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

NDA 206830

AVRIDI IR Oxycodone Tablets

5 mg, 10 mg, 15 mg, 20 mg, or 30 mg

Food Effect

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Background

- Bioequivalence (BE) based program for oxycodone OCI/AVRIDI formulation
  - End of phase 2 meeting in 2013: Discussed BE with 15 mg and biowaiver for 30 mg.
  - No Pre-NDA meeting held.
- NDA submission
  - 505(b)(2) referencing Roxicodone NDA (021011)
  - Fasted BE Study OCI1002
    - Bioequivalence established with regard to Cmax and AUC
    - Results are not discussed
  - Fed BE Study OCI1003
    - Results will be discussed

Previously Approved IR Oxycodone Products

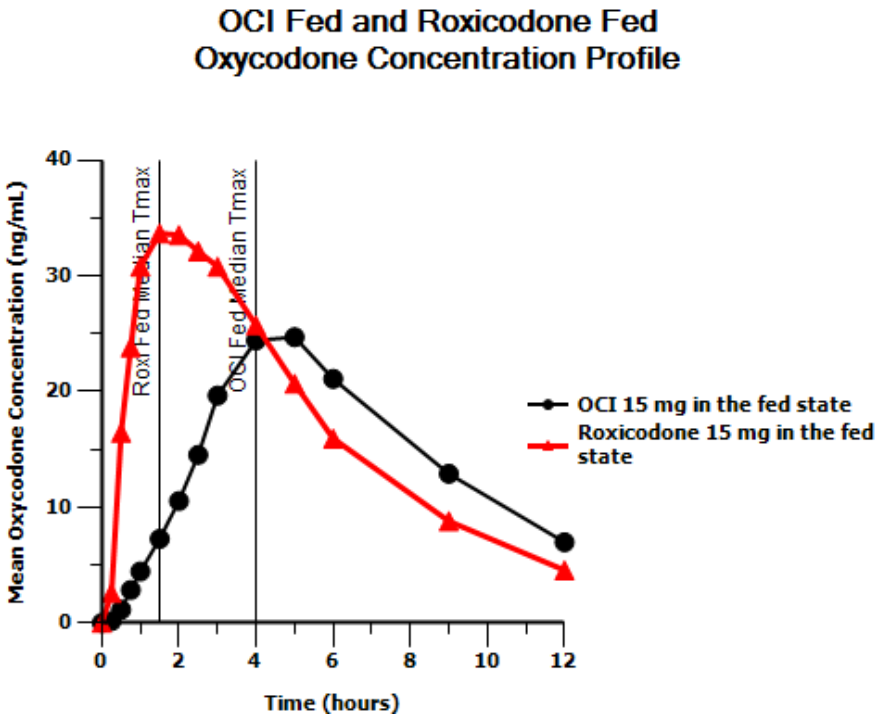
No Abuse Deterrent claims

- Roxicodone IR Tablets
  - Food effect results for the tablet are not described in label
- Roxicodone IR Oral Solution
  - Food effect: Tmax delayed from 1.25 hr to 2.5 hr.

