

Clinical Considerations in the Evaluation of the Safety and Effectiveness of Hydexor

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Agenda

- Introduction
- Study Population
- Safety evaluation with a focus on CNS adverse events (AEs)
- Indication

Introduction

- Hydexor is a fixed-dose combination product that contains the analgesics hydrocodone and acetaminophen in combination with the antiemetic promethazine
- Sponsor's proposed indication
 - “The short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV). Hydexor is indicated when alternative treatments for pain are inadequate.”
 - Novel Indication
- Hydexor has not been formulated with features intended to deter abuse, similar to all other hydrocodone/acetaminophen products currently available on the market

Phase 3 Study Population

- The Sponsor conducted two Phase 3 efficacy and safety studies intended to support the use of Hydexor for the proposed indication
 - One in dental pain (Study CLCT-002) and one in post-bunionectomy pain (study CLCT-003)
- Both studies enrolled a population of patients that were anticipated to be prone to opioid-induced nausea/vomiting
 - Assessment was based on the results of the Nausea Prone Questionnaire (NPQ) +/- a hydrocodone challenge
 - Based on these assessments, patients were classified as
 - “Likely Nausea-Prone”
 - “Possible Nausea-Prone”
 - Additionally, the protocol allowed investigators to enroll up to 10% of patients who did not meet the predefined nausea-prone criteria but were thought to be nausea-prone based on clinical judgment

Nausea-Prone Results – Randomized Patients

Study CLCT-002 – Randomized Patients

Category	N (%)
Likely Nausea-Prone	367 (79%)
Possible Nausea-Prone	78 (17%)
Investigator Discretion	21 (5%)
Total	466

Study CLCT-003 – Randomized Patients

Category	N (%)
Likely Nausea-Prone	383 (69%)
Possible Nausea-Prone	132 (24%)
Investigator Discretion	37 (7%)
Total	552

FDA Statistical Review by Dr. James Travis

Safety Evaluation

- Opioid-related safety was proactively assessed on the Opioid Symptoms Scales (OSS) in Studies CLCT-002 and CLCT-003
 - Proactive monitoring of the frequency and severity of nine opioid-related AEs
 - Confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizziness
 - OINV was not measured on the OSS, but was measured as an efficacy measure in the two Phase 3 efficacy studies
 - Patients completed separate 0-to-10 Likert scales for each symptom on the OSS

Opioid-induced Symptoms in the Pooled Efficacy Studies

OSS Rating	Opioid-induced Symptom	Hydexor (N=463) N (%)	Norco (N=455) N (%)	Placebo (N=100) N (%)
Mild, Moderate and Severe (OSS Rating=1-10)	Confusion	149 (32)	106 (23)	10 (10)
	Constipation	205 (44)	216 (48)	20 (20)
	Difficulty Concentrating	241 (52)	206 (45)	36 (36)
	Difficulty Voiding	47 (10)	38 (8)	6 (6)
	Drowsiness	431 (93)	403 (89)	69 (69)
	Dry Mouth	331 (72)	288(63)	53 (53)
	Headache	328 (71)	328 (72)	77 (77)
	Itchiness	251 (54)	239 (53)	36 (36)
	Lightheaded/Dizzy	303 (65)	303 (67)	35 (35)

Severe Opioid-induced Symptoms (Study CLCT-002)

Opioid-Induced Symptom	Hydexor (N=211) N (%)	Norco (N=205) N (%)	Placebo (N=50) N (%)
Total Number of Severe OSS Opioid-Induced Symptoms	664	423	61
Number of Subjects with at Least One Severe OSS	114 (54)	107 (52)	20 (40)
Confusion	14 (7)	5 (2)	0
Constipation	17 (8)	23 (11)	2 (4)
Difficulty Concentrating	25 (12)	18 (9)	4 (8)
Difficulty Voiding	4 (2)	1 (1)	0
Drowsiness	97 (46)	76 (37)	8 (16)
Dry Mouth	26 (12)	15 (7)	3 (6)
Headache	41 (19)	36 (18)	14 (28)
Itchiness	11 (5)	11 (5)	0
Lightheaded/Dizzy	41 (19)	37 (18)	3 (6)

Severe Opioid-induced Symptoms (Study CLCT-003)

Opioid-Induced Symptom	Hydexor (N=252) N (%)		Norco (N=250) N(%)		Placebo (N=50) N (%)	
	Days 1-2	Days 3-5	Days 1-2	Days 3-5	Days 1-2	Days 3-5
Total Number of Severe OSS Opioid-induced Symptoms	389	276	222	157	29	4
Number of Subjects with at Least One severe OSS	125 (50)	83 (33)	88 (35)	54 (22)	10 (20)	3 (6)
Confusion	6 (2)	2 (1)	0	1 (0)	0	0
Constipation	16 (6)	30 (12)	18 (7)	35 (14)	2 (4)	1 (2)
Difficulty Concentrating	20 (8)	7 (3)	8 (3)	3 (1)	2 (4)	0
Difficulty Voiding	1 (0)	0	2 (1)	1 (0)	0	0
Drowsiness	105 (42)	46 (18)	53 (21)	12 (5)	4 (8)	0
Dry Mouth	38 (15)	31 (12)	17 (7)	5 (2)	4 (8)	0
Headache	27 (11)	19 (8)	27 (11)	14 (6)	6 (12)	0
Itchiness	15 (6)	13 (5)	11 (4)	9 (4)	1 (2)	1 (2)
Lightheaded/Dizzy	18 (7)	12 (5)	19 (8)	9 (4)	1 (2)	1 (2)

CNS Safety Summary

- Although the results of the Opioid Symptom Scale (OSS) demonstrated a relatively modest increase in CNS adverse events for Hydexor compared to Norco, there was an increased frequency of severe CNS AEs (e.g., confusion, difficulty of concentration, and drowsiness) for Hydexor
- There were no discontinuations due to AEs in the Phase 3 efficacy and safety studies
 - Study CLCT-006 (open-label safety study) - one discontinuation due to several AEs, including somnolence
- There were no deaths or nonfatal CNS serious adverse events that were attributed to Hydexor

Indication

- The Sponsor has proposed an indication that includes the “prevention ***and reduction*** of OINV”.
 - The preferred primary OINV endpoint consists of vomiting or use of antiemetic medication and reflects the prevention of OINV rather than a reduction in symptoms in patients experiencing OINV
 - Therefore, the appropriate indication for the OINV component would be the “prevention of OINV”
- The indication should reflect that Hydexor be used in patients who are expected to be prone to nausea and vomiting
 - Enriched study population
 - Increased rate and severity of CNS AEs
 - Other ***potential*** serious AEs in the promethazine label

THE END

Utilization Patterns for Combination Hydrocodone-Acetaminophen, Selected Opioid Analgesics, and Promethazine-Containing Products

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

February 14, 2018



Outline

- Sales distribution
- Outpatient retail utilization
 - Patient-level data
 - Prescription data
 - Prescriber specialty
 - Drugs indicated for treatment of nausea and vomiting
 - Claims and survey based analysis of concurrent use
- Limitations
- Summary of findings

