



Drug Utilization Patterns for Hydrocodone ER and Other ER/LA Opioid Analgesics 2011-2015

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Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and
the Drug Safety and Risk Management Advisory Committee (DSaRM) Joint
Meeting

June 7, 2016

Outline

- Sales Distribution
- Prescription Utilization
- Prescriber Specialty
- Limitations
- Summary

Extended Release (ER)/ Long Acting (LA) Opioid Analgesics

- **Oral-dosage Forms:**

- Hydrocodone
- Methadone
- Morphine
- Oxycodone
- Hydromorphone
- Oxymorphone
- Tapentadol

- **Transdermal Delivery (TD) Systems:**

- Fentanyl
- Buprenorphine

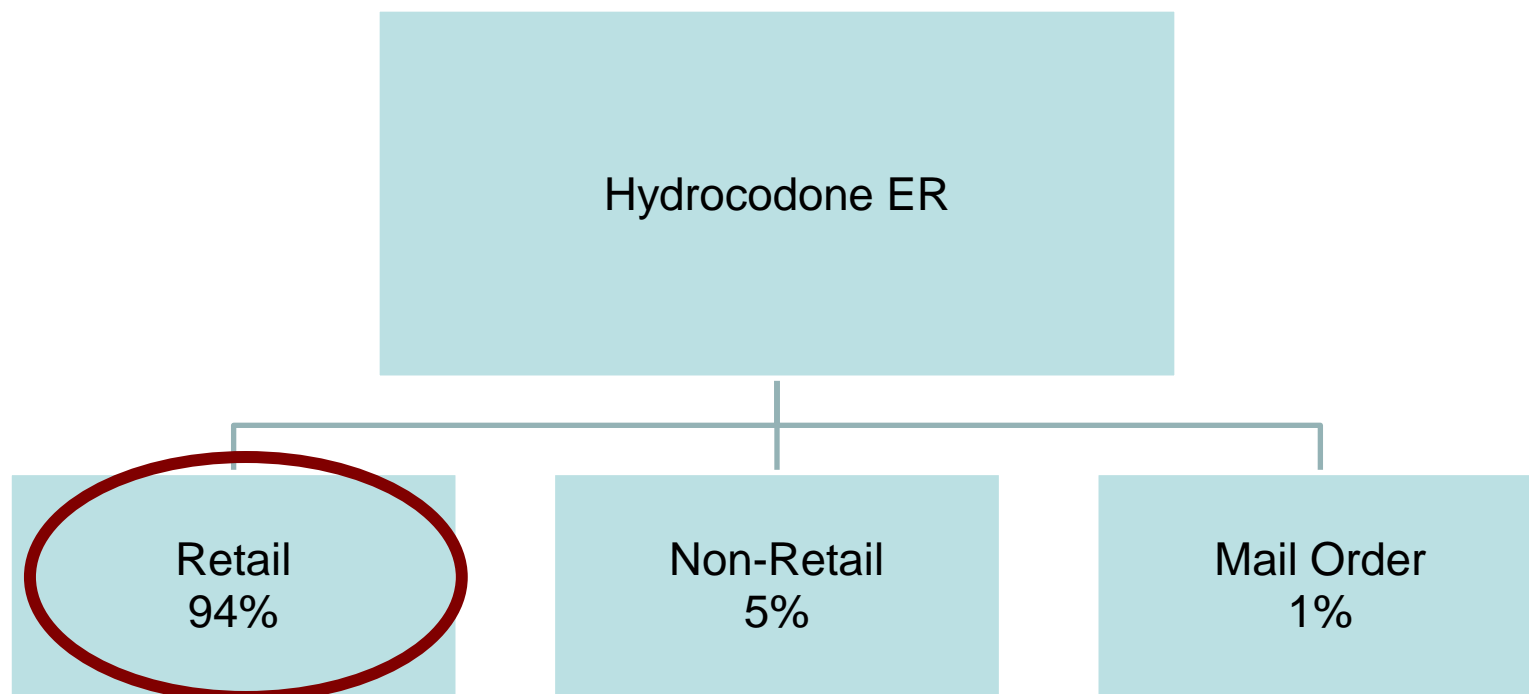
Sales Distribution Data

- IMS National Sales Perspectives Database™
- Captures sales of drug products from manufacturers to all retail and non-retail settings
 - Retail chain pharmacies, mail-order pharmacies, hospitals, etc.
- Data are nationally projected
- Does not represent actual patient use

