FDA Introductory Remarks

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting

January 15, 2020 (PM Session)

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Discussion Point #1

Please discuss whether the Applicant has demonstrated that AXIMRIS XR (oxycodone extended-release tablets) has properties that can be expected to deter abuse by the following routes:

- Intravenous
- Intranasal
- Oral

Discussion Point #2

The Applicant is requesting approval of AXIMRIS XR as an analgesic with properties expected to deter abuse by the intravenous route. Discuss the implications of approval of Aximris XR that can be expected to deter abuse by a single route.

Discussion Point #3

Discuss whether you have any concerns regarding the impact of AXIMRIS XR on public health. Take into consideration its potential effect on abuse of extended-release oxycodone as well as potential consequences of administration of this product by unintended routes.

Discussion Point #4

Discuss whether the benefits outweigh the risks for the proposed indication. Discuss if any additional data are needed for this application to be approved.

Voting Question

Do you recommend approval of AXIMRIS XR (oxycodone extended-release tablets) 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?


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Use, Misuse, Abuse and Deaths Involving Oxycodone and Other Opioids in the United States

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Assessing the Benefits and Risks of Prescription Opioid Analgesics

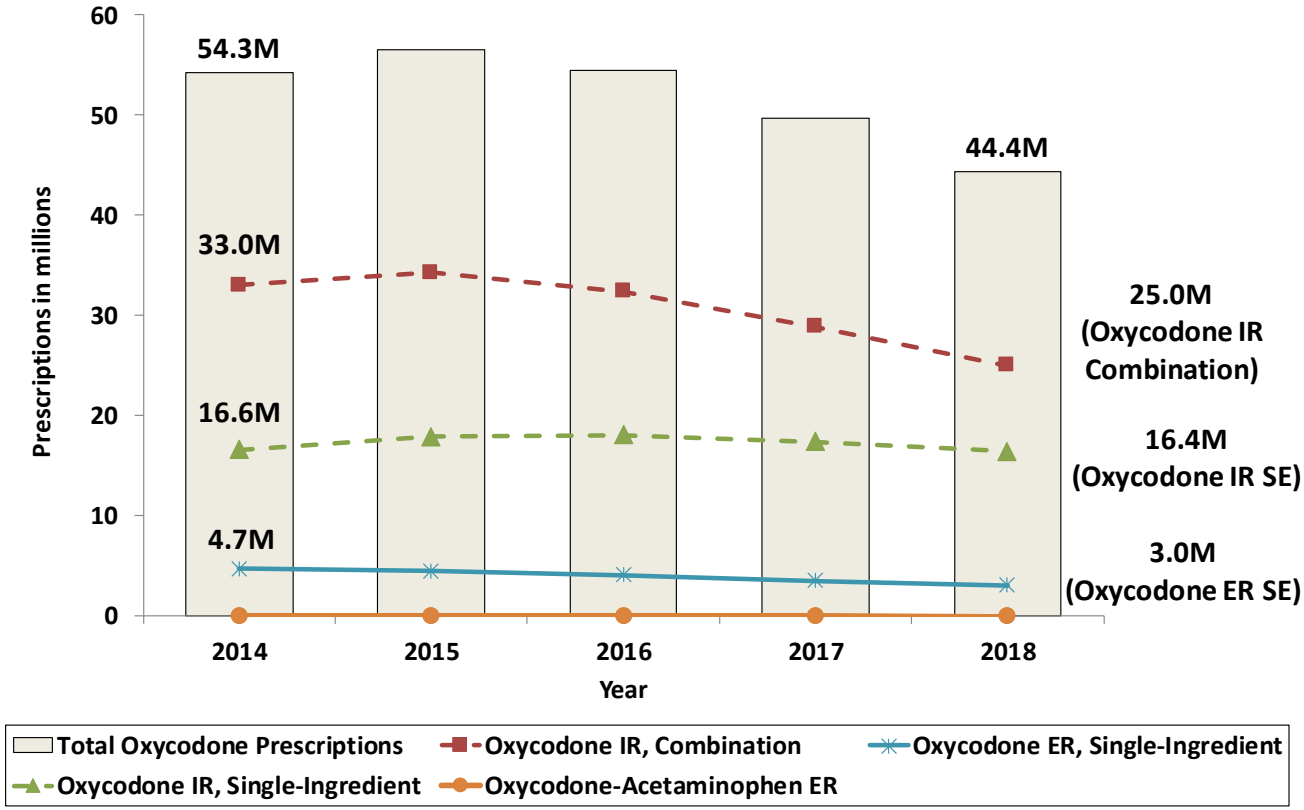
- Draft Guidance – "Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework: Guidance for Industry" (FDA, 2019)
  - "FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others."

Objectives

1. Describe utilization patterns of oxycodone products and other prescription opioid analgesics
2. Present epidemiologic data on misuse, abuse and deaths involving oxycodone products and other opioids
   - Focus on route of abuse
   - The Applicant is requesting approval of Aximris XR as an analgesic with properties expected to deter abuse by the intravenous route