Drugs Included in Analyses



Selected Opioid Analgesics Products

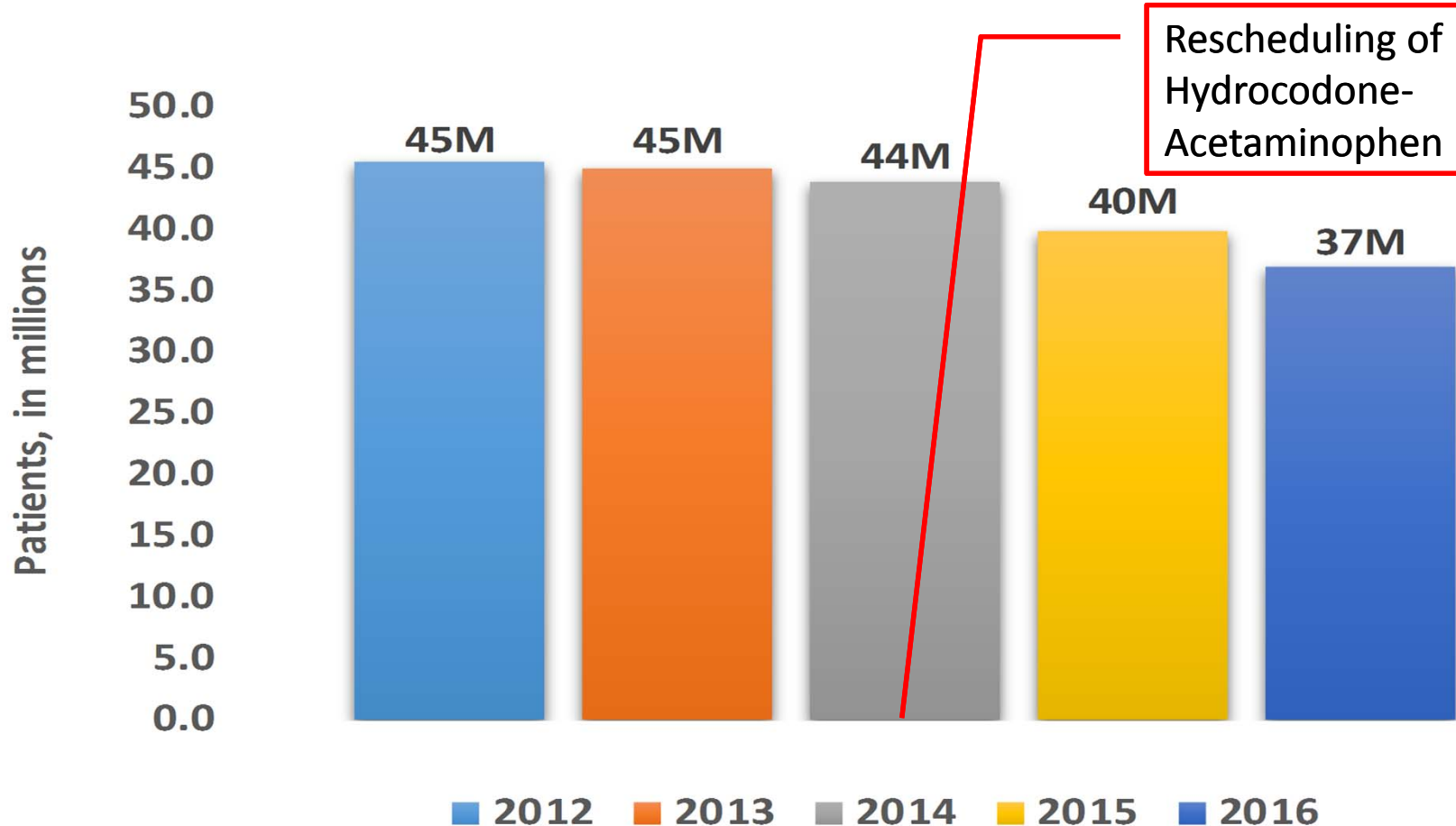
- Immediate-Release (IR) Products
 - Oral Combination
 - Hydrocodone-Acetaminophen
 - Oxycodone-Acetaminophen
 - Oral Single-Ingredient
 - Hydromorphone
 - Morphine
 - Oxycodone
 - Oxymorphone
 - Tapentadol

Promethazine-Containing Products

- Oral and Suppository
 - Single-ingredient
 - Promethazine
 - Combination
 - Promethazine-Codeine-Phenylephrine
 - Promethazine-Codeine
 - Promethazine-Dextromethorphan
 - Promethazine-Meperidine
 - Promethazine-Phenylephrine
 - Promethazine-Pseudoephedrine

Patient Data: Hydrocodone-Acetaminophen

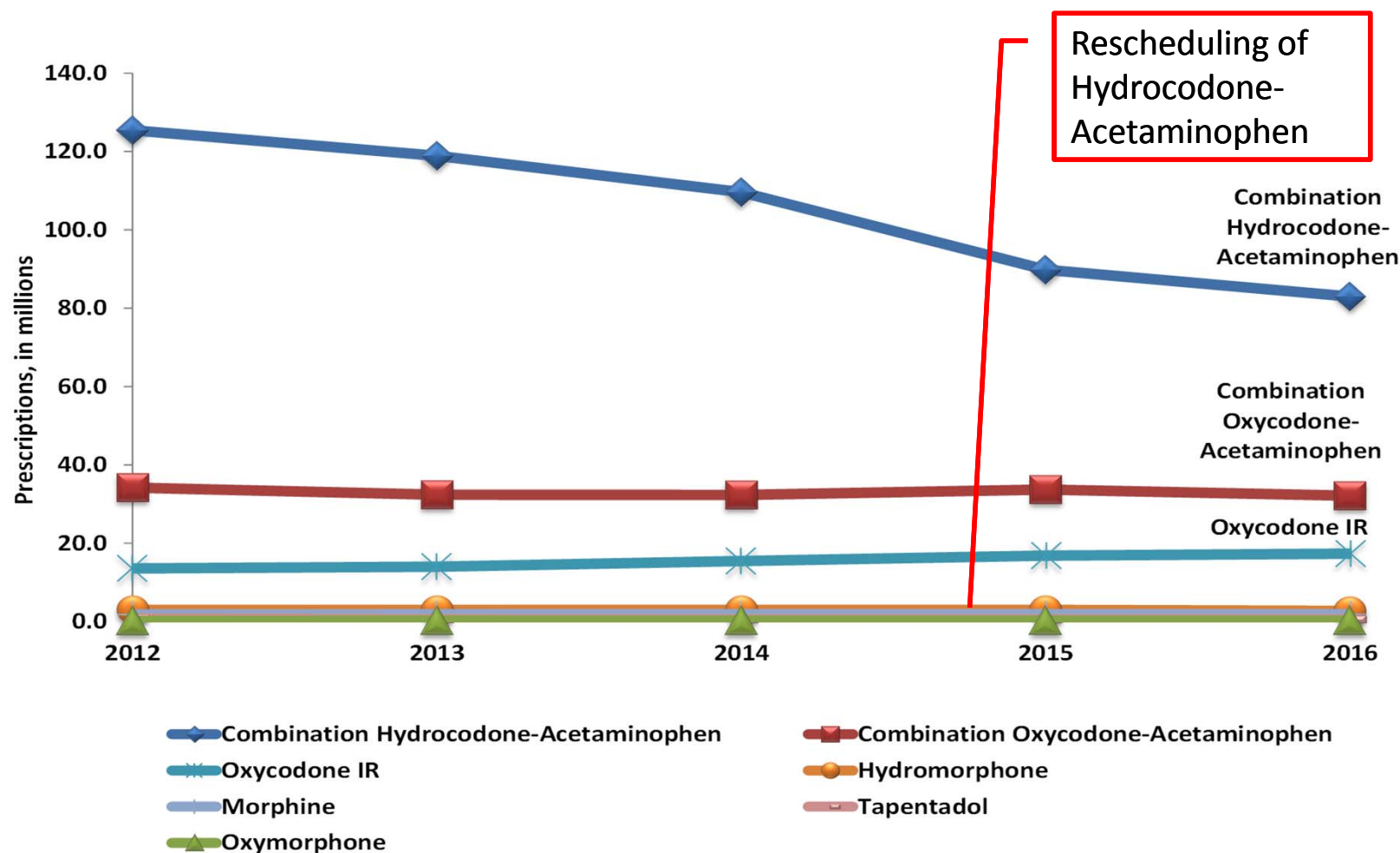
FDA



Nationally Estimated Number of Patients Receiving a Dispensed Prescriptions for Hydrocodone-Acetaminophen from the U.S. Outpatient Pharmacies

