunders study[40] was >50 mg MED, therefore, it did not directly address the 100 mg MED cutoff.

2. Cited Data Do Not Define a Relationship between Opioid Dose and Emergency Room Visits

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[45] *See* Gomes T, Mamdani MM, Dhalla IA, *et al.*, Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med, 2011; 171: 686-91.

[46] *See* Braden JB, Russo J, Fan MY, *et al.* Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 201 0; 170:1425-32.

[47] *See* Saunders KW, Dunn KM, Merrill JO, *et al.*, Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med, 2010;25:310-5.

[48] Saunders KW, Dunn KM, Merrill JO, *et al.*, Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med, 2010;25:310-5.

FDA does not agree with PROP's contention that the Braden study[49] demonstrated a clear dose-response relationship between high dose opioid therapy and emergency room visits for recipients of chronic opioid therapy for non-cancer pain. Braden *et al.* examined the association between opioid dose and emergency room visits in two populations: a national, commercially insured population and a state-based publicly insured population. The study categorized opioid dose according to 3 levels: (1) 0 MED to the median MED of the population at issue[50] (Category 1); (2) the median MED of the given population to 120 mg MED/day (Category 2); and (3) >120 mg MED/day (Category 3). When compared to Category 1 patients, Category 2 and Category 3 patients appeared to have an increased risk of emergency room visits—but only in one study population. Furthermore, Category 3 patients did not appear to have a greater risk of emergency room visits than Category 2 patients in that study population. Taken together, the findings of this study were inconclusive with respect to the relationship between opioid dose and emergency room visits. Furthermore, FDA is concerned that this study did not fully adjust for important factors that may confound the association between opioid dose and health services use, such as race and income.[51] FDA therefore concludes that the Braden study does not support PROP's request to limit the maximum daily dose of opioids.

3. *Cited Data Do Not Define a Relationship between Opioid Dose and Death*

PROP cites three observational studies (by Dunn, *et al.*,[52] Bohnert, *et al.*,[53] and Gomes, *et al*[54]) to support that higher doses of opioids are associated with higher risks of overdose-related death. Although these studies have several important limitations,[55] FDA agrees

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[49] Braden JB, Russo J, Fan MY, *et al.*, Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med, 2010; 170:1425-32.

[50] Note that the mean MED was different in the two study populations.

[51] Examples of other potential confounders include past health service use, alcohol use, or numbers of total medications used concurrently with opioids. *See* Braden JB, Russo J, Fan MY, *et al.*, Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med, 2010; 170:1425-32.

[52] Dunn KM, Saunders KW, Rutter CM, *et al.*, Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of Internal Medicine, 2010; 152:85-92.

[53] Bohnert AS, Valenstein M, Bair MJ, et al., Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA, 2011; 305:1315-21.

[54] Gomes T, Mamdani MM, Dhalla IA, et al., Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med, 2011; 171: 686-91.

[55] For example, the Dunn and Gomes studies did not discuss the reason the patients had been prescribed opioid therapy. It is possible that the patients' underlying illnesses (or the severity thereof) may have increased the risk of death or other adverse events—and without additional information, FDA cannot evaluate PROP's assumption that these adverse events can be attributed to opioid use alone. None of the three studies—Dunn, Bohnert, or Gomes—examined the role of the opioid's formulation (e.g., IR vs. ER/LA opioids) in their analyses, and it is possible that different formulations may have differing impacts on overdose-related outcomes. In addition, none of the three studies included data about what doses the patients actually took (as opposed to the doses they were prescribed), or data about whether the patients complied with the instructions they received about proper opioid use. Indeed, in the Bohnert study, almost half of the decedent population experienced an unintentional opioid-related death when the maximum prescribed dose was equal to 0 mg per day—which raises questions not only about the amount of opioids

that these studies appear to credibly suggest a positive association between high-dose opioid use and the risk of overdose and/or overdose mortality. Indeed, these studies appear to demonstrate a statistically significantly higher risk of overdose death among those taking opioid doses of >100 mg MED compared to those taking opioid doses of 1-19 mg MED.

Unfortunately, the point at which the risk of overdose-related death increases enough to change the benefit-risk assessment of the studied opioids cannot be determined from these studies. Determining such a threshold would require a better understanding of how risk of overdose and/or overdose mortality changes along the continuum of opioid dose (from 0 mg through the highest doses taken by patients). This dose-response (*i.e.* overdose and/or overdose mortality) relationship should be analyzed treating opioid use as a continuous variable or using categories defined by small increments (*e.g.*, 1 mg MED, or per 5 mg MED). Thus, even though the aforementioned studies demonstrated a statistically significantly higher risk of overdose death for patients taking the highest studied doses compared with patients taking the lowest studied doses, the threshold for an increased risk associated with these drugs could actually be considerably lower or higher than a maximum daily dose of 100 mg MED.