Product with some description in section 9

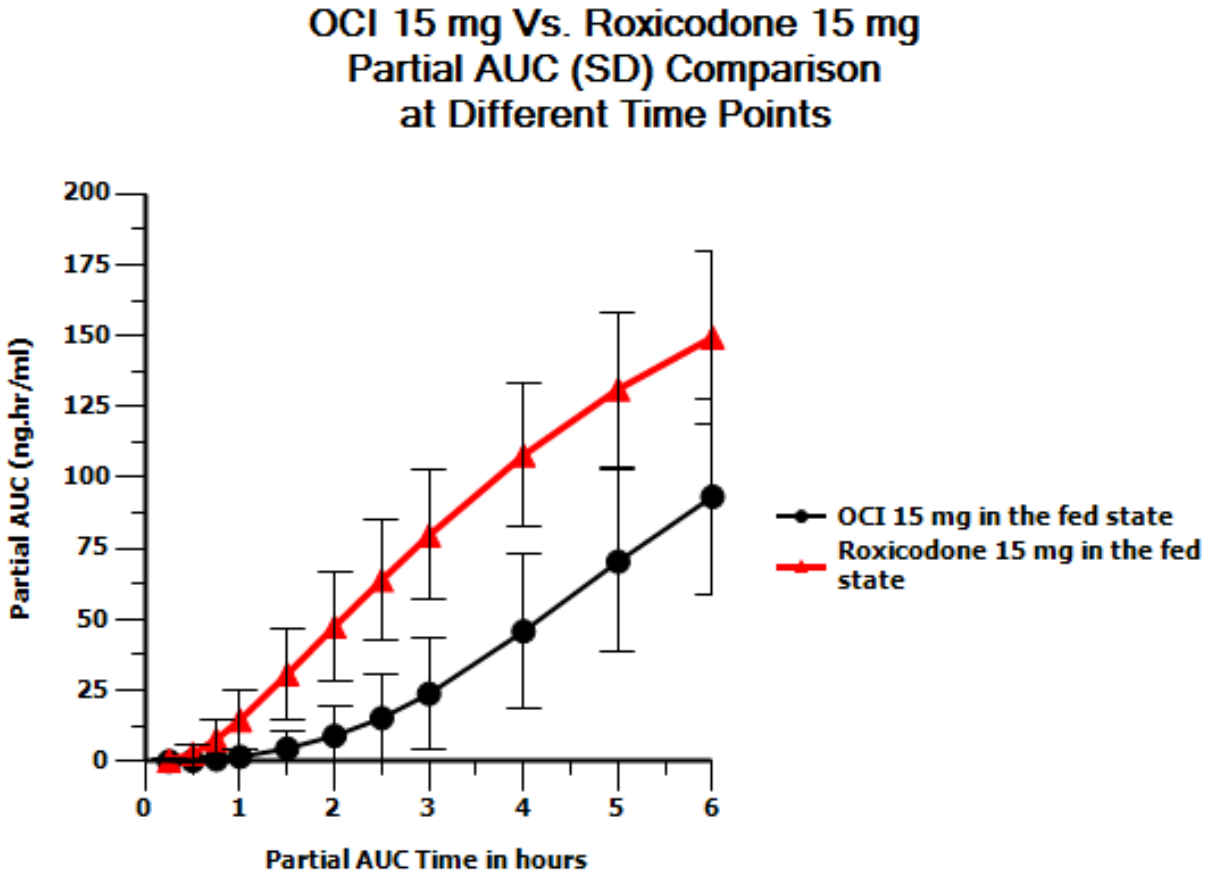
- Oxaydo Tablets
  - Description of adverse effects following intranasal abuse.
  - Clinical significance has not yet been established.

Comparison of Oxycodone PK Profile
OCI Tablet: FED BE Study OCI1003 (n=51)