Source: IQVIA, Total Patient Tracker (TPT). Years 2012-2016. Data extracted December 2017.

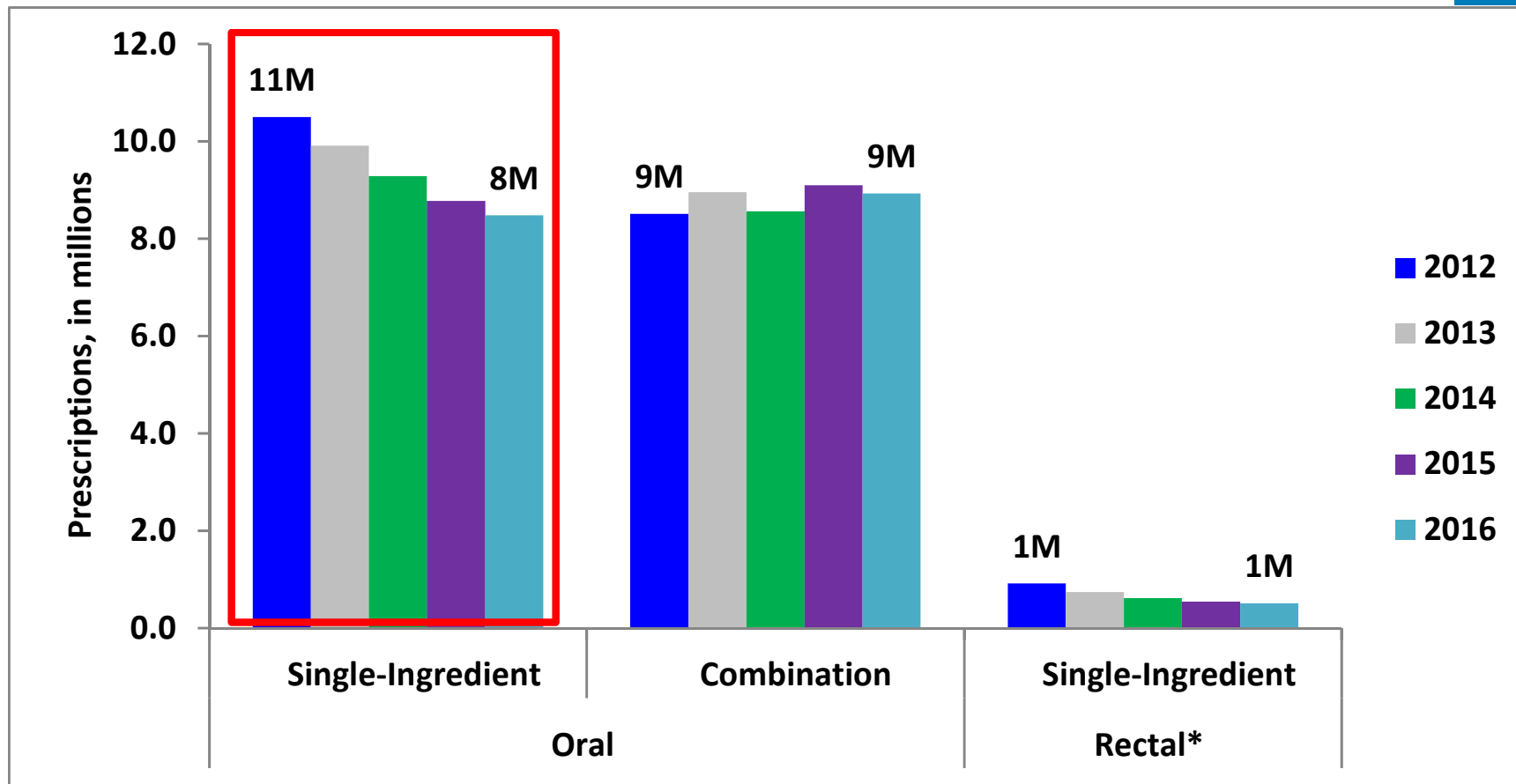
Prescription Data: Hydrocodone-Acetaminophen and Selected Opioid Analgesic Products



Nationally Estimated Number of Dispensed Prescriptions for Hydrocodone-Acetaminophen and Selected Opioid Analgesic Comparator from U.S. Outpatient Retail Pharmacies

Source: IQVIA, National Prescription Audit (NPA). Years 2012 - 2016. Data extracted December 2017

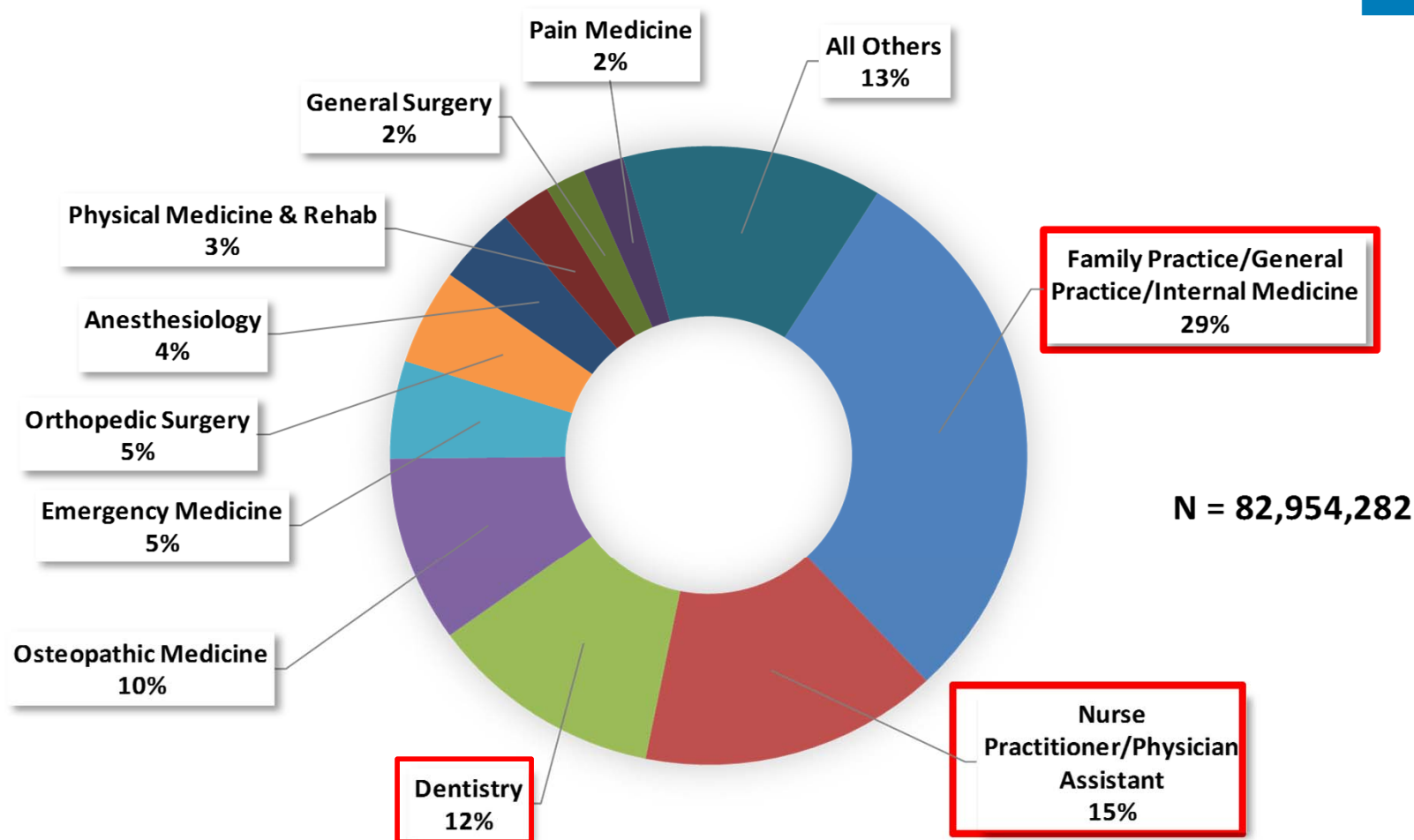
Prescription Data: Promethazine-Containing Products



