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FDA Drug Safety and Risk Management
& Anesthetic and Analgesic Drug Advisory
Committees

Oxycodone extended release capsule

June 26, 2018

(I have no financial conflict of interest)

FDA Epidemiology Review

- Over the period 2010-2015, deaths involving oxycodone, remained high, with a total of 32,128 deaths occurring over this time frame. In evaluating any new oxycodone-containing product for approval, *it is essential to consider the public health risks as well as potential benefits.*
- Public health benefits of abuse-deterrent opioid analgesics have been proposed, though *no data demonstrating such benefit has been submitted and reviewed by FDA, and published studies evaluating such benefits have limitations.*

FDA Epidemiology Review (cont'd)

Data from individuals entering treatment for substance use disorder suggest that oral abuse is the most common route of exposure for ER/LA oxycodone formulations (60%) with abuse-deterrent (AD) properties.

Paradoxically, crush-resistant tablets (CRT) appear to be abused significantly more frequently by alternative oral modes of administration (i.e., chewing, dissolving in mouth) than non-CRT.

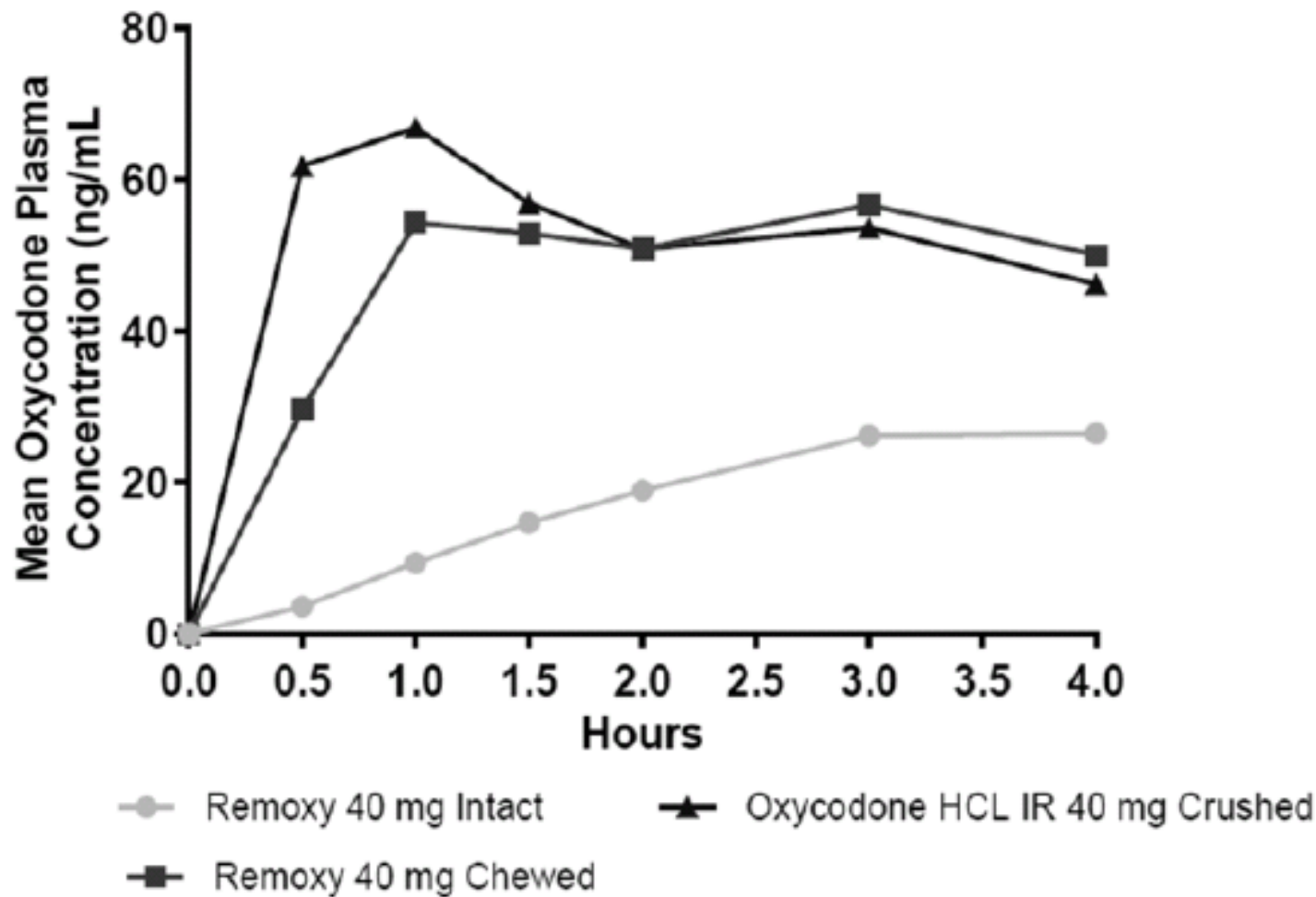


Figure 1: Mean concentration profile of oxycodone following oral administration of different treatments in Study B4501016.

Source: Excerpt from Clinical Pharmacology Review Dated 8/31/2016

Mean concentration profile of oxycodone after oral administration with different treatments

Table 1: Summary Statistics of Oxycodone Pharmacokinetics in Study B4501016.

	Intact Remoxy 40 mg	Chewed Remoxy 40 mg	Crushed IR Oxycodone HCl 40 mg
C _{max} [ng/mL]	30.3 (31)	64.4(23)	82.1 (28)
T _{max} [hr]	4.33 (2.2-12.2)	2.15 (0.7-5.2)	1.15 (0.6-6.2)