Sales Distribution Data

Year 2015

IMS Health, IMS National Sales Perspective™, Extracted March 2016



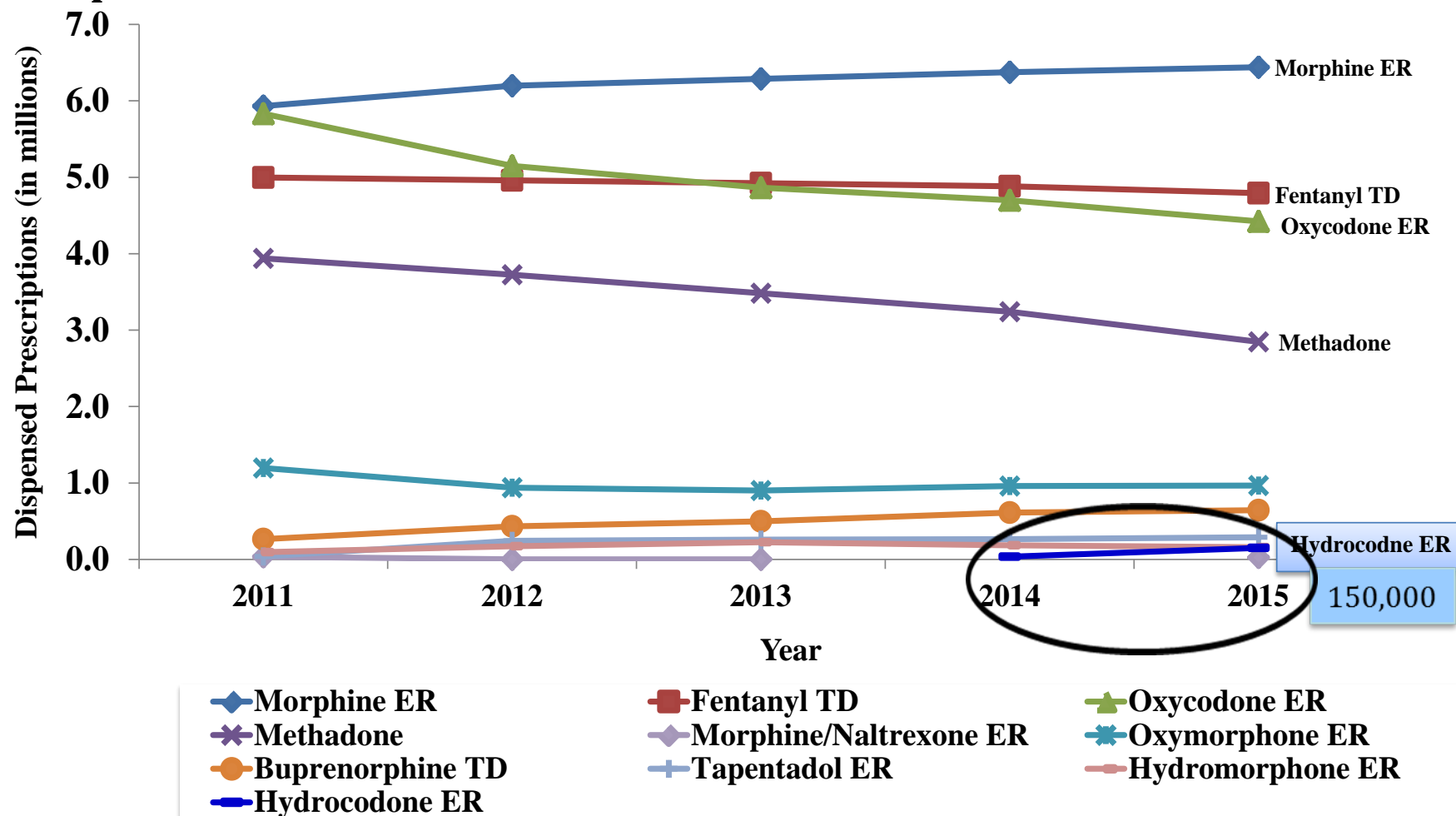
Database Descriptions

Prescription Utilization and Prescriber Specialty Data:

- IMS Health, National Prescription Audit™ (NPA) Database
- Measures dispensing of prescriptions out of retail pharmacies into the hands of consumers
- Data can be stratified by prescriber specialty

Prescription Drug Utilization:

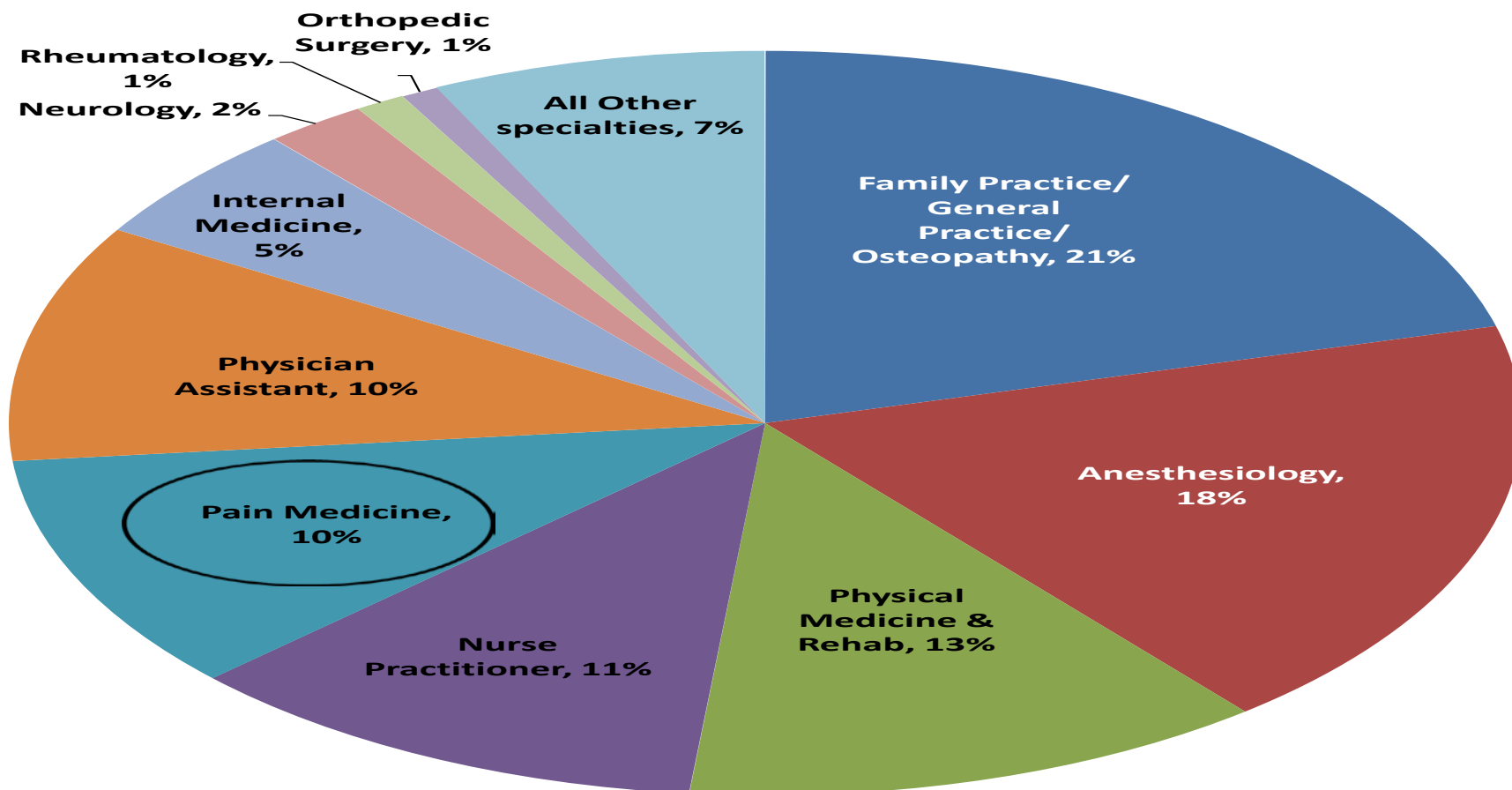
Nationally estimated number of prescriptions dispensed for ER/LA opioid analgesics from U.S. outpatient retail pharmacies, 2011-2015



Source: IMS, National Prescription Audits (NPA). Data extracted March 2016

Top Prescriber Specialty: 2015

Top 10 prescriber specialties by the nationally estimated number of prescriptions dispensed for hydrocodone ER from U.S. outpatient retail pharmacies



Source: IMS Health, National Prescription Audit (NPA). Year 2015. Extracted March 2016.