Nationally Estimated Number of Dispensed Prescriptions for Oral and Rectal Promethazine-Containing Products, by Single-Ingredient and Combination, from U.S. Outpatient Retail Pharmacies

Source: IQVIA, National Prescription Audit (NPA). Years 2012 - 2016. Data extracted December 2017

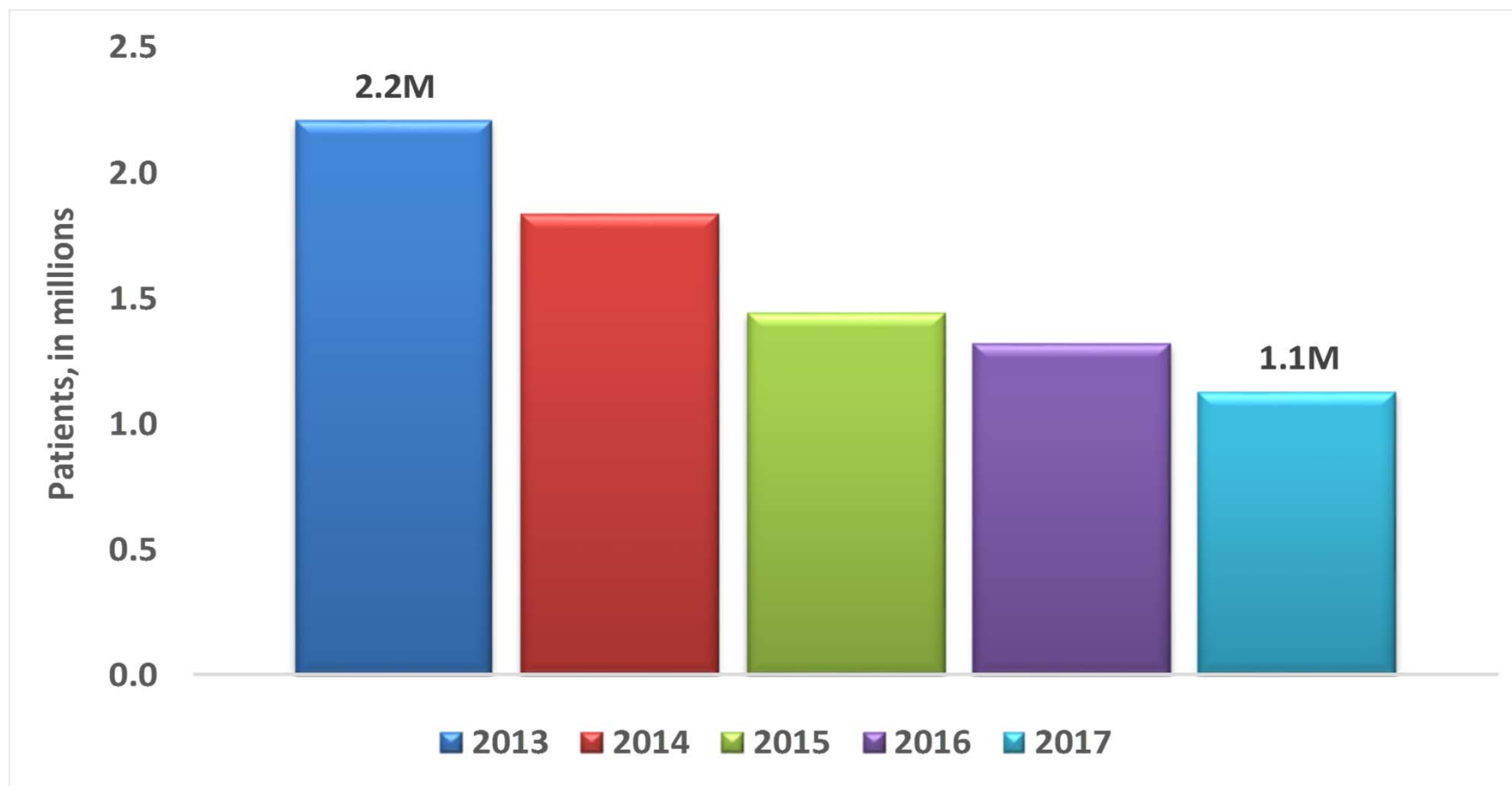
Top Prescriber Specialties



Nationally Estimated Number of Dispensed Prescriptions for Hydrocodone-Acetaminophen from U.S. Outpatient Retail Pharmacies, Stratified by Top 10 Prescriber Specialties in 2016

Source: IQVIA, National Prescription Audit (NPA). January 2016 - December 2016. Data Extracted December 2017
www.fda.gov