B. Maximum Duration of Treatment

The PROP Petition requests that FDA "[a]dd a maximum duration of 90 days for continuous (daily) use" (Petition at 2). In support of this request, the Petition alleges that "[l]ong-term safety and effectiveness of managing [pain] with opioids has not been established." After a review of the literature cited in the Petition, and an assessment of other relevant information discussed below, FDA has determined that limiting the duration of use for opioid therapy to 90 days is not supportable. Thus, the Agency denies this request.

1. Treatment Guidelines

In support of its request, PROP cites to the American Pain Society-American Academy of Pain Medicine Opioids Guidelines. However, these guidelines state that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients.[56] The guidelines recommend individualized care, management plans, and monitoring—not a maximum duration of treatment.[57] For example, they note that "proper patient selection is critical," requiring "a comprehensive benefit-to-harm evaluation that weighs the

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the patients actually took, but also the possibility that other causes of death may have mistakenly been assessed as opioid-related. Furthermore, the Dunn study described only 6 deaths in its discussion of 51 overdose-related outcomes, and it did not differentiate between deaths and other overdose outcomes in its analysis. Thus, it is less informative on the question of an association between opioid dose and death.

[56] *See* Chou R, Fanciullo GJ, Fine PG, *et al.*, American Pain Society- American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. J Pain, 2009; 10:113-130.

[57] *See generally id.*

potential positive effects of opioids on pain and function against potential risks."[58] The guidelines also strongly recommend that "[o]pioid selection, initial dosing, and titration . . . be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms."[59] The decision whether to proceed with opioid therapy, according to the guidelines, "should be intentional and based on careful consideration of outcomes" of the initial course of opioid treatment, which should be treated as a "short-term, therapeutic trial lasting from several weeks to several months."[60]

These guidelines are consistent with the new indication for ER/LA opioids: a focus on treatment decisions that include a thorough patient-specific assessment of the appropriateness of ER/LA opioids for that patient, and that reflect careful thought by prescribers and patients alike.

2. Cited Data on Persistence of Chronic Pain and Long-Term Opioid Use Are Inconclusive

PROP cites surveys by Sullivan, *et al.*[61] and Eriksen, *et al.*[62] to support its assertion that "[r]ecent surveys of [chronic non-cancer pain] patients receiving [chronic opioid therapy] have shown that many continue to experience significant chronic pain and dysfunction" (Petition at 2). The Eriksen survey supports this assertion but is insufficient to conclude that chronic opioid therapy causes or contributes to chronic pain and dysfunction, or that it is ineffective in treating chronic pain and dysfunction. Although the survey found that the pain severity reported at the time of the survey was higher among respondents who were using opioids than those who were not using opioids, there was no assessment of pain severity prior to the time of the survey. Thus, patients who were using opioids could have suffered from higher levels of pain pre-survey than those who were not using opioids. Pain *improvement* was not measured.

The Sullivan survey found that patients with chronic non-cancer pain treated with chronic opioid therapy reported being in pain 162 of the past 180 days (90% of days), and 92% of that sample reported pain on at least 90 days. These data suggest that patients on chronic opioid therapy experienced significant chronic pain, and that they continued to experience pain throughout their therapy. However, the study did not survey similar patients who did *not* receive opioid treatment. Without such a comparison group, it is unclear what the patients' pain trajectory would have been had they not been on chronic opioid therapy. Thus, this survey does not address the question of whether chronic non-cancer pain patients fare better or worse on chronic opioid therapy.

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[58] *Id.* at 115.

[59] *Id.* at 117.

[60] *Id.*

[61] Sullivan MD, Von KM, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. Pain 2010;149(2):345-353.

[62] Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain 2006;125(1-2):172-179.

3. *Cited Data on Long-term Opioid Use and Addiction Do Not Establish a Threshold for Maximum Duration of Use*

PROP's Petition contends that opioids should be given a maximum duration of use based in part on a study of "[a] large sample of medical and pharmacy claims records[, which] found that two-thirds of patients who took opioids on a daily basis for 90 days were still taking opioids five years later" (Petition at 2).

FDA disagrees with this statement.[63] Although the study follow-up lasted roughly 5 years, not all patients who were started on chronic opioid therapy were followed for that duration. Approximately half of the study population was followed two years or less (the median follow-up time was around 2 years). Throughout the course of the study period, some patients were censored due to death, disenrollment from health coverage, or other reasons. Patients who were censored may have had a different duration of therapy than those who continued to be followed. In FDA's view, the study showed that, among patients who were followed for 4.8 years, two-thirds were still taking opioids at the end of this period.