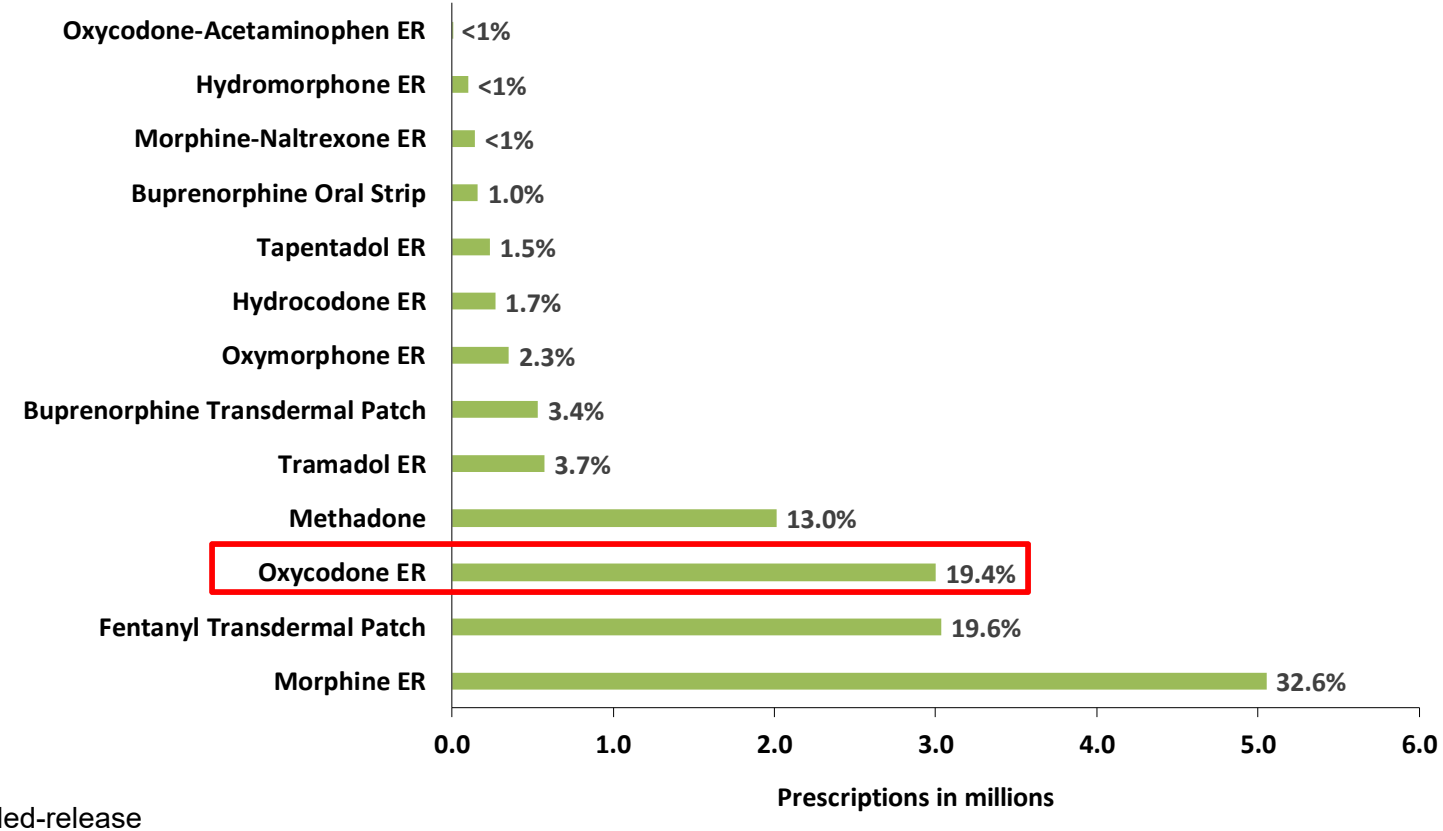
Oxycodone Utilization Patterns

Total Oxycodone Prescriptions in U.S. Decreased from 2014 through 2018



IR: Immediate-release; ER: Extended-release; SE: Single-entity; Estimated number of prescriptions dispensed for oxycodone-containing analgesic products from U.S. retail pharmacies, 2014-2018; Source: Symphony Health PHAST™ Prescription Monthly. 2014-2018. Data extracted June 2019.

Extended-release Oxycodone is One of the Most Commonly Dispensed Extended-release Opioids 2018