Limitations:

- Only outpatient retail pharmacy use was assessed
- Top specialties captured as reported by the prescription data

Summary:

- Uptake in hydrocodone ER prescriptions dispensed was approximately 150,000 prescriptions in 2015
- Hydrocodone ER products accounted for less than 1% of prescriptions dispensed for the ER/LA opioid analgesics market
- Top prescriber specialties:
 - Family Practice/General Practice/Osteopathy

NDA 207975

Vantrela ER (hydrocodone bitartrate)
Extended-Release Tablets

Labeling Section 9: Drug Abuse

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June 7, 2016

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

Outline

- Overview of Section 9.2 Drug Abuse
- Class language on drug abuse
- Risks specific to abuse of VANTRELA ER
- Abuse Deterrence Studies
 - In vitro testing
 - Clinical human abuse potential studies
- Abuse potential endpoints
 - *Drug Liking and Take Drug Again*
- Types of studies: Oral and intranasal abuse potential studies
- Summary of the product's abuse-deterrent properties

Section 9.2 Abuse

- VANTRELA ER contains hydrocodone, a substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone
- VANTRELA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion [*see Warnings and Precautions (5.1)*]
- The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse
- All patients treated with opioids require careful monitoring for signs of abuse and addiction

Section 9.2 Abuse

Risks Specific to Abuse of Vantrela ER

- VANTRELA ER is for oral use only
- Abuse of VANTRELA ER poses a risk of overdose and death
 - The risk is increased with concurrent use of alcohol and other central nervous system depressants
- Taking cut, broken, chewed, crushed, or dissolved VANTRELA ER enhances drug release and increases the risk of overdose and death

Abuse Deterrence Studies

In Vitro Testing

- Physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation of VANTRELA ER
- Results support that VANTRELA ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some extended-release properties despite manipulation
- When VANTRELA ER was subjected to attempts at small volume extraction, the resulting material was viscous and resisted passage through a hypodermic needle

Clinical Abuse Potential Studies

- The abuse potential of oral or intranasal administration of VANTRELA ER following physical manipulation was studied in 2 randomized, double-blind, active- and placebo-controlled studies in non-dependent opioid abusers
- **Take Drug Again** was measured on a bipolar 100-point Visual Analog Scale (VAS) where 0 represents strongest negative response (definitely would not take the drug again), 50 represents a neutral response, and 100 represents the strongest positive response (definitely would take the drug again)
- **Drug Liking** was measured on a bipolar 100-point VAS scale where 0 represents maximum disliking, 50 represents a neutral response (neither like nor dislike), and 100 represents maximum liking

Oral Abuse Potential Study

- In a randomized, double-blind, placebo- and active-controlled, 4-period crossover study in non-dependent opioid abusers, 35 of the 49 enrolled subjects completed all treatment conditions: 45 mg VANTRELA ER (intact), 45 mg VANTRELA ER (finely crushed), 45 mg hydrocodone bitartrate powder (immediate release (IR) condition), and placebo
- The oral administration of finely crushed VANTRELA ER was associated with statistically significantly lower mean scores for Drug Liking and Take Drug Again ($P < 0.001$ for both), compared with powdered hydrocodone as summarized in the following table