Patient Data: Concurrency Data

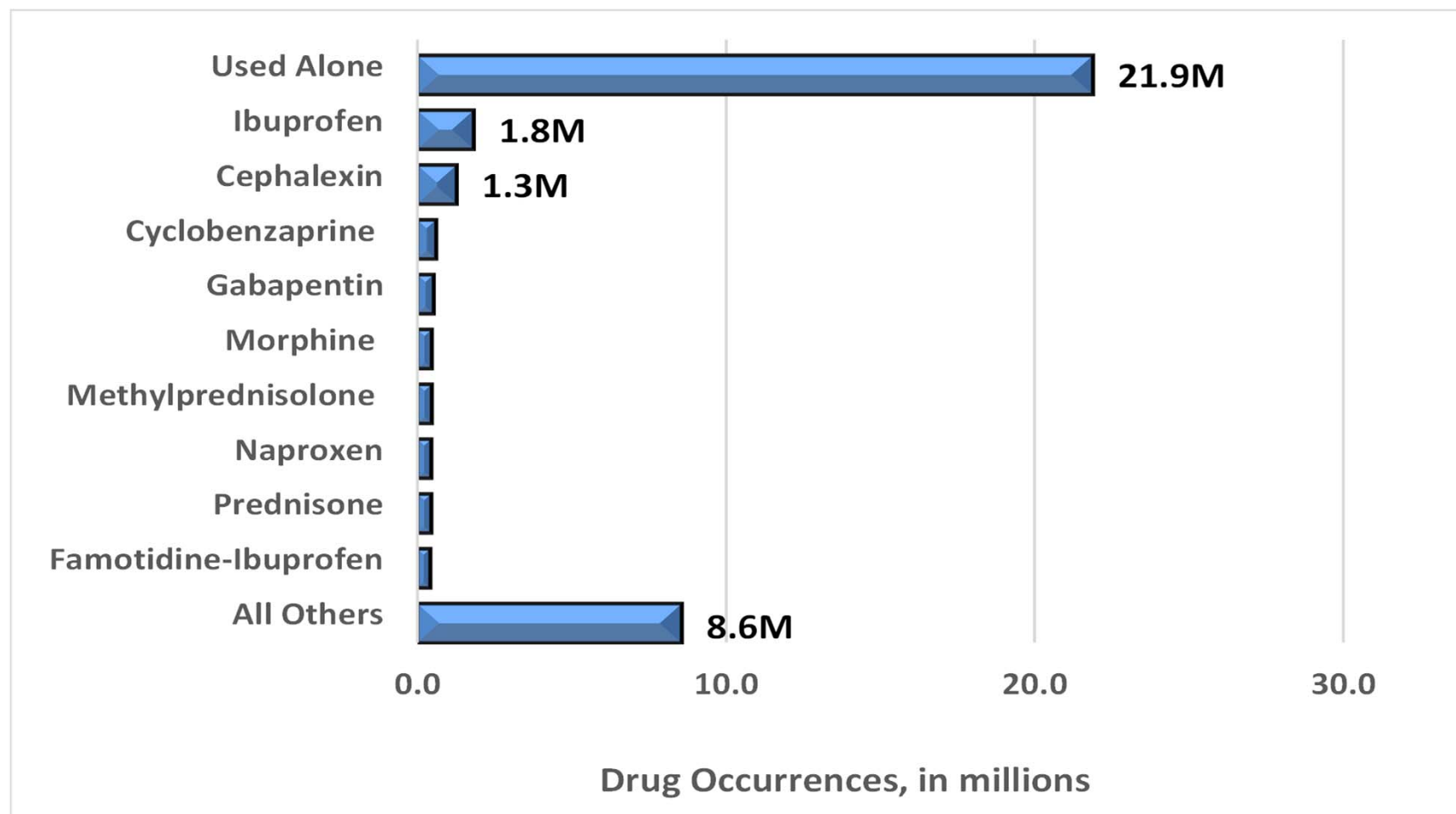


Nationally Estimated Number of Patients with Concurrent Prescription Claims for Hydrocodone-Acetaminophen and Single-Ingredient Promethazine* Products , from U.S. Outpatient Retail Pharmacies

*Include oral and rectal formulations only

Source: Symphony Health Solutions' Integrated Dataverse. Years 2013 - 2017. Data extracted January 2018.

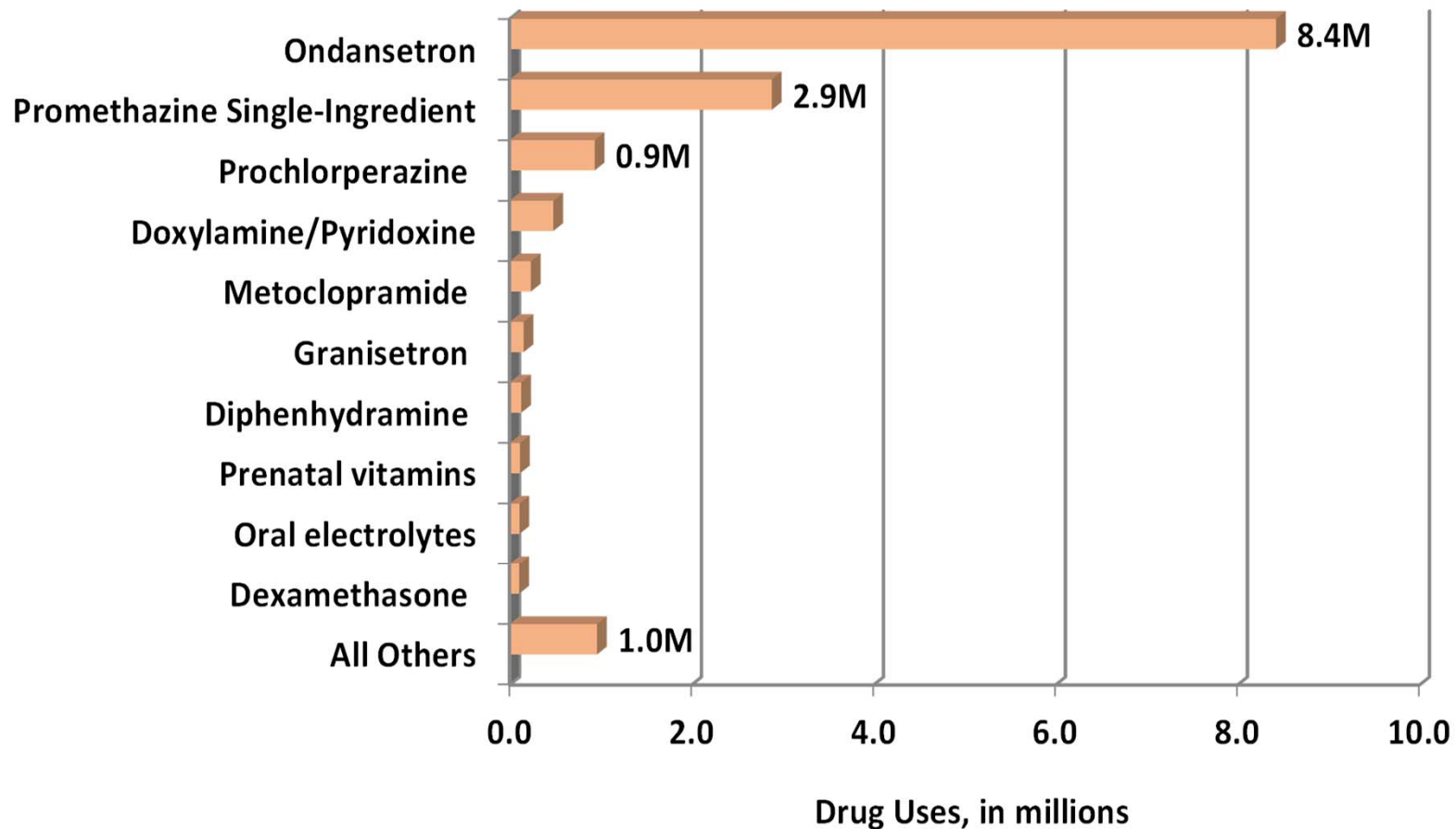
Survey Data: Hydrocodone-Acetaminophen Concomitant Use 2016



Top Drug Occurrences for Combination Hydrocodone-Acetaminophen, Used alone or with Another Drug, as Reported by Office-Based Physician Surveys in 2016

Source: Syneos Health, TreatmentAnswers™. Year 2016. Data extracted December 2017.