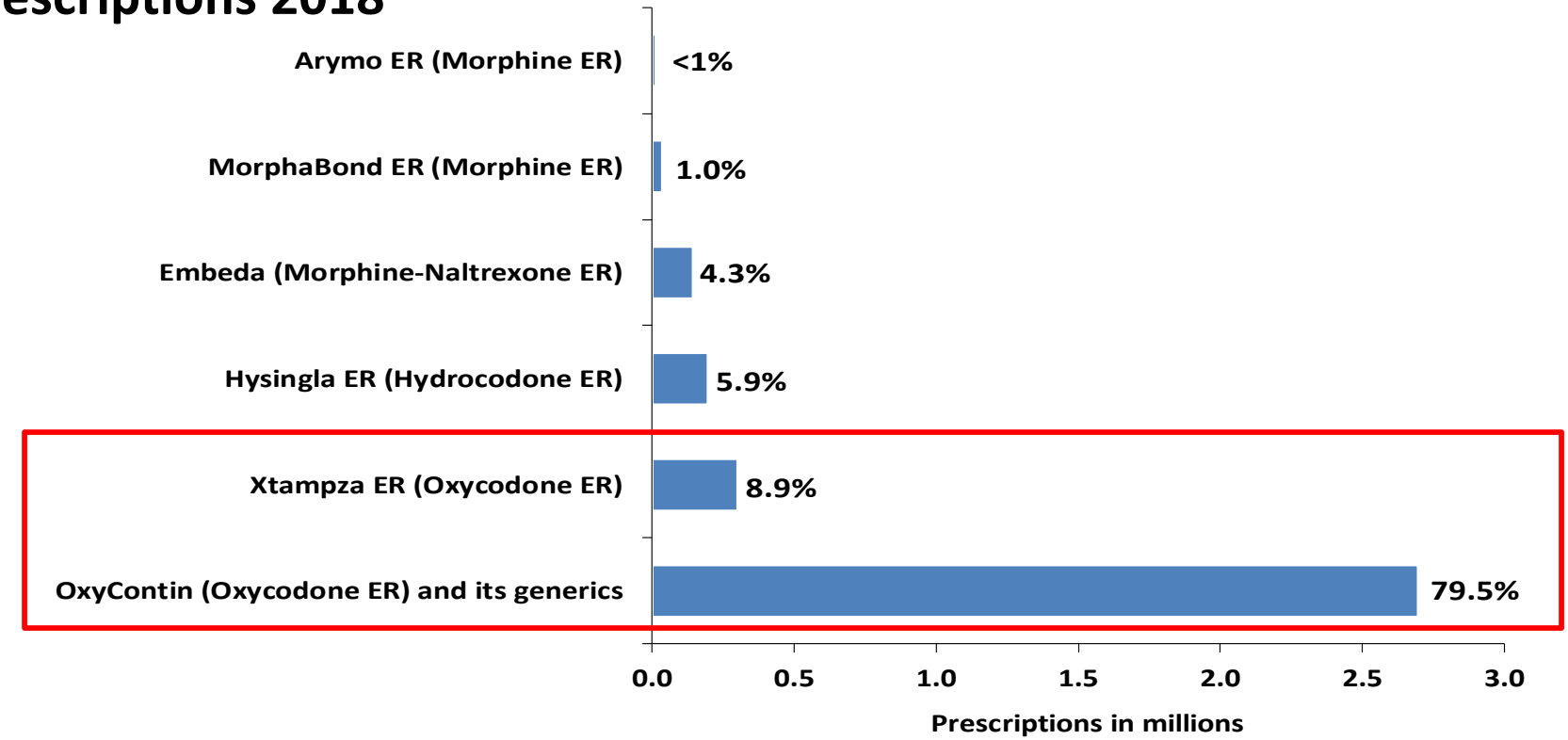


ER: Extended-release

Estimated number of prescriptions dispensed for extended-release opioid-containing analgesic products from U.S. retail pharmacies, 2018

Source: Symphony Health PHAST™ Prescription Monthly 2018. Data extracted June 2019.

Extended-release Oxycodone Products Make Up ~90% of ADF Prescriptions 2018



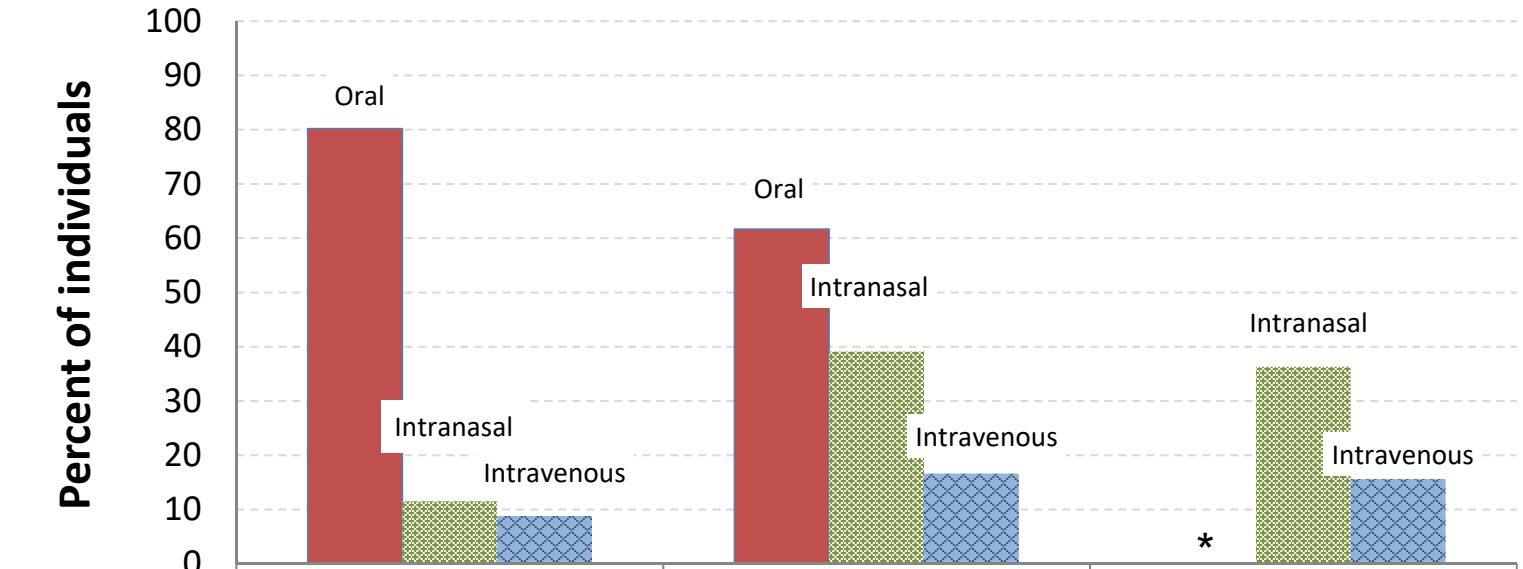
ADF: Abuse-deterrent formulation; ER: Extended-release

Estimated number of prescriptions dispensed for opioid-containing analgesic products with formulation properties designed to deter abuse from U.S. retail pharmacies, 2018

Source: Symphony Health PHAST™ Prescription Monthly 2018. Data extracted June 2019.