AUC _{0-1h} [ng hr/mL]	2.38 (77)	20.39 (66)	39.335 (41)

Findings from Oral Abuse Potential Studies

- *Study B4501016*: the maximum concentration for intact Remoxy, 30.2 ng/ml, achieved at 4.33 hours, occurred at 30 minutes for chewed Remoxy, its own C_{max} being achieved in about an hour.
- *Study B45011039*: a 3-fold increase in C_{max} when Remoxy ER was chewed and swallowed orally compared to those administered the intact drug

Other findings from Oral Abuse Potential Studies (cont'd)

Study B4501016: though chewed Remoxy 40 mg had statistically significantly lower average Emax of High than crushed oxycodone, it failed to demonstrate a minimum of 5% reduction in mean of Emax of High compared to crushed oxycodone IR 40 mg.

Study B4501016: chewed Remoxy 40 mg had a statistically significantly larger mean Emax than intact Remoxy 40 mg.

FDA conclusion (briefing page 60):

The earlier Tmax and the high relative bioavailability compared to intact product indicate that the proposed product may not deter oral abuse by chewing.

Does the U.S. Need another Oxycodone Product?

“Consumption of oxycodone was concentrated in the United States (72.9 per cent of the world total). Global consumption of oxycodone was 79.6 tons in 2016.” [meaning 58 tons were consumed in the US that year.]

from the 2017 UN International Narcotics Control Board Narcotic Drugs Report

Daily Oxycodone Doses in 58 Tons

58 tons = 58,000 Kg = 58 billion mg

Oxycontin defined daily dose = 75 mg

Thus, 773 (58 B/75) million daily oxycodone doses are consumed a year in the U.S., world “leader” in population-adjusted oxycodone consumption.

All but six of the other 166 countries in this UN report had population-adjusted oxycodone consumption less than one fourth of the U.S.