Survey Data: Drugs for Nausea and Vomiting 2016



Top 10 Drugs Associated with Diagnosis (ICD-10) Codes for Nausea and Vomiting, as Reported by Office-Based Physician Surveys in 2016

Source: Syneos Health, TreatmentAnswers™. Year 2016. Data extracted December 2017.



Limitations

- Only dispensing patterns in the outpatient retail setting was assessed
- Concurrency data based on prescription claims
 - Prescriptions may be written by different prescribers
 - Indication of use is not known
- Concomitant prescribing and diagnoses information based on the survey data are not linked to dispensed prescriptions
- Concomitant prescribing and diagnoses data were derived from surveys of office-based physician practices



Key Findings

- Outpatient utilization decreased for
 - Hydrocodone-acetaminophen
 - Single-ingredient promethazine products
- Concurrent prescription claims for hydrocodone-acetaminophen and single-ingredient promethazine decreased
- No mentions of concomitant prescribing for hydrocodone-acetaminophen and promethazine by the same prescriber during the same office visit
- Ondansetron was the drug most frequently mentioned for treatment of nausea and vomiting in outpatient setting followed by promethazine



Thank you



Postmarketing Data on Misuse and Abuse of Hydrocodone and Promethazine

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Anesthetic and Analgesic Drug Products Advisory Committee
(AADPAC) and Drug Safety and Risk Management (DSARM)
Advisory Committee Meeting for Hydexor
February 14, 2018



Background

Purpose of Epidemiology Review



- 2017 NASEM Report¹ recommends developing a regulatory framework for opioids that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse to ensure that ... as actually used, the drugs provide benefits that clearly outweigh their harms.
- Goal of epidemiology review was to provide descriptive postmarketing data to help inform the risk-benefit evaluation of Hydexor

1. National Academies of Sciences, Engineering, and Medicine. 2017. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: The National Academies Press.



Misuse and Abuse Definitions

- The definitions of misuse and abuse vary according to the source of data
- Unless otherwise specified in relation to a specific data source, we use the following definitions of misuse and abuse:
 - ***Abuse***: the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect
 - ***Misuse***: the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse



Hydrocodone Misuse and Abuse

Hydrocodone Use and Misuse* in the U.S.



National Survey on Drug Use and Health (NSDUH), 2016

	Age (in years)	Any Pain Reliever	Hydrocodone Products
Past Year <u>Use</u>, N in thousands (%)	12 or older	91,846 (34.1)	54,807 (20.3)
	12 to 17	4,732 (19.0)	1,240 (5.0)
	18 to 25	10,407 (30.1)	5,923 (17.1)
	26 or older	76,706 (36.5)	47,644 (22.7)
Past Year <u>Misuse</u>, N in thousands (%)	12 or older	11,517 (4.3)	6,924 (2.6)
	12 to 17	881 (3.5)	349 (1.4)
	18 to 25	2,454 (7.1)	1,552 (4.5)
	26 or older	8,181 (3.9)	5,023 (2.4)
<u>% Misuse Among Past-year Users</u>	12 or older	12.5	12.6
	12 to 17	18.6	18.6
	18 to 25	23.6	26.2
	26 or older	10.7	10.5

***Misuse defined here as “use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor”**

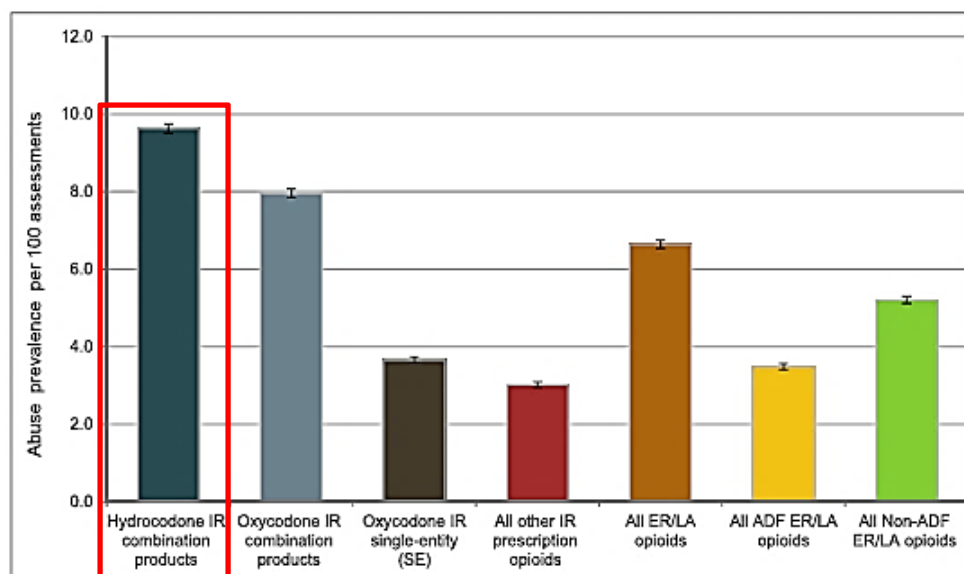
Table generated using 2016 *National Survey on Drug Use and Health: Detailed Tables*. Substance Abuse and Mental Health Services Administration, Rockville, MD



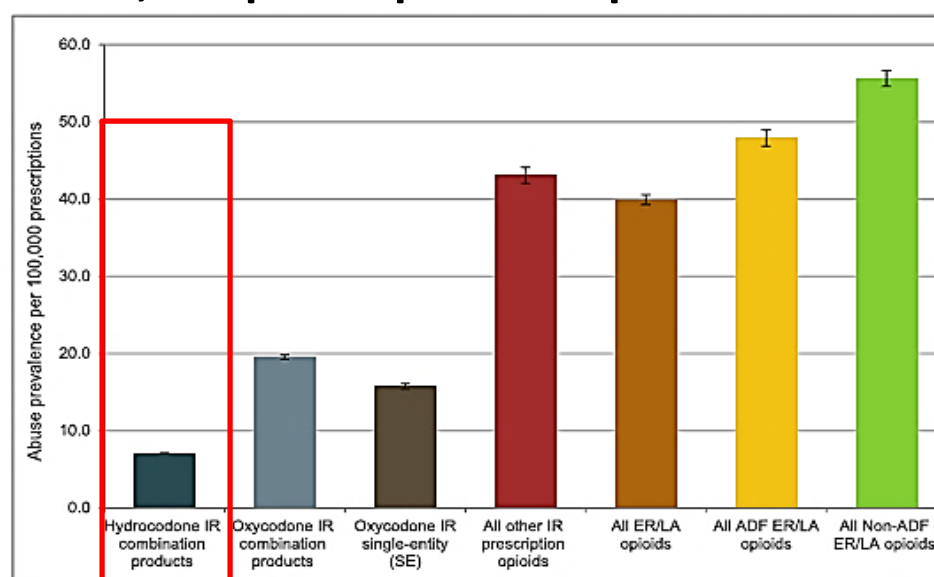
Hydrocodone IR Combination Product Abuse

in the National Addictions Vigilance Intervention and Prevention Program
(NAVIPPRO®) Addiction Severity Index—Multimedia Version (ASI-MV®)
surveillance network, 1/1/2012 - 6/30/2015