Oral Abuse Potential Study

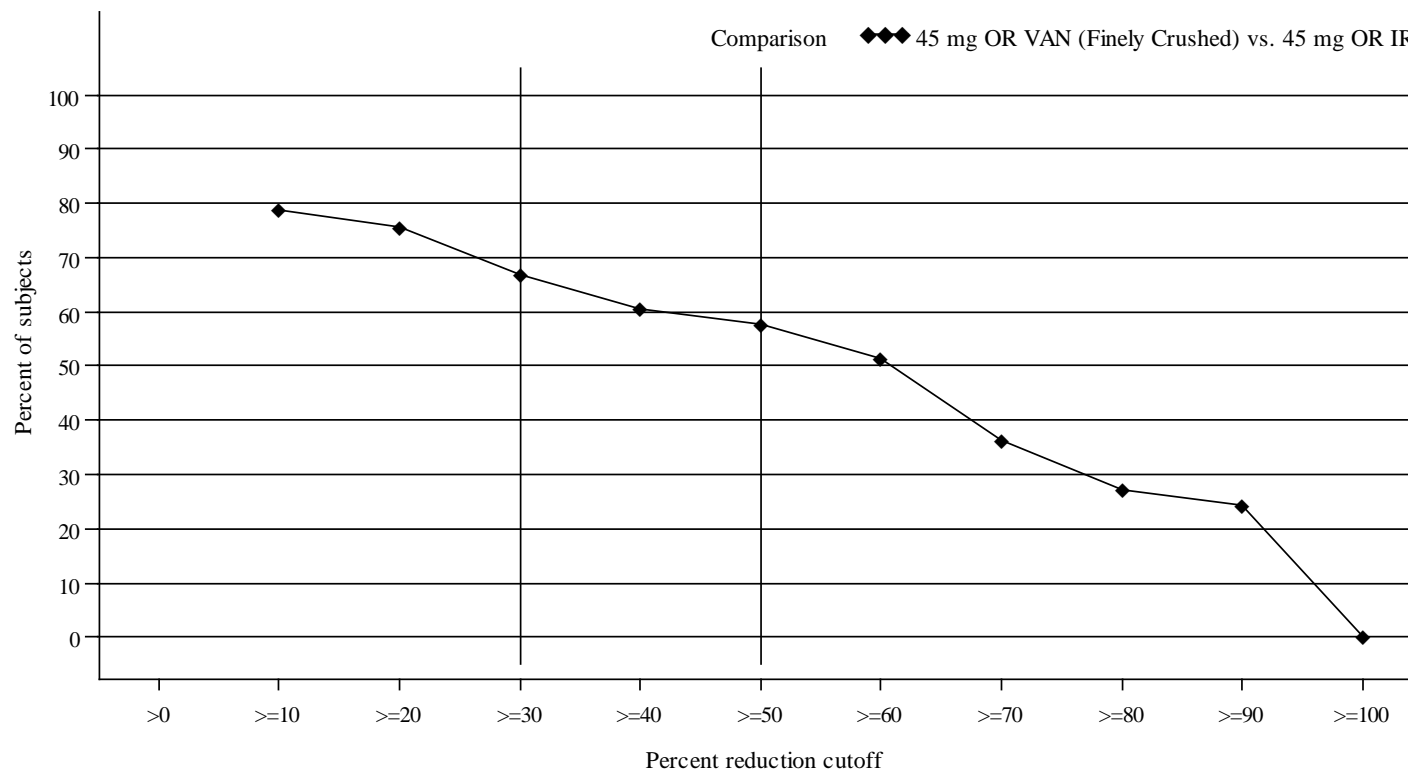
Table 4: Summary of Maximum Drug Liking (Emax) and Take Drug Again (Emax) Following Oral Administration

Measure	Statistic	Placebo (N=35)	Hydrocodone IR 45 mg (N=35)	VANTRELA ER 45 mg (finely crushed) (N=35)	VANTRELA ER 45 mg intact (N = 35)
Drug Liking	Mean (SE)	53.4 (1.80)	85.0 (2.31)	65.6 (2.46)	54.5 (1.02)
	Median (Range)	51.0 (50-100)	88.0 (50-100)	60.0 (50-98)	51.0 (50-70)
Take Drug Again	Mean (SE)	46.3 (2.88)	75.1 (3.04)	55.9 (3.53)	48.5 (2.77)
	Median (Range)	50.0 (0-98)	74.0 (42-100)	56.0 (2-97)	50.0 (1-100)

Source: Proposed Vantrela ER label

Oral Abuse Potential Study

Figure 2: Percent Reduction in Emax for Drug Liking for Finely Crushed VANTRELA ER (OR VAN) vs Immediate Release Hydrocodone (OR IR), Oral Administration



Source: Proposed Vantrela ER label

A comparison of maximum Drug Liking for orally administered finely crushed VANTRELA ER as compared to IR hydrocodone is shown in the graph

Intranasal Abuse Potential Study

- In a randomized, double-blind, placebo-and active-controlled study in non-dependent opioid abusers, 34 of the 45 subjects enrolled completed all treatment conditions: intranasal administration of 45 mg VANTRELA ER (finely milled), 45 mg hydrocodone bitartrate powder (immediate release condition), oral administration of 45 mg VANTRELA ER (intact), and intranasal administration of placebo
- The intranasal administration of finely milled VANTRELA ER was associated with statistically significantly lower mean and median scores for Drug Liking and Take Drug Again ($P < 0.001$ for both), compared with powdered hydrocodone as summarized in the following table