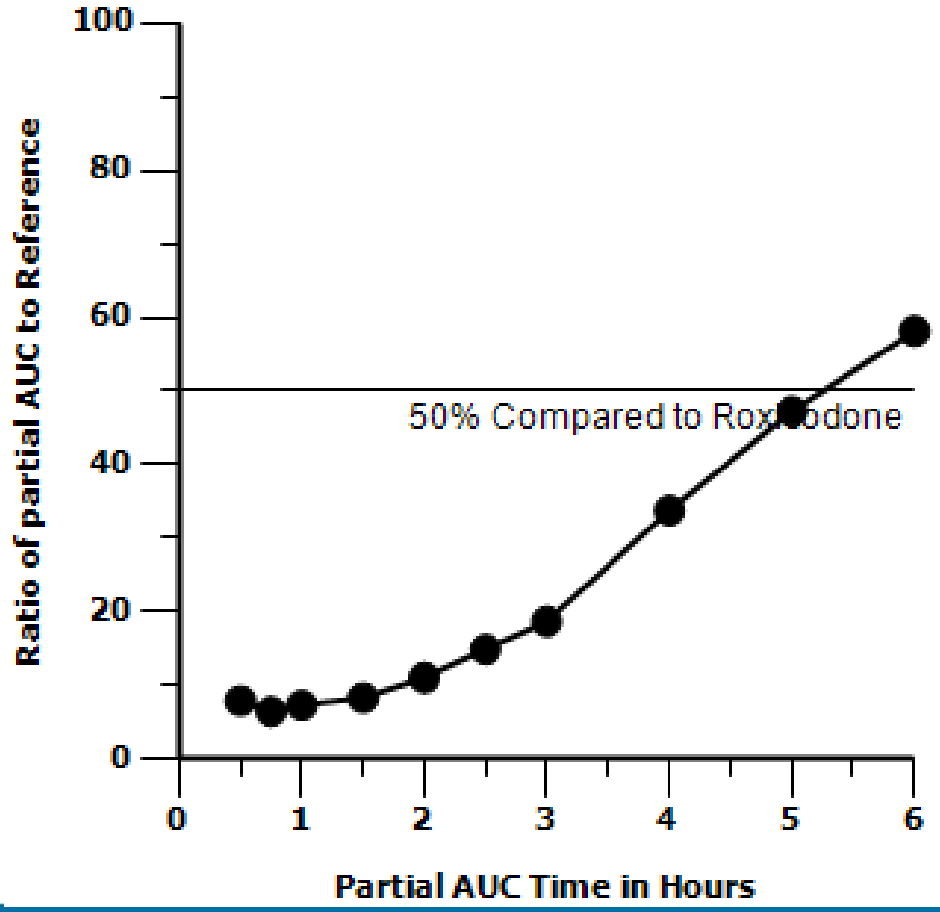


- Decreased rate of absorption (Median Tmax) is profound.
- OCI Fed: Tmax Median 4 h (Range 1 to 9 hr), ~27% decrease in Cmax noted.
- Roxi Fed: Tmax Median: 1.5 h Range (0.5 – 4 h)

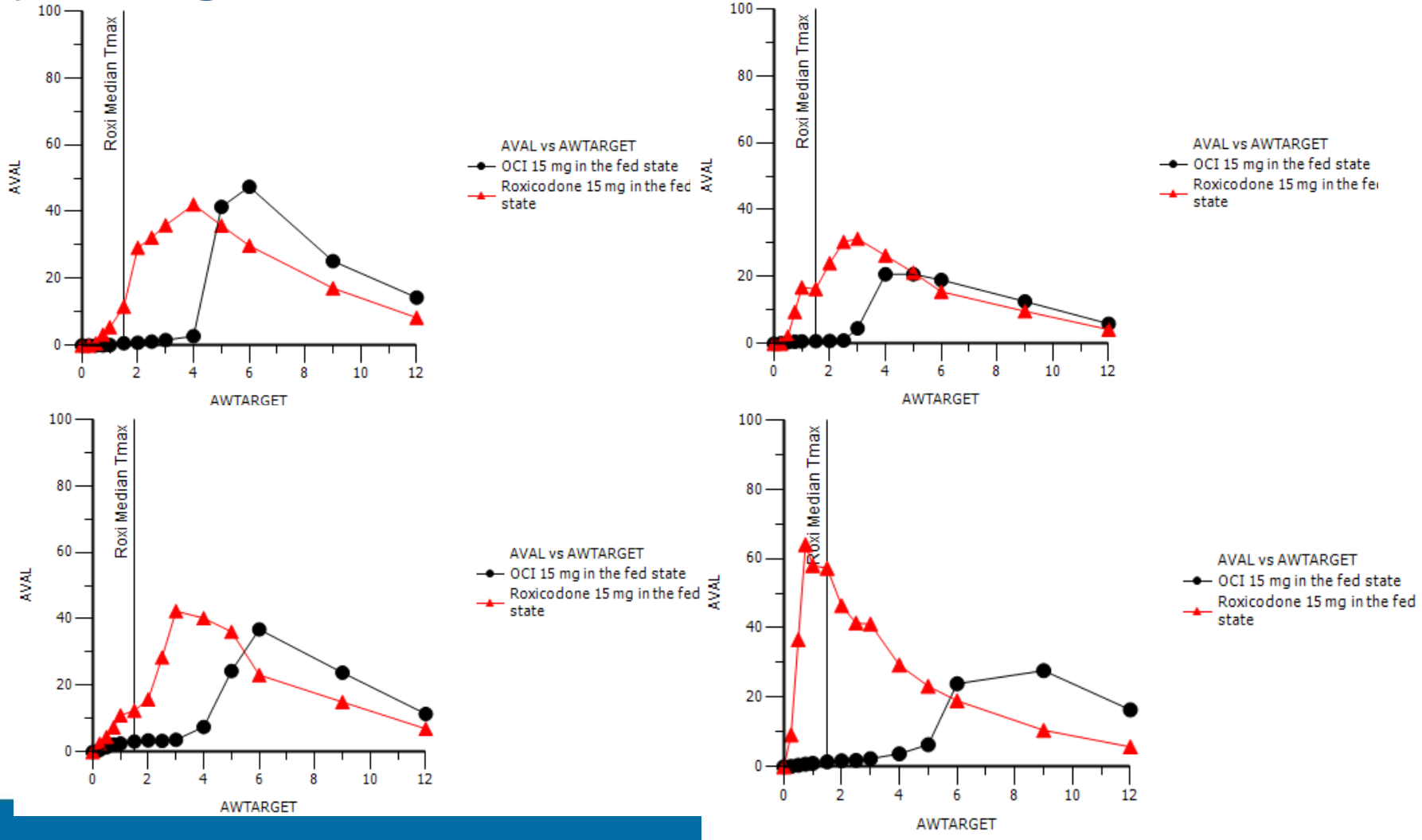
Oxycodone Systemic Exposure (Partial AUC's) For AVRIDI or OCI Fed Are Significantly Lower Compared to Roxicodone Fed Over 4 – 6 hours