**Prevalence of past 30-day abuse per
100 assessments**



**Prevalence of past 30-day abuse per
100,000 prescriptions dispensed**



Figures from Cassidy et al., *Pharmacoepidemiol Drug Saf* 2017

Calls to U.S. Poison Control Centers



Total and single-substance intentional hydrocodone/acetaminophen exposures among individuals 12+ years of age, National Poison Data System (NPDS) 2010-2016

Exposure Reason	Total Exposures		Single-Substance	
	N	%	N	%
Intentional Exposures	102,732		32,043 (31.2%)*	
Abuse	11,957	11.6%	4,363	13.3%
Misuse	14,058	13.7%	7,502	23.0%
Suspected Suicides	70,822	68.9%	18,075	57.2%
Unknown	5,895	5.7%	2,103	6.6%

*Percent of total intentional exposures

Analyses conducted by Sara Karami, PhD
DEPI I, OSE, CDER, FDA

Hydrocodone-related Emergency Department (ED) Visits in 2016



Implicated Product(s)	Case Type							
	Abuse		Therapeutic Misuse		Unknown Intent		Other Therapeutic Adverse Event	
	Cases in sample	National Estimate	Cases in sample	National Estimate	Cases in sample	National Estimate	Cases in sample	National Estimate
Any Hydrocodone-containing Product Implicated	73	5,093	34	3,365	87	8,287	249	23,388
Hydrocodone-containing Product Implicated Alone	30	2,075	22	2,082	32	2,792*	153	14,508

*Coefficient of variation >30%

Data provided by the CDC Division of Healthcare Quality Promotion, using data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, 2016.

Hydrocodone-involved Deaths



Hydrocodone-involved deaths among individuals 12+ years of age, by year, National Vital Statistics System-Mortality (NVSS-M) and Drug-Involved Mortality (DIM) 2010-2015

Year	Total deaths involving hydrocodone	Hydrocodone only drug mentioned, N (% of total)	Flagged as misuse/abuse, N (% of total)
2010	3,152	232 (7.4)	1,174 (37.2)
2011	3,507	243 (6.9)	1,350 (38.5)
2012	3,346	265 (7.9)	1,297 (38.8)
2013	3,419	298 (8.7)	1,358 (39.7)
2014	3,580	304 (8.5)	1,480 (41.3)
2015	3,342	252 (7.5)	1,353 (40.5)
TOTAL	20,346	1,593 (7.8)	8,012 (39.4)

Analyses conducted by Sara Karami, PhD
DEPI I, OSE, CDER, FDA

Route of Abuse for Hydrocodone Combination Products



- In 2016, FDA reviewed epidemiologic data on route of abuse for hydrocodone combination products¹
 - Route patterns vary widely, depending on the population
 - Abuse is primarily oral
 - Intranasal abuse
 - Common in some populations, particularly those with more advanced substance use disorders
 - Generally not the preferred or exclusive route
 - Intranasal drug abuse can cause nasal tissue necrosis and fungal infections, but incidence is unknown²⁻⁴
 - Injection abuse is very infrequent

1. FDA Briefing Document: Joint Meeting of AADPAC and DSARM Advisory Committees, May 5, 2016. Epidemiology Review: Review of hydrocodone combination product postmarketing abuse studies.

2. Yewell et al., *Ann Otol Rhinol Laryngol* 2002

3. Alexander et al., *Laryngoscope* 2012

4. Volser et al., *Int Forum Allergy Rhinol* 2014



Promethazine Misuse and Abuse

Calls to U.S. Poison Control Centers



Total and single-substance intentional promethazine exposures among individuals 12+ years of age, National Poison Data System (NPDS) 2010-2016

Exposure Reason	Total Exposures		Single-Substance Exposures							
			Overall		Single-Ingredient		Containing Codeine		Other [#]	
	N	%	N	%	N	%	N	%	N	%
Promethazine										
Intentional Exposures	15,119		4,293	(28.4%)*	3,063	(71.3%)^	697	(16.2%)^	533	(14.1%)^
Abuse	1,451	9.6%	570	13.4%	233	7.6%	207	29.7%	130	24.4%
Misuse	1,516	10.0%	855	19.7%	450	14.7%	231	33.1%	174	32.6%
Suspected Suicides	11,240	74.3%	2,517	58.7%	2,138	69.8%	194	27.8%	185	34.7%
Unknown	912	6.0%	351	8.3%	242	7.9%	65	9.3%	44	8.3%
Promethazine & Hydrocodone/Acetaminophen										
Intentional Exposures	1,300									
Abuse	79	6.1%								
Misuse	85	6.5%								
Suspected Suicides	1,076	82.8%								
Unknown	60	4.6%								

*Percent of total intentional exposures

^Percent of single-substance exposures

#Includes single-substance exposures to promethazine products containing dextromethorphan, meperidine, pseudoephedrine, and/or ethanol

Analyses conducted by Sara Karami, PhD
DEPI I, OSE, CDER, FDA



Promethazine-related ED Visits in 2016

Implicated Product(s)	Case Type							
	Abuse		Therapeutic Misuse		Unknown Intent		Other Therapeutic Adverse Event	
	Cases in sample	National Estimate	Cases in sample	National Estimate	Cases in sample	National Estimate	Cases in sample	National Estimate
Any Promethazine-containing Product Implicated	18*	--	1	--	8	--	27	2,307
Promethazine-containing Product Implicated Alone	4	--	1	--	3	--	13	--

***Includes 10 single-ingredient promethazine cases and 8 promethazine/codeine cough syrup cases**

-- Case numbers were not large enough to generate reliable national estimates for these case types.

Data provided by the CDC Division of Healthcare Quality Promotion, using data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, 2016.

Promethazine-involved Deaths



Promethazine-involved deaths among individuals 12+ years of age, by year, National Vital Statistics System-Mortality (NVSS-M) and Drug-Involved Mortality(DIM) 2010-2015

Year	Total deaths involving promethazine	Promethazine only drug mentioned, N (% of total)	Flagged as misuse/abuse, N (% of total)
2010	283	4 (1.4)	95 (33.6)
2011	274	5 (1.8)	89 (32.5)
2012	275	3 (1.1)	90 (32.7)
2013	254	2 (0.8)	94 (37.0)
2014	310	3 (1.0)	114 (36.8)
2015	300	7 (2.3)	104 (34.7)
TOTAL	1,696	24 (1.4)	586 (34.6)

Analyses conducted by Sara Karami, PhD
DEPI I, OSE, CDER, FDA



Literature on Promethazine Misuse and Abuse

- Promethazine/codeine cough syrup abuse¹⁻³
 - Known by names such as “purple drank” and “lean,” primarily abuse of cocktails containing codeine-promethazine cough syrup
 - Popularized in the 1990s by a number of rap artists, primarily in the Houston, Texas area
 - Quite common in specific population subgroups and regions, much less so in others

1. Peters et al., *J Drug Education* 2003.

2. Peters et al., *J Psychoactive Drugs* 2007.

3. Agnich et al., *Addict Behav* 2013

Literature on Promethazine Abuse and Misuse



- Study of injection heroin users in Vietnam¹
 - 75% reported promethazine use in conjunction with heroin injection.
 - Described using to augment a suboptimal heroin dose or pre-dosing in anticipation of impending withdrawal.
 - Most stated they disliked the actual effects of promethazine, including occasional hallucinations.
- Study of San Francisco methadone maintenance patients²
 - 26% urines tested positive for promethazine; only 15% of these had an active prescription for promethazine.
 - Study authors also noted, from their own clinical practice, anecdotal reports of promethazine use by methadone maintenance patients to potentiate the “high” from methadone.