FDA also does not agree that these data necessarily reflect a safety concern specific to longer term use. Although some portion of these results certainly could be explained by adverse outcomes (*e.g.*, addiction in opioid therapy patients), other factors may also be associated with low discontinuation rates (*e.g.*, certain intractable or recalcitrant pain conditions that may require longer treatment periods). The referenced study did not collect data on why patients continued or discontinued opioid therapy, and without this information, it would be premature to restrict opioid use to a 90-day maximum duration treatment period.

The Petition also asserts that "[r]ecent surveys using [Diagnostic and Statistical Manual of Mental Disorders] DSM criteria found high rates of addiction in [chronic non-cancer pain] patients receiving [chronic opioid therapy]" (Petition at 2). FDA agrees with this assertion.[64] However, the cited surveys did not suggest that chronic opioid therapy causes addiction, or vice versa. Both addiction and chronic opioid therapy were measured at one point in time, so it is unknown which happened first: addiction or chronic opioid therapy.

The cited literature does not identify a duration threshold beyond which the risk of addiction outweighs the benefits of opioid treatment. PROP has selected a 90-day limit, but provides no evidence that addiction (however it is defined) increases significantly after 90 days of use such that it would support a labeling change. Nevertheless, the high

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[63] *See* Martin BC, Fan MY, Edlund MJ, DeVries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med 2011;26(12):1450-1457.

[64] However, the recently published Diagnostic and Statistical Manual of Mental Disorders – V (DSM V) combines the substance abuse and substance dependence categories into a single disorder measured on a continuum, to try to avoid an inappropriate linking of "addiction" with "physical dependence," which are distinct issues. *See* American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC: American Psychiatric Association, 2013.

rates of addiction shown in the cited literature are concerning enough to require further exploration in postapproval studies.

4. Cited Data Are Insufficient to Explain Association between Opioid Use and Mental Health Co-Morbidities

The Petition asserts that "[p]atients with mental health and substance abuse co-morbidities are more likely to receive [chronic opioid therapy] than patients who lack these risk factors, a phenomenon referred to as adverse selection." In support of this assertion, PROP cites to a study by Edlund *et al.*,[65] which examined trends in opioid prescribing among individuals with non-cancer pain, with and without mental health and substances disorders.

Although the Edlund study supports the association between current mental health and substance abuse co-morbidities and current use of chronic opioid therapy, FDA is unable to determine the reasons for this association in a cross-sectional analysis. This study only depicts the frequencies and prevalence of chronic opioid therapy in different sub-populations at one point in time, and the temporal relationship between mental health and substance abuse comorbidities and opioid therapy cannot be established. Thus, it is difficult to form any conclusions based on this study regarding the relationship between mental health/substance abuse disorders and the initiation, dose and duration of chronic opioid therapy. In sum, FDA agrees with the study's authors that the cited study does not conclude that the association between opioid use and mental/substance use disorder is due to any one specific factor.[66]

FDA acknowledges that patients with these co-morbid conditions may be at higher risk of adverse outcomes—possibly because they may be more likely to be treated with other psychoactive drugs. The results of the Edlund study thus underscore the need for prescribers to evaluate carefully whether and under what circumstances to prescribe opioids (particularly in high doses) to patients with these co-morbidities.[67] However, the findings of the Edlund study do not support PROP's argument that opioid labeling should include a maximum daily dose or a maximum duration of use.

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[65] Edlund MJ, Fan MY, DeVries A, Braden JB, Martin BC, Sullivan MD. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP Study. Clin J Pain 2010;26:1-8.

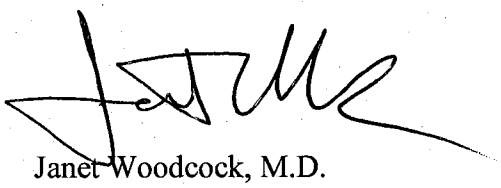
[66] The authors state that they "cannot definitively state why NCPC enrollees with MH [mental health]/SUDs [substances use disorders] were more likely to receive opioids than NCPC [non-cancer pain conditions] enrollees without MH/SUDs, and to receive them chronically[...]." *Id.* at 6.

[67] For example, section 5.1 of ER/LA opioid analgesic labeling, as provided for in the safety labeling change notification letters referred to above, contains the following language: "Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of [Tradename] for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as [Tradename], but use in such patients necessitates intensive counseling about the risks and proper use of [Tradename] along with intensive monitoring for signs of addiction, abuse, and misuse."

V. CONCLUSION

For the reasons stated above, the Petition is granted in part and denied in part.

Sincerely,



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