Discussion Questions and Vote

Has the Applicant demonstrated that Remoxy has properties that can be expected to deter abuse by the:

a. Oral route of administration? Will likely increase this predominant form of abuse, thus abuse-enhancing, not abuse-detering

c. IV route of administration? No evidence of superiority over other abuse-deterrent oxycodone products

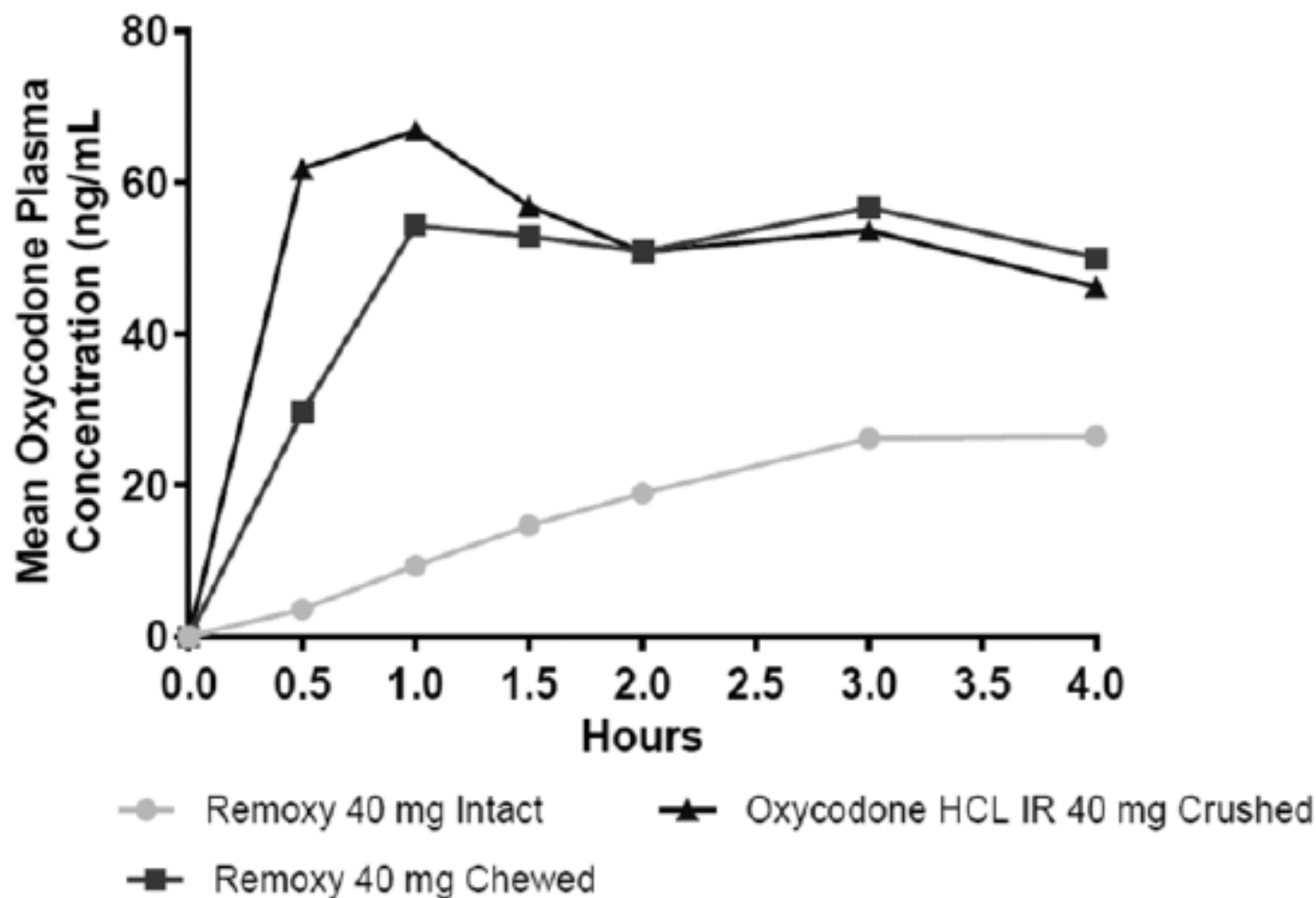


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Discussion Questions and Vote

Does the committee have concerns regarding the impact of Remoxy on public health?

Yes, for reasons stated by the FDA and discussed today, the impact on increased oral abuse.

Should Remoxy be approved?

No, since neither your committees nor the FDA want to further increase U.S. oxycodone abuse, a likely if not certain outcome if Remoxy is approved. The idea that there are no alternative treatments to Remoxy is preposterous.