1. Clatts et al., *Substance Use and Misuse* 2010
2. Shapiro et al., *J Addict Med* 2013

Anecdotal Data on Combined Promethazine and Opioid Abuse: Internet Drug Abuse Discussion Forum Posts¹



Themes	Examples
Belief that promethazine increases the euphoric effects of opioids	<ul style="list-style-type: none"><i>...since taking them with my Roxicodones, I will NEVER take [opiates] alone without Promethazine. That's how much of a diff there is. I'm so much more doped out and euphoric, and have a bunch more doses left over for those painful days. Win, win.</i>
Belief that promethazine has other desirable effects, including sedation, when used with opioids for abuse	<ul style="list-style-type: none"><i>Promethazine is generally regarded as potentiating all opiates by making the nod more intense. If you like your high to be really mellow, sink into the bed, sleep for a day kind of experience 25mg promethazine before and another 25mg during will go down nicely...</i>
Promethazine effects, including sedation, undesirable when used with opioids for abuse	<ul style="list-style-type: none"><i>Do not bother with the promethazine. It just makes you more sedated and I find it "clouds" my opiate high/euphoria.</i>

1. All posts were from Bluelight.org and drugs-forum.com discussion threads

Key Data Limitations



- National survey data (NSDUH)
 - Potential misidentification of products
 - Non-response bias
- Poison control center call data (NPDS)
 - Only capture misuse/abuse events if resulted in a call to a PCC
 - Fraction of events captured is unknown, may vary across time or products
 - Unattended out-of-hospital deaths unlikely to be captured
 - Products can be misidentified
- ED visit surveillance data (NEISS-CADES)
 - Only include cases that result in an ED visit and that do not result in death before or during ED evaluation.
 - Quality of data depends on the completeness and accuracy of medical record documentation



Key Data Limitations

- Mortality data (DIM)
 - Data rely on death certifier mentions of drugs on death certificate
 - Likelihood of investigating and reporting specific drug involvement varies across jurisdictions and over time
 - Misuse and abuse may not be explicitly mentioned, even when they occurred
- Data collected from people entering or being assessed for treatment (NAVIPPRO ASI-MV) and other enriched samples
 - Potential misidentification of products
 - Non-representative (convenience) samples
- Internet drug abuse discussion forum postings
 - Non-systematic search
 - Potential misidentification of products
 - No way to verify information, rumors/hearsay sometimes reported

Summary



- As with all opioids, the overall risk-benefit balance of Hydrexor includes potential harms associated with misuse and abuse
- Hydrocodone is widely misused and abused, often in combination with other drugs, resulting in thousands of poison center calls, ED visits and deaths each year
- However, relative to their very large prescription volume, hydrocodone combination products appear to be less likely to be abused than most other opioid analgesics
- Hydrocodone combination product route of abuse:
 - Predominantly oral
 - In populations with more advanced substance use disorders, intranasal abuse is common, if not the preferred or exclusive route
 - Injection is infrequent



Summary

- The postmarketing data indicate that promethazine is also misused and abused
 - to a lesser extent than hydrocodone
 - usually in combination with opioids or other drugs
- Promethazine abuse and misuse occur with both single-ingredient and promethazine/codeine combination cough products
- Promethazine contributes to several hundred deaths each year, but the vast majority of these involve other drugs
- Anecdotal data suggest some individuals who abuse opioids believe promethazine enhances the desirable effects of opioids, whereas others do not



Thank You

Summary of FDA Findings

Ellen Fields, MD, MPH

Deputy Director

DAAAP, CDER, FDA



Overview

- Drug Utilization
- Clinical efficacy and safety-Phase 3
- Human abuse potential study
- Epidemiologic data on abuse
- Conclusions



Drug Utilization

- HC/APAP is most frequently prescribed outpatient opioid analgesic in the US
- Outpatient utilization decreased for
 - Hydrocodone-acetaminophen
 - Single-ingredient promethazine products
- Concurrent prescription claims for hydrocodone-acetaminophen and single-ingredient promethazine decreased
- No mentions of concomitant prescribing for hydrocodone-acetaminophen and promethazine by the same prescriber during the same office visit
- Ondansetron was the drug most frequently mentioned for treatment of nausea and vomiting in outpatient setting followed by promethazine



Efficacy

- Hydexor was evaluated in two Phase 3 studies, in patients prone to or anticipated to experience nausea and vomiting with opioid administration
- Replicated data demonstrated analgesic effect of Hydexor AND efficacy compared to Hydrocodone/APAP for prevention of OINV
- Indication should specify prevention of OINV in patients expected to be prone to nausea and vomiting

Safety Phase 3 Studies

- Typical opioid adverse reactions
- Increase in CNS-related adverse reaction compared to Norco, likely related to promethazine, predominantly drowsiness and lightheadedness



Human Abuse Potential Study

- HAP study conducted to determine whether promethazine might reduce negative effects of hydrocodone and increase drug-liking of Hydexor
- No statistically significant differences in positive or negative subjective responses when HYDEXOR was compared to HC + APAP
- HYDEXOR did produce a statistically significant increase in drowsiness compared to HC + APAP, suggesting that PMZ produces an additional degree of sedation. However, this effect did not influence the abuse potential of HYDEXOR in this study.
- The data from this study support the conclusion that there are no differences in the abuse potential of HYDEXOR compared to HC + APAP. Thus, the presence of PMZ in HYDEXOR does not alter the abuse potential of the drug product, as measured in a controlled study environment.
- Hydexor will be placed under Schedule II of the CSA

Epidemiologic Data on Abuse



- As with all opioids, the overall risk-benefit balance of Hydrexor includes potential harms associated with misuse and abuse
- Hydrocodone is widely misused and abused, often in combination with other drugs, resulting in thousands of poison center calls, ED visits and deaths each year
- However, relative to their very large prescription volume, hydrocodone combination products appear to be less likely to be abused than most other opioid analgesics
- Hydrocodone combination product route of abuse:
 - Predominantly oral
 - In populations with more advanced substance use disorders, intranasal abuse also occurs, but is not the preferred or exclusive route
 - Injection is infrequent



Epidemiologic Data on Abuse

- The postmarketing data indicate that promethazine is also misused and abused
 - to a lesser extent than hydrocodone
 - usually in combination with opioids or other drugs
- Promethazine abuse and misuse occur with both single-ingredient and promethazine/codeine combination cough products
- Promethazine contributes to several hundred deaths each year, but the vast majority of these involve other drugs
- Anecdotal data suggest some individuals who abuse opioids believe promethazine enhances the desirable effects of opioids, whereas others do not



Conclusions

- Hydexor appears to be safe and effective in the proposed patient population, with some increase in CNS effects compared to hydrocodone/APAP alone
- Hydexor is not intended to be an abuse-deterrent formulation, similar to all other marketed HC/APAP combinations
- The HAP study demonstrated no difference in abuse potential
- Epidemiologic data and postmarketing anecdotal information show there may be some misuse and abuse of promethazine along with opioids to enhance their effects,
- Hydexor will be indicated for use in patients prone to OINV
- If approved, Hydexor will be under Schedule II of the CSA and will be subject to the class-wide opioid REMS



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Thank you