Routes of Misuse and Abuse

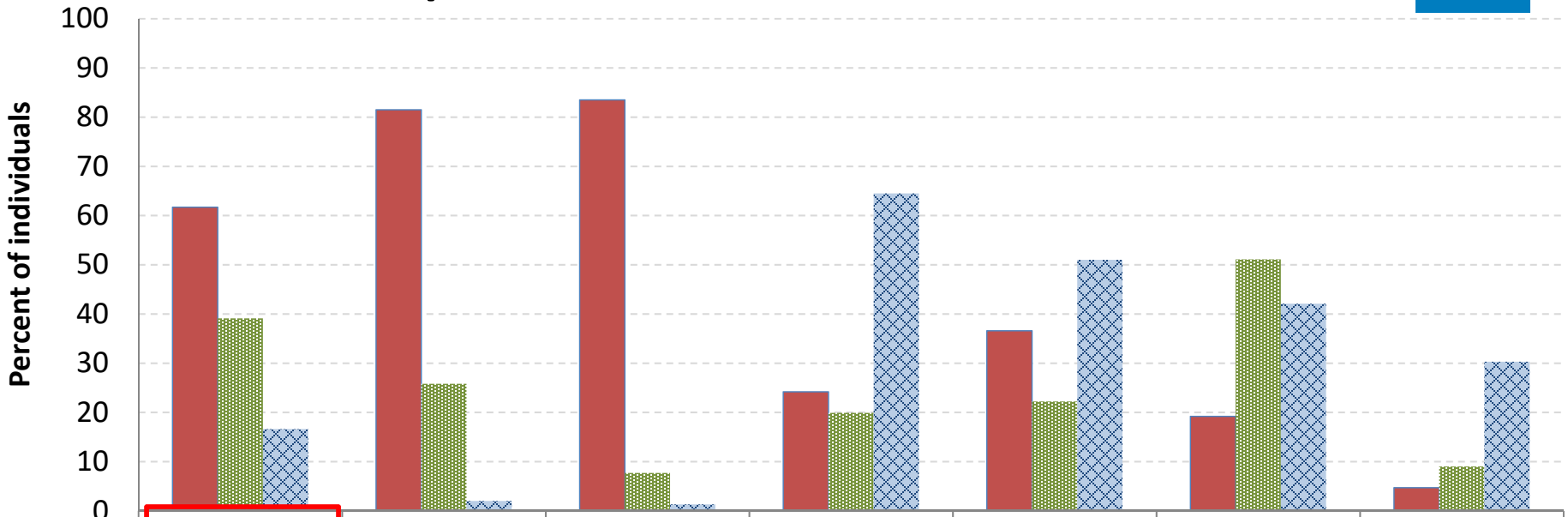
Oxycodone Primarily Abused by Oral and Intranasal Routes



	NPDS	NAVIPPRO	RADARS
Oral	80.2	61.7	*Not collected
Intranasal	11.5	39.1	36.3
Intravenous	8.8	16.6	15.6

NPDS: calling poison centers, 2012-2017; NAVIPPRO: assessed/seeking substance-use disorder treatment, 2016-2017; RADARS: entering public and private opioid-use disorder treatment, 2016-2017

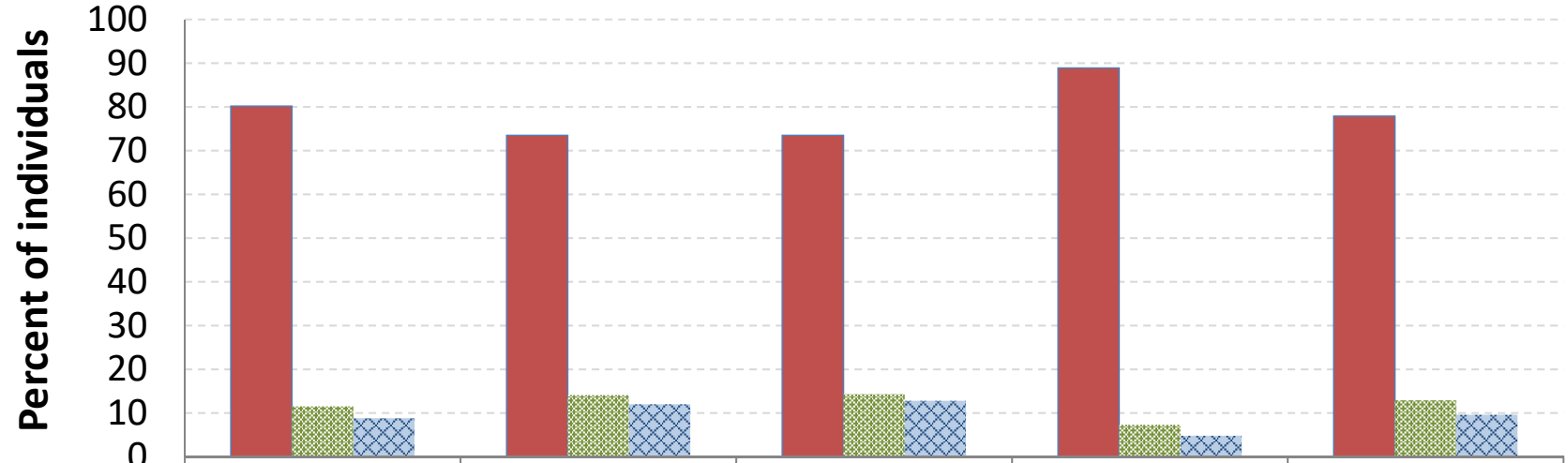
Intravenous Oxycodone Abuse is Less Common Compared to Other Abused Opioids; NAVIPPRO, 2016-2017



	Oxycodone	Hydrocodone	Tramadol	Hydromorphone	Morphine	Oxymorphone	Fentanyl
Oral	61.7	81.5	83.5	24.2	36.6	19.2	4.7
Intranasal	39.1	25.8	7.7	19.9	22.2	51.1	9
Intravenous	16.6	2	1.3	64.5	51	42.1	30.3

NAVIPPRO: Percent of individuals reporting route of abuse among individuals reporting past-month abuse of that substance, 2016-2017

Oral Abuse Most Common Regardless of Oxycodone Formulation; Intravenous Abuse More Common for ER and IR Single-entity Oxycodone; NPDS, 2012-2017

