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OXFORD

LETTER TO THE EDITOR

In response to Gudin et al. — Comparing the Effect of Tampering on the Oral Pharmacokinetic Profiles of Two Extended-Release Oxycodone Formulations with Abuse-Deterrent Properties

Dear Editor,

Gudin et al. [1] describe the effects of tampering on the oral pharmacokinetic (PK) profiles of two extended-release (ER) oxycodone formulations with abuse-deterrent properties (ADP), Oxycodone DETERx (approved as Xtampza ER) and OxyContin administered intact and crushed, and with food. The following misleading statements and conclusions made by the authors warrant further clarification:

- ""It is likely that the ability to retain ER features following manipulation will make it less attractive to abusers compared to existing ADFs. . ."" This statement implies that these PK results are supported by comparative pharmacodynamic (drug liking effects) or human abuse potential study data, when such is not the case.
- PK profiles of Xtampza ER and OxyContin were examined when ingested with food, ""as this is a common form of administration in the intended patient population."" This statement is misleading as it suggests Xtampza can be dosed with or without regard to food, when such is not the case. Xtampza ER can only be taken with carefully modulated complete food intake. Failure to follow this stringent procedure, either by physician or patient, will result in variability in the extent of oxycodone absorption and ultimately impact the safety and efficacy of Xtampza ER.
- ""Although results of this study showed some minor differences in the PK profile between intact Oxycodone DETERx and intact OxyContin, the two products were bioequivalent on C_{max}, AUC_{last}, and AUC_{inf}."" Authors fail to clarify that Xtampza ER is not bioequivalent to OxyContin in fasting condition. Stated as such, this statement invites the potential for serious dosing errors with OxyContin.

The publication states that crushed Xtampza ER and crushed IR oxycodone were prepared using the same method, while crushed OxyContin was prepared using a different method [1]. The authors do not speak to the difficultly in or practicality of reducing the particle size of OxyContin. The difficulty in or time and effort required to crush OxyContin tablets is only one impediment to preparing OxyContin for abuse. The hydrogelling property of the OxyContin formulation contributes to reduced liking via the intranasal route, as demonstrated by OxyContin human abuse potential studies [2–4]. Further, in vitro studies have clearly demonstrated the difficulty in preparing OxyContin for injection [5,6]. These study results formed the basis of OxyContin being the first opioid to receive FDA-approved abuse-deterrence labeling [6].

The authors' conclusion, ""It is likely that the ability to retain ER features following manipulation will make it less attractive to abusers compared to existing ADFs,"" is not adequately supported by the data presented by Gudin et al. [1]. This statement implies that these PK results are supported by comparative pharmacodynamic (PD; drug liking effects) or human abuse potential study data, when this is not the case. It is important to clarify that no head-to-head PD or human abuse potential studies comparing Xtampza ER and OxyContin have been performed, and the extrapolation of PK results to imply PD outcomes is not supported by data.

Overall abuse deterrence is a cumulative property and must be studied in multiple ways. While separate in vitro and human abuse potential studies with OxyContin and Xtampza ER have resulted in similar US Food and Drug Administrtion (FDA)–approved labeling describing their ADP and expected impact on reducing intranasal and intravenous abuse [6,7], neither product has received FDA-approved labeling regarding oral abuse and neither is abuse-proof as abuse by injection, intranasal, and oral routes is still possible [6,7]. Only real-world epidemiological studies can adequately demonstrate whether a product with ADP results in meaningful reductions in abuse, misuse, and related adverse outcomes. These data do not yet exist for Xtampza ER. Epidemiologic studies evaluating the impact of OxyContin on real-world outcomes of abuse are ongoing. To date, OxyContin is the only opioid with ADP to have published data from 10 epidemiologic studies that have demonstrated decreases in abuse, overdose, and diversion [8].

Xtampza ER bioavailability is lower vs OxyContin under fasting conditions, and its bioavailability increases with fat/calorie content, which can vary depending on type of meal. As a result, the FDA concluded that these products are not bioequivalent, as clearly stated in the Xtampza ER Full Prescribing Information (FPI) [7]. Consistent with the dosing in the pivotal efficacy trial, the Xtampza ER FPI emphasizes that it ""must be taken with food"" and ""with approximately the same amount of food for every dose in order to ensure consistent plasma levels are achieved"" [7]. As noted by the FDA during the Xtampza ER Advisory Committee meeting,

this is a concern: "Because most opioids are labeled to be taken without regard to food, prescribers and patients may not comply with labeling for this product based on long-standing behaviors" [9]. The FDA also concluded that inconsistent administration of Xtampza ER with regard to type of meal or fed/fasting state may result in increased risk of adverse events and accidental overdose" [9]. Therefore, health care professionals should be aware of this important dosing distinction of Xtampza ER from most other opioids, including OxyContin. Unlike Xtampza ER, OxyContin can be administered without regard to food [6].

Opioids with ADP are a new and evolving area of research and an important part of a comprehensive intervention strategy to promote safe prescription opioid use. The FDA recognizes that the science of abuse deterrence is relatively new and the formulation technologies and the analytical, clinical, and statistical methods for evaluating these technologies are rapidly evolving [10]. Consequently, health care professionals may not have a thorough understanding of the different types of abuse deterrence studies and what the results tell us about opioids with potential ADP. This letter seeks to reduce the possible misinterpretation of these study data.

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References

1 Gudin J, Levy-Cooperman N, Kopecky EA, Fleming AB. Comparing the effect of tampering on the oral pharmacokinetic profiles of two extended-release oxycodone formulations with abuse-deterrent properties. Pain Med 2015;16(11):2142–51.

2 Harris SC, Perrino PJ, Smith I, et al. Abuse potential, pharmacokinetics, pharmacodynamics, and safety of intranasally administered crushed oxycodone HCl abuse-deterrent controlled-release tablets in recreational opioid users. J Clin Pharmacol 2014;54(4):468–77.

3 Perrino PJ, Colucci SV, Apseloff G, Harris SC. Pharmacokinetics, tolerability, and safety of intranasal administration of reformulated OxyContin tablets compared with original OxyContin tablets in healthy adults. Clin Drug Investig 2013;33(6):441–9.

4 Sellers EM, Perrino PJ, Colucci SV, Harris SC. Attractiveness of reformulated OxyContin tablets: Assessing comparative preferences and tampering potential. J Psychopharmacol 2013;27(9):808–16.

5 Cone EJ, Giordano J, Weingarten B. An iterative model for in vitro laboratory assessment of tamper deterrent formulations. Drug Alcohol Depend 2013; 131(1–2):100–5.

6 OxyContin [Full Prescribing Information]. Stamford, CT: Purdue Pharma L.P. 2016.

7 Xtampza ER [Full Prescribing Information]. Cincinnati, OH: Patheon Pharmaceuticals. 2016.

8 Coplan PC, Chilcoat HD, Butler SF, et al. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. Clin Pharmacol Ther 2016;100 (3):275–86.

9 US Food and Drug Administration. Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, NDA 208090 Xtampza Oxycodone ER Capsules. September 11, 2015. FDA Presentations. Food Effect with Xtampza ER. Nallani SC. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting Materials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM462850.pdf (accessed June 2016).

10 US Department of Health and Human Services, Food and Drug Administration and Center for Drug Evaluation and Research. FDA Guidance for Industry Abuse-Deterrent Opioids- Evaluation and Labeling. April 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf (accessed June 2016).