Intranasal Abuse Potential Study

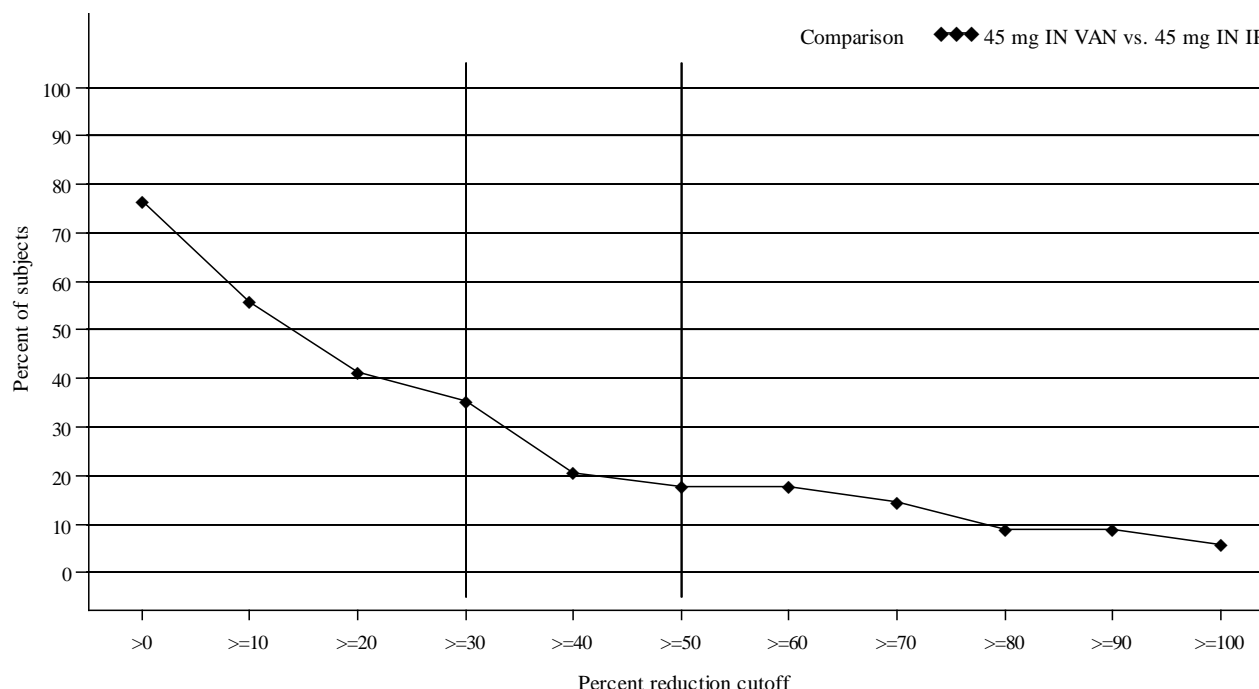
Table 5: Summary of Maximum Drug Liking (Emax) and Take Drug Again (Emax) Following Intranasal Insufflation

Measure	Statistic	Placebo IN (N=34)	Hydrocodone IR 45 mg (N=34)	VANTRELA ER 45 mg Finely Milled (N=34)
Drug Liking	Mean (SE)	58.6 (1.94)	80.2 (2.16)	72.8 (2.35)
	Median (Range)	52.0 (50-90)	79.0 (57-100)	72.5 (50-100)
Take Drug Again	Mean (SE)	56.4 (2.13)	75.5 (2.57)	67.5 (3.45)
	Median (Range)	50.0 (34-90)	76.5 (43-100)	67.0 (30-100)

Source: Proposed Vantrela ER label

Intranasal Abuse Potential Study

Figure 4: Percent Reduction in Maximum Drug Liking for Finely Milled VANTRELA ER vs Immediate-Release Hydrocodone Following Intranasal Administration



Source: Proposed Vantrela ER label

A comparison of maximum Drug Liking for intranasally administered finely milled VANTRELA ER (IN VAN) as compared to IR hydrocodone (IN IR) is presented in Figure 4

Summary

- The in vitro data demonstrate that VANTRELA ER has physical and chemical properties that are expected to deter intravenous abuse
- The data from the in vitro studies and clinical studies indicate that Vantrela ER has physicochemical properties that are expected to reduce abuse via the oral route and via the intranasal route. **However, abuse of VANTRELA ER by the intravenous, nasal, and oral routes is still possible**
- Additional data, including epidemiological data, when available, may provide further information on the impact of VANTRELA ER on the abuse liability of the drug