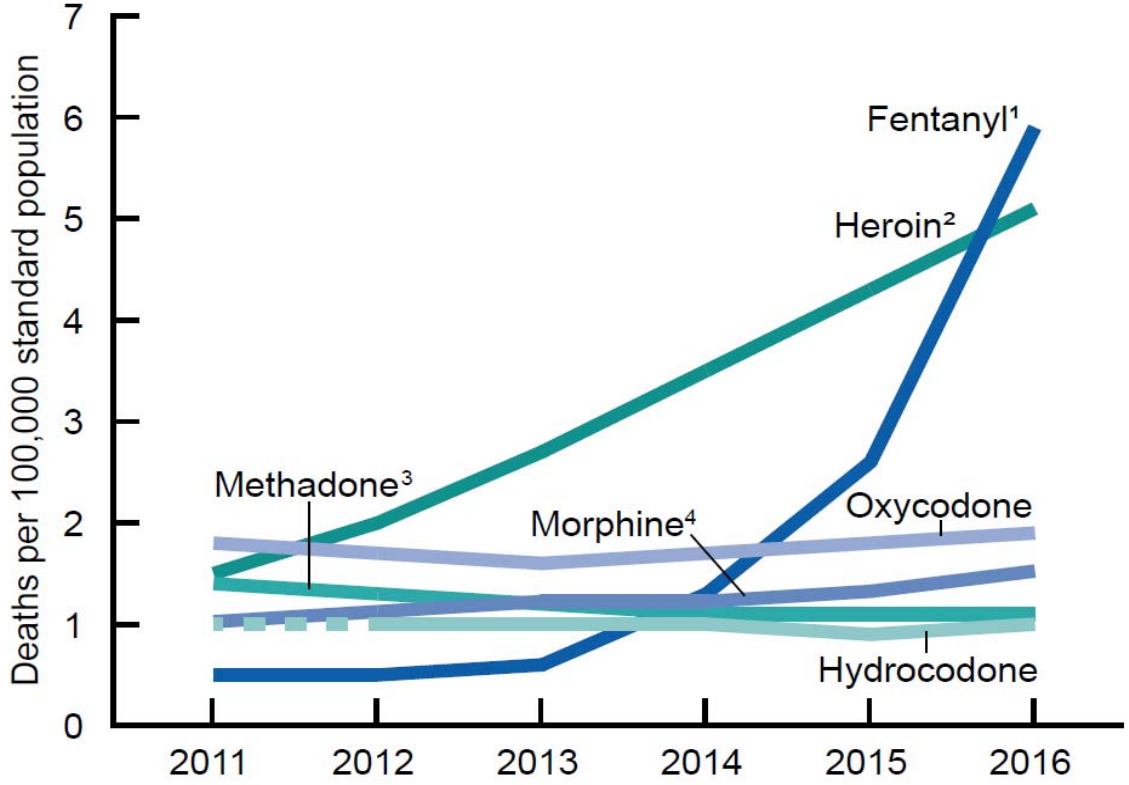


	Oxycodone (any)	Extended-release*	Immediate-release, single-entity	Immediate-release, combination	Oxycodone (not specified)
Oral	80.2	73.5	73.5	88.9	77.9
Intranasal	11.5	14.1	14.3	7.3	12.9
Intravenous	8.8	12	12.8	4.8	9.6

*All currently marketed ER oxycodone are ADFs; AAPCC NPDS: Percentage (%) of single-substance abuse exposure calls reporting specific exposure routes for oxycodone and selected other opioids among individuals 12 years of age and older, 2012-2017

Overdose Deaths

Fatal Overdose Rates Involving Fentanyl and Heroin Increased, Oxycodone Remained Stable; NVSS, 2011-2016



Age-adjusted rates for drug overdose deaths involving selected opioids, 2011–2016
Source: Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14.

Limitations

Key Limitations of Data Sources

- NPDS
  - Under-capture of exposures, particularly overdoses resulting in out-of-hospital death
  - The proportion of cases captured may vary over time and across drugs
- NAVIPPRO™/RADARS® TCP
  - Data may not be nationally representative
  - Product misclassification may occur due to self-report
- NVSS-M/DIM
  - Reliance on literal text of death certificates is likely to miss some proportion of opioid-related deaths that do not contain information on specific drugs and proportion of deaths missing this information changes over time

NPDS: National Poison Data System; RADARS TCP: Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program; NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; NVSS-M: National Vital Statistics System, Mortality; DIM: Drug-Involved Mortality

Conclusions

- ER oxycodone makes up ~90% of ADF opioid prescriptions in U.S.
- Oxycodone products are most often abused via oral route.
- Intravenous oxycodone abuse appears less common, compared to other abused opioids:
  - hydromorphone, morphine, oxymorphone, and fentanyl.
- Compared to combination products, intravenous abuse more common for ER and IR single-entity oxycodone products among callers to poison centers.
- Despite large increases in rates of overdose deaths involving fentanyl and heroin between 2011 and 2016, rates of overdose deaths involving oxycodone remained stable.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Nonclinical Safety Assessment of Aximris XR Excipients

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AADPAC/DSaRM Advisory Committee Meeting
January 15, 2020 (PM Session)

Overview

- The Agency has no nonclinical safety concerns with the excipients used in Aximris XR when the product is used as intended (oral).
- We agree with the Applicant that there are limited toxicology data regarding risk of intranasal and inhalation use.
- The Agency generally agrees with the Applicant's conclusion that, based on the limited data available, the risk from misuse of the Aximris XR drug product via the intravenous (IV) route of administration is likely similar to that of the referenced product, OxyContin.
- **FDA cannot rule out the possibility that adverse effects could occur with administration of manipulated Aximris XR for IV use.**

Safety Assessment of Excipients

- There is no formal FDA guidance document for evaluating the safety of oral drug products administered by unintended routes of administration.
- FDA evaluates the safety of excipients for the intended route of administration in accordance with the FDA guidance to industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.
- Intended reformulations of oral products to an IV drug product requires IV toxicology studies (local and systemic) and blood compatibility studies in accordance with the FDA guidance for industry: *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternative Route*.
- In the past, the Agency did not require an assessment of oral drug product excipient safety via IV or other unintended routes.