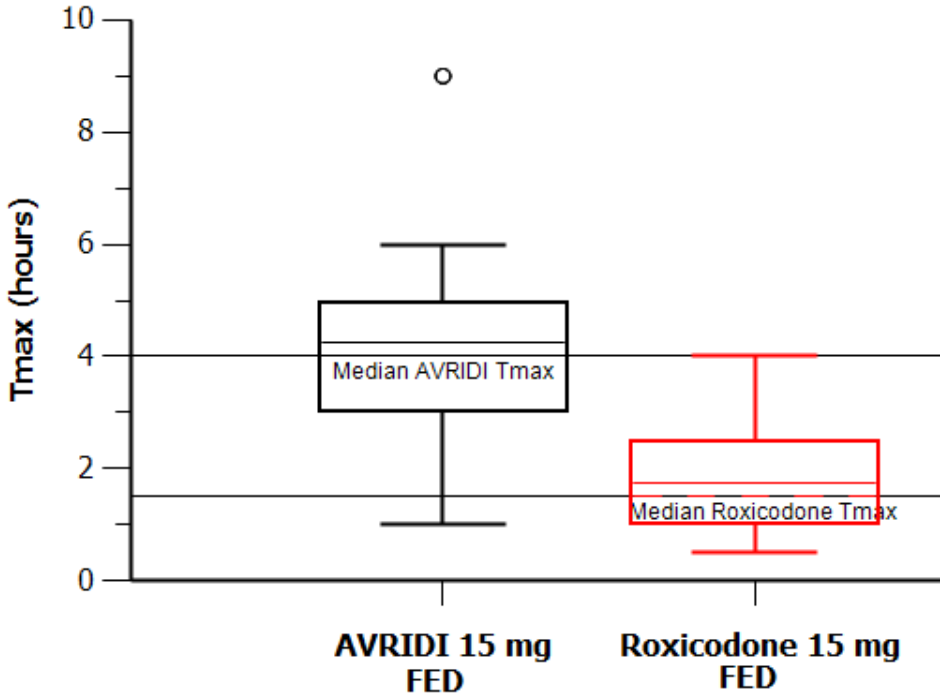
Compared to Roxicodone Fed AVRIDI Fed Treatment Takes Longer to Achieve Comparable Systemic Exposure

