

Response to Crudele et al. Commentary on Mayock et al. “In Vitro Drug Release after Crushing: Evaluation of Xtampza[®] ER and Other ER Opioid Formulations”

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Dear Editor,

We appreciate Crudele and Giordano [1] taking the time to read our publication “In Vitro Drug Release after Crushing: Evaluation of Xtampza[®] ER and Other ER Opioid Formulations” [2], which reported on the ability of oxycodone DETERx (Xtampza ER, Collegium Pharmaceutical, Inc., Canton, MA, USA) and other commercially available extended-release (ER) opioid formulations with and without physicochemical abuse-deterrent characteristics to be manipulated by crushing in an in vitro setting. We are grateful to the editors for a chance to respond to their comments.

We would like to take this opportunity to address the broad comments made by Crudele and Giordano; to provide context for the design of the in vitro study presented in our publication; and to provide additional background on the comprehensive program that was conducted to assess the abuse deterrent properties of Xtampza ER.

In their letter, Crudele and Giordano point out that formulations with abuse deterrent properties (including Xtampza ER) are not abuse-proof, and do not address abuse via oral overconsumption. We agree with these statements. We have never maintained that Xtampza ER is abuse-proof nor that it is impossible to defeat its abuse-deterrent features. In our recent paper we indeed described

our label and the absence of a particular warning about chewing or crushing and swallowing. The absence of this label warning is supported by in vitro and clinical studies and is a relevant point of differentiation between Xtampza ER and other products. However, we have never claimed that Xtampza is not a Schedule II opioid with the same need for caution with regard to abuse and dependence that applies to all products in this class.

In the introduction to our publication, we acknowledged that reformulated OxyContin[®] has been shown, in real-world studies, to result in reductions in abuse via nasal and IV routes. Indeed, as described and acknowledged in the Results section of the publication, OxyContin was not effectively crushed by all of the household tools tested in the study. However, when assessed using in vitro dissolution techniques, Xtampza ER, an abuse-deterrent formulation of oxycodone, maintained its extended-release characteristics after crushing with commonly available household tools, while other commercially available extended-release opioids, including OxyContin, did not maintain their extended-release properties after crushing. These data suggest that there are differences between ER formulations, including those with ADF properties, when manipulated with household tools. The purpose of the study in question and the fact that some of the formulations included in the analysis had abuse deterrent properties while others did not, was clearly specified in the abstract. It is important for stakeholders, including healthcare providers and payers, to understand the performance of both ADF and non-ADF formulations after manipulation with household tools. Crushing is often a precursor to abuse via multiple routes, and a recent study showed that among oral

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abusers, the prevalence of manipulation of crush-resistant tablets (including OxyContin) prior to oral abuse is 42%. Importantly, crushing also occurs during inadvertent misuse, for example when a patient cannot swallow a tablet, they may cut or crush the formulation, potentially putting themselves at significant risk for “dose dumping” and enhanced adverse events [3]. Furthermore, an understanding of the ability of formulations without ADF labeling to withstand physical manipulation is particularly important when policies require patients to fail some of the non-ADF formulations tested here prior to being able to receive an ADF formulation.

The Xtampza ER development program was conducted in accordance with the US Food and Drug Administration (FDA) Guidance on the Development of Abuse Deterrent Opioids [4] with feedback from the FDA. Prior to the approval of Xtampza ER, the FDA held an Advisory Committee Meeting on 11 September 2015, in which the results of the abuse deterrent development program were discussed in depth. This discussion covered, among other topics, the results of a rigorous *in vitro* (Category 1) program that included multiple potential methods to manipulate and extract oxycodone from Xtampza ER (and in some cases, the currently marketed version of OxyContin) for abuse, including those specific to wax-based formulations, solvents of various pH and polarity, and heating. The result of this Advisory Committee meeting was a unanimous vote in favor of approval of Xtampza ER, which was followed by FDA approval with abuse-deterrent labeling with respect to the nasal and IV routes of abuse. In November of 2017, the FDA approved a label update for Xtampza ER that included comparative data demonstrating that Xtampza ER maintained its extended release profile after crushing with the most effective tool identified in *in vitro* studies, while OxyContin did not. That label update also included an additional oral human abuse potential study, which demonstrated that Xtampza ER had significantly lower drug liking and willingness to take the drug again compared to immediate-release oxycodone after chewing

and administering orally. The results of this study supported the addition of an oral abuse-deterrence claim.

Thank you for the opportunity to respond to this letter. We hope that our comments have reassured journal readership regarding the adequacy of the development program and abuse deterrent testing conducted for Xtampza ER, as well as the relevance of the present publication, which focused on the *in vitro* impact of crushing of opioid products with and without physico-chemical abuse deterrent properties.

Compliance with ethical standards

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Conflict of interest All authors are employees of Collegium Pharmaceutical, Inc.

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