Postmarketing Experience With Opana ER

Unanticipated outcomes with the introduction of an abuse-deterrent (AD) opioid formulation to the market (Opana ER):

- Adverse events resulting from manipulation of the formulation for use by the unintended IV route of administration
  - Anemia, thrombocytopenia, thrombotic microangiopathy (TMA), acute kidney injury, retinal damage, cardiac involvement
- Data also supported a shift from intranasal route of abuse to the more dangerous intravenous route of abuse
  - Increase in outbreaks of HIV and Hepatitis C in drug users who were sharing manipulated reformulated Opana ER

Current FDA Approach to Excipient Safety For AD-Opioids via Unintended Routes

- We require applicants to provide a risk assessment of the potential adverse effects and risks associated with abuse of the final drug product, ideally based on results of Category 1 studies.
    - e.g., in vitro assessments, analysis of the Category 1 data with literature-based assessment of risk, and/or nonclinical studies
- An adequate assessment of the potential risks associated with non-oral abuse of the final drug product formulation is needed to determine the complete benefit-risk profile of the drug product.
- We include potential excipient-related adverse events from abuse of opioid drug products in Section 9.2 of the prescribing information.

Reformulated Opana ER Investigation

- Guinea pigs were injected with PEO+ (polyethylene oxide 7,000,000 Da plus other excipients) at doses that were predicted to mimic dosing in humans who manipulated Opana ER for IV use.
  - Material was administered either once or 5 times at 1.5 hour intervals.
  - Measured PEO plasma levels were consistent with predicted human plasma levels based on amount of PEO extractable from Opana ER.
- Animals demonstrated anemia, thrombotic microangiopathy (TMA), and acute kidney injury consistent with human adverse events.
- Not due to lack of blood compatibility directly.

Hunt et al. (2017) Blood 129(7): 896-905

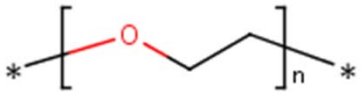
Key Point

- The risk of TMA from PEO in various AD-opioid drug products cannot be simply extrapolated across the class based on reformulated Opana ER.
  - Other FDA-approved opioids also contain PEO (e.g., OxyContin, Hysingla, Arymo, Zohydro) and do not appear to carry the same risk for TMA as reformulated Opana ER
  - However, there are published reports of TMA with IV OxyContin (Australia)

Key Point

- Differential risk could theoretically be based on:
  - Differences in manufacturing processes, curing methods, heat, additives, etc.
  - Differences in molecular weight (MW) of PEO used
  - Differences in methods used to prepare these products for IV abuse
  - Differential patterns of abuse of the drug substances and/or drug products

Polyethylene Oxide Polymers in AD Opioids



Data to date suggest potential TMA risk if HMW PEO (≥ 2 million) is extracted and injected; There are inadequate data for HMW PEOs < 2 million

MW~100,000 g/mol

Liquids → Waxy solids → Powders

"Polyethylene glycols" "Polyethylene oxides"

PEGs ≤ 600 MW in IV products

MW = 2 million[1]

OxyContin MW = 4 million[2]

Opana ER MW = 7 million[3]

Aximris XR MW = 4 million

[1]FDA Advisory Committee Meeting (November 14, 2018)
[2]Purdue Pharma (2009) FDA Advisory Committee Meeting Open Public Session
[3]Hunt et al. (2017)

Applicant's Approach for IV Risk Assessment of Aximris XR

- Characterized compounds in the Category 1 syringeable material, compared the profile to similarly manipulated OxyContin, and completed a literature-based toxicological risk assessment
- Conducted In vitro hemocompatibility testing of Category 1 syringeable material with human blood
- Conducted a 3-day IV toxicity study of Category 1 syringeable material in female rabbits

Characterization and Literature-based Risk Assessment of Syringeable Material

- Over 60 chemicals were detected above 5 mcg from both Aximris XR and OxyContin.
  - Many (~50) of the compounds from Aximris XR were also found in OxyContin
  - Each formulation had unique compounds as well
    - 7 from Aximris XR
    - 10 from OxyContin
- Permissible Daily Exposure (PDE) were estimated from existing literature toxicology data.
- PDEs suggest a relatively low risk for any given compound.

Characterization and Literature-based Risk Assessment of Syringeable Material

- Limitations to this analysis:
  - The safety of the combination of the chemicals cannot be evaluated via literature reviews.
  - There are no data on compounds over 600 Daltons.
  - The analysis was limited in scope (nonvolatile compounds not evaluated).
  - It is unknown what, if any, large MW PEO entities may be present in the syringeable material.
  - The lack of validated assays reduces the confidence in the identification and quantitation of the chemicals.

In Vitro Hemocompatibility Testing

- We agree that the Category 1 syringeable material tested is not expected to result in hemolysis or flocculation in vitro.
- However, Hunt et al. data argues that an in vivo study is necessary to evaluate risk for TMA.
  - Likely an indirect effect due to increased sheer stress in microvasculature and deposition of free hemoglobin in tissues.