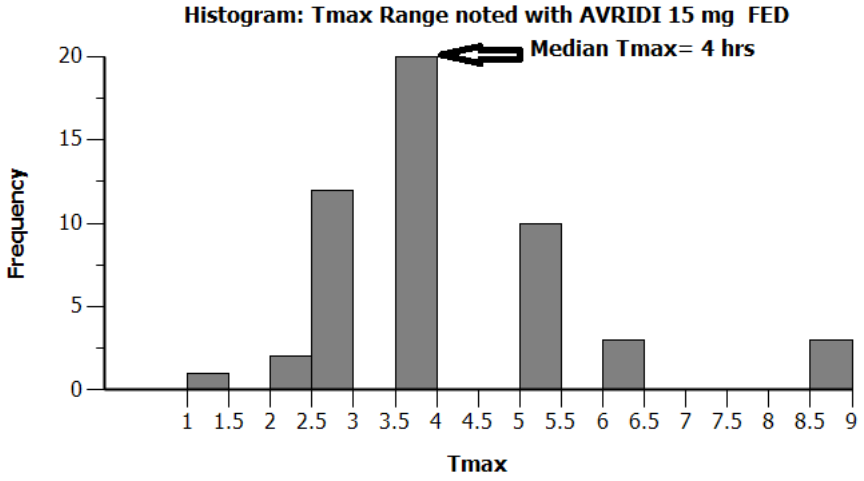


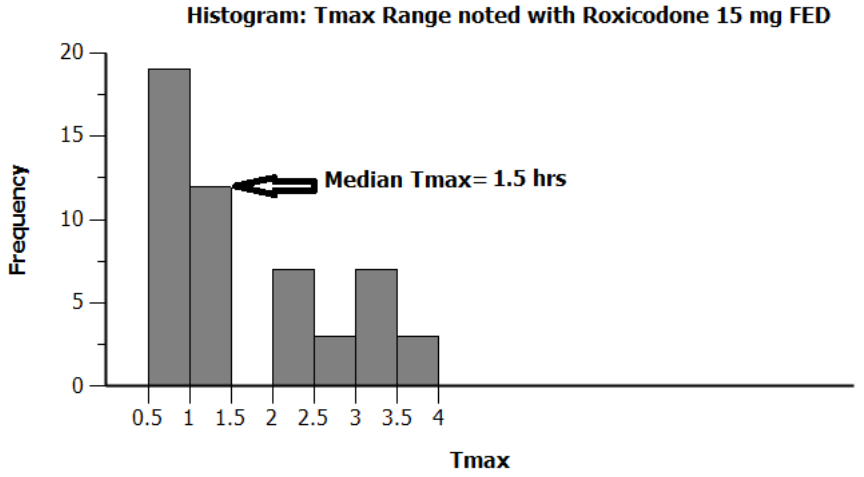
Examples of Worst Case Delay in Tmax with OCI (•)when given with food.



Time to Achieve Peak Oxycodone Plasma Concentrations is Longer With AVRIDI Under Fed-State Compared to Roxicodone







Conclusion

- When taken with food
  - Absorption of oxycodone from AVRIDI is substantially delayed.
    - AVRIDI Tmax: Median 4h; Range 1 – 9 h.
    - Roxicodone Tmax: Median 1.5 h; Range 0.5 – 4 h.
  - Oxycodone exposure with AVRIDI is low over 4 – 6 hr compared to Roxicodone
    - As demonstrated by substantially lower partial AUC.
  - AVRIDI takes longer to achieve comparable systemic exposure compared to Roxicodone.
  - Existing IR products do not show delayed Tmax to this extent.