Intravenous Toxicological Study in Rabbits

- IV toxicity study in female rabbits (one injection for 3 days)
  - Typical opioid effects observed (clinical signs, decreased body weight)
  - Altered organ weights (⬇thymus, ⬆adrenal, and ⬆ovary)
  - Some increases in severity or incidence of histopathological findings in lung, liver, and kidney
    - Suggests the potential for toxicity with more frequent and/or repeated misuse
  - No evidence of anemia or thrombotic microangiopathy (TMA) under the conditions tested

Intravenous Toxicological Study in Rabbits

- Limitations
  - Histopathological analysis was limited (not all organs evaluated)
  - Duration of study tests only a single dose for 3 days which does not mimic the likely clinical misuse pattern
  - No recovery group

Overall Assessment

- Injecting any manipulated oral drug can result in significant toxicity (e.g., granulomas, thrombotic microangiopathy, risk of spread of infectious disease).
- Based on the limited data available, Aximris XR is likely to have a similar risk profile for unintended IV route of exposure as OxyContin.
- If the HMW PEO in this product is able to be extracted into an IV syringe and injected, we would expect similar results as noted with reformulated Opana ER (dose- and duration-dependent toxicity due to PEO accumulation).
- FDA cannot rule out the possibility that adverse effects, including TMA, could occur with administration of manipulated Aximris XR for IV use.
- Aximris XR, if approved, would likely have similar warnings in labeling regarding risk of IV injection of manipulated drug products as other AD-opioids.

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Agency Interpretation of In Vitro and Human Abuse Potential Studies

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January 15, 2020 (PM Session)
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Objectives

Sponsor Submitted Studies Relevant to Abuse-Deterrent Assessment

- Oral Human Abuse Potential (HAP) Study OXC3/4/1117
- Intranasal Human Abuse Potential (HAP) Study OXC/2/0816
- Category 1 In Vitro Intravenous Injection studies

Provide Some Comments Regarding the Following:

- Physical manipulations used
- Primary comparison for assessing abuse-deterrent properties
- Use of OxyContin as a comparator
- General findings regarding Category 1 *in vitro* intravenous studies

Treatments

- Oral HAP Study
  - Manipulated 40 mg Aximris XR Tablets
  - Manipulated 40 mg Oxycodone Immediate-Release Tablets
  - Manipulated 40 mg OxyContin Tablets (Exploratory)
  - Placebo

- Intranasal HAP Study
  - Manipulated 30 mg Aximris XR
  - Manipulated 30 mg Oxycodone Immediate-Release Tablets
  - Manipulated 30 mg OxyContin Tablets (Exploratory)
  - Placebo

- Category 1 In Vitro Intravenous Injection
  - Whole or Manipulated 80 mg Aximris XR tablets
  - Whole or Manipulated 80 mg OxyContin tablets

Manipulations

HAP Studies and Category 1 Studies

- Physical manipulation method used represented a worst case scenario based on previous Category 1 physical manipulation results thereby providing substantial particle size reduction of Aximris XR and OxyContin tablets.

- OxyContin tablets, but not Aximris XR tablets, provides substantial resistance to physical manipulation.

- Whereas the extent of manipulation was necessary for OxyContin tablets, it was not for Aximris XR tablets. Simple tools could have been used for substantial particle size reduction of Aximris tablets but not OxyContin tablets to a fine powder for insufflation.

Oral and Intranasal HAP Studies:

Abuse-Deterrent Assessment

- Both HAP study protocols were of typical design for collection of pharmacodynamic data from non-dependent recreational opioid users. Primary subjective measures included visual analogue scales (VAS) for Drug Liking and Take Drug Again. Secondary measures included High VAS and Overall Drug Liking.

- The assessment of possible abuse deterrence was based on the primary comparison of manipulated Aximris XR tablets to manipulated Oxycodone IR.

- Manipulated Aximris XR tablets resulted in maximum oxycodone plasma levels equal to or higher than that produced by manipulated Oxycodone IR tablets

- For primary comparison, no statistically significant differences were observed for maximum effect (Emax) on subjective measures of Drug Liking VAS (primary), Take Drug Again VAS (primary), High VAS (secondary), or Overall Drug Liking VAS (secondary).

- Collectively these results suggest that under the manipulation conditions used, the extended release properties for oxycodone in Aximris XR tablets were defeated.

Oral and Intranasal HAP Studies

- Manipulated OxyContin was included as an exploratory arm.
- For both studies, manipulated OxyContin demonstrated similar effects to manipulated Oxycodone HCl IR with respect to Emax for Drug Liking, Take Drug Again, High, and Overall Drug Liking, thereby suggesting no evidence of potential abuse-deterrent effects by oral or intranasal administration.
- OxyContin has an intranasal but not oral abuse-deterrent claim.
- Failure of OxyContin to demonstrate an intranasal abuse deterrent effect in the present study is most likely due to the substantial physical manipulation utilized in the study.

In Vitro Intravenous Studies Submitted Under Review Cycle 1

- Use of non-heat pretreated tablets – Whole and Manipulated
- Some 10 mg tablets and all 80 mg tablets – Aximris XR and OxyContin
- Commonly used solvent for preparing solutions for intravenous injection.
- Under various conditions regarding solvent volume, solvent temperature, and extraction duration, non-heat pretreated, whole or manipulated Aximris XR and OxyContin tablets did not result in suitable solutions for intravenous injection due to either limited oxycodone extraction or to viscosity issues (syringeability).

In Vitro Intravenous Studies Submitted Under Review Cycle 2

- Use of Heat Pretreated Tablets – Whole and Manipulated
- 80 mg Tablets – Aximris XR and OxyContin
- Several solvents evaluated – 2 mL, 5 mL, and 10 mL
- Results assessed using the findings of Colucci et. al., (2014)*
  - One minute infusion of 4.9 mg oxycodone to non-dependent recreational opioid users.
  - Mean Emax for Drug Liking and High VAS of 96.4 and 94.6, respectively.
  - Mean Emax of Take Drug Again of 82.0

*Colucci et. al., 2014. Clinical Drug Investigation, 34: 421-429.

In Vitro - Intravenous Studies
Review Cycle 2

Pre-Heated 80 mg Tablet	Extraction (Minutes)	Starting mL	mL Recovered	Mg Oxycodone Recovered	Oxycodone Conc. mg/mL
Manipulated					
Aximris XR	0.5	2	0.3	8.3	----
OxyContin	0.5	2	1.7	55.0	32.3
Aximris XR	0.5	5	1.3	16.3	12.5
OxyContin	0.5	5	4.3	62.2	14.5
Aximris XR	0.5	10	3.5	22.5	6.4
OxyContin	0.5	10	9.2	64.2	7.0
Whole					
Aximris XR	30	2	1.2	15.7	13.1
OxyContin	30	2	1.4	19.2	13.7
Aximris XR	30	5	4.3	19.1	4.4
OxyContin	30	5	4.3	24.0	5.6
Aximris XR	30	10	8.9	23.0	2.6
OxyContin	30	10	9.1	25.0	2.7

In Vitro - Intravenous Studies
Review Cycle 2

- Heat Pretreated Manipulated Tablets – Volume and Oxycodone Recovered were less for 80 mg Aximris XR compared to 80 mg OxyContin.

- Heat Pretreated Whole Tablets – Volume and Oxycodone Recovered were more similar between 80 mg Aximris XR and 80 mg OxyContin.

- With the exception of manipulated Aximris XR in 2 mL, resulting solutions from either product could likely support intravenous abuse, particularly in non-dependent users.
  - OxyContin supports more multiple injections – One User or Multiple Users.

- 80 mg Tablets Used – Questionable to what extent lower dosage strengths may be used for intravenous abuse.

Conclusions

- The oral and intranasal HAP studies, as well as the Category 1 intravenous studies utilized a worst case scenario for physical manipulation of Aximris XR and OxyContin tablets. Such manipulation was necessary for OxyContin but not for Aximris XR, which, of the two, is more susceptible to physical manipulation.

- Oral and intranasal HAP studies demonstrated that manipulated Aximris XR tablets maximum oxycodone plasma levels as well as reinforcing subjective effects that were not different from immediate release oxycodone. This does not support potential deterrent effects of Aximris XR to oral or intranasal abuse.

- The failure of OxyContin (exploratory arm) to display an intranasal abuse-deterrent effect may be related to the extent of manipulation conducted. OxyContin is a hard tablet and requires advanced tools and additional work to undergo particle size reduction suitable for insufflation.

Conclusions

- Category 1 intravenous studies, as conducted in support of NDA 209653, demonstrate:
  - Manipulated, **non-heat pretreated** Aximris tablets and OxyContin tablets can not be used for preparing solutions for intravenous abuse thereby supporting a potential deterrent effect of these non-heat pretreated products to intravenous abuse. (1st Review Cycle)
  - Manipulated, **heat pretreated** 80 mg Aximris Tablets and 80 mg OxyContin tablets can be used to prepare solutions for intravenous abuse in non-dependent subjects. (2nd Review Cycle) Generally, fluid and oxycodone recovered was lower following use of 80 mg manipulated Aximris XR tablets compared to following 80 mg OxyContin tablets. This may suggest an incremental improvement of heat pretreated Aximris tablets over heat pretreated OxyContin tablets in deterring intravenous abuse under the manipulation conditions examined.

Clinical Summary

Aximris XR

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January 15, 2020 (PM Session)
FDA Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety & Risk Management Advisory Committee (DSaRM)

Outline

- Safety Findings from Human Abuse Potential Studies
- Benefit-Risk Assessment
- Considerations of Abuse-Deterrent Opioid Formulations

Safety Findings - Intranasal HAP Study

- Highest overall incidence of adverse events (AEs) occurred in the Aximris XR ground treatment group.
- The Agency does not consider the slightly higher incidence of nasal congestion in the Aximris XR ground treatment group to have a clinically meaningful deterrent effect, since there was no correlation between this finding and the clinical endpoints in the HAP study.

Safety Findings - Oral HAP Study

- Aximris XR milled in solution and OxyContin milled in solution had an overall incidence of adverse events (AEs) at approximately 95% each.
- Subjects in the Aximris XR intact treatment group had a lower incidence of AEs (72%) compared to other treatment groups except placebo (25%).

Potential Aximris XR Benefits

- If labeled with abuse-deterrent properties, Aximris XR would be an additional product with the potential to increase barriers for misuse and abuse.
- It would provide additional treatment options for the intended patient population.

Risks Associated with Intended Use

- Opioids carry serious risks for numerous safety concerns including abuse, misuse, addiction, and intentional or accidental overdose which may result in respiratory depression and death.
- All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Potential Risk Associated with Unintended Use

- Intravenous
  - Inactive ingredients in Aximris XR can result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular heart injury, embolism, and death.
  - Cases of thrombotic microangiopathy have been reported in another oxycodone extended-release formulation.
  - Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Potential Risk Associated with Unintended Use (cont'd)

- Intranasal
  - Prolonged intranasal opioid abuse has been reported to be associated with nasal necrosis, nasal septum perforation, olfactory nerve damage, other localized tissue damage, and overdose.

Abuse-Deterrent Formulations Considerations to Public Health

- Abuse-deterrent opioid formulations are developed to increase barriers for misuse and abuse, not for addictive properties.
- The public health impact of abuse-deterrent formulation opioids in a real world post-marketing setting is unclear.
- The Agency is cognizant of the public health concern of potentially approving another opioid and adding new opioids into the marketplace.
- A recent study (Chai, et al) found that approval of new branded opioid products alone does not appear to be a primary driver of increased opioid prescribing.
- This same study found that the number of opioid analgesic prescriptions dispensed has declined since 2012, despite an increasing number of opioid analgesic approvals.

Chai G, et al, New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015, Anesthesiology, Volume 128, No 5, May 2018, pages 953-966.

Abuse-Deterrent Formulations Considerations to Public Health (cont'd)

- Potential unintended adverse consequences
  - A shift to more dangerous routes of abuse (e.g., nasal to the more dangerous intravenous) based on properties of the formulation
  - Use of tampering methods that could result in harmful effects
  - Potential safety concerns related to the abuse-deterrent formulation
- Unknown safety of excipients by unintended routes of administration


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