Thanks

Clinical Implications of AVRIDI's Food Effect

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Outline

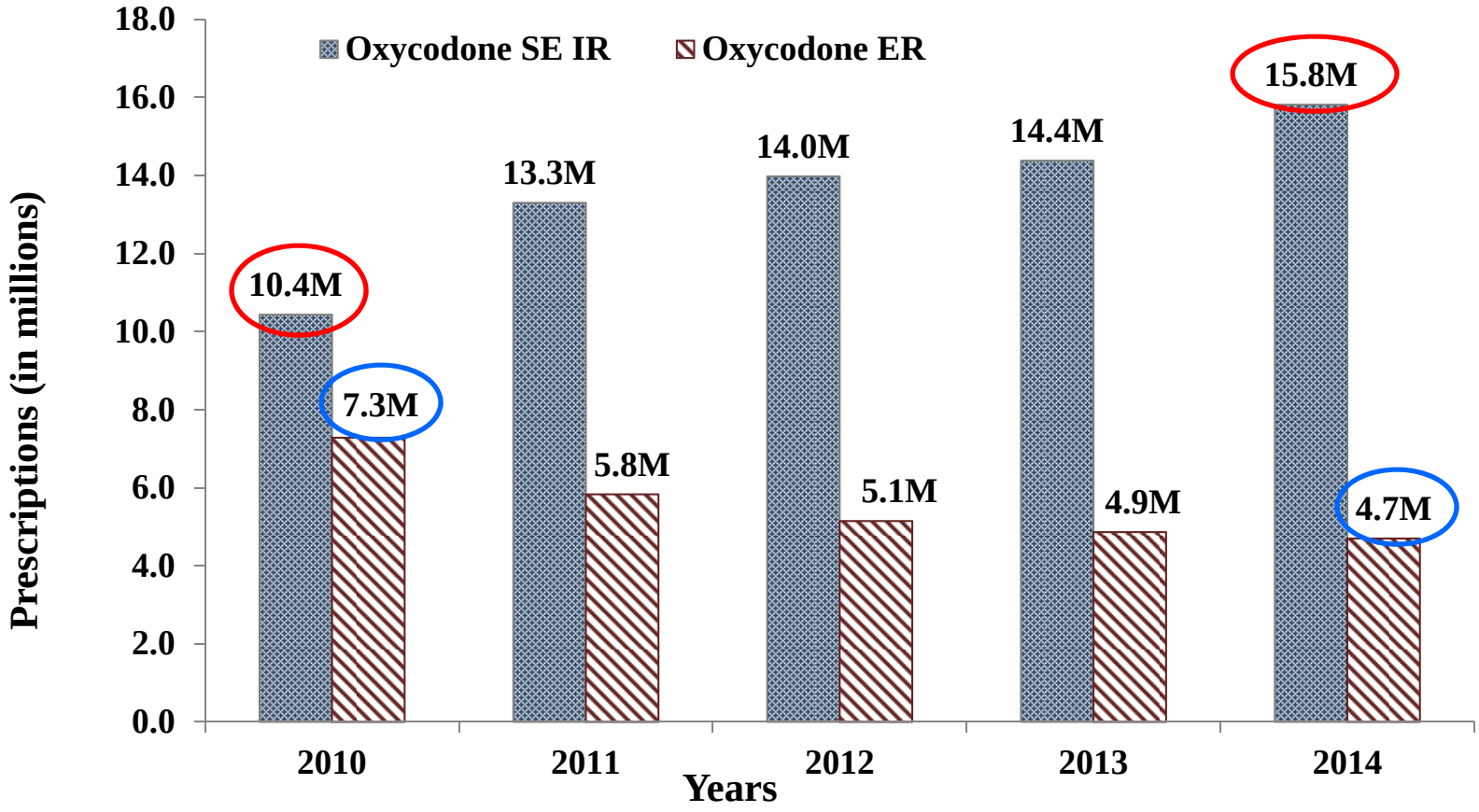
- Drug utilization patterns of oxycodone
- Label instructions for administration of opioids
- Clinical implications of AVRIDI's food effect

Dispensed Prescription Data U.S. Outpatient Retail Pharmacies, 2010-2014

Dispensed Prescription Data: Outpatient Retail Pharmacy Settings

- IMS Health, National Prescription Audit (NPA™)
- Captures U.S. adjudicated prescription activity
  - Across all payment types
- Data are nationally projected to the outpatient pharmacy retail setting
  - Over 2.7 billion prescription claims/year
  - Approximately 57,000 pharmacies

Oxycodone SE IR and ER Prescription Data



Nationally estimated number of prescriptions dispensed for oxycodone single entity (SE) immediate release (IR) and oxycodone extended release (ER) products from U.S. outpatient retail pharmacies, 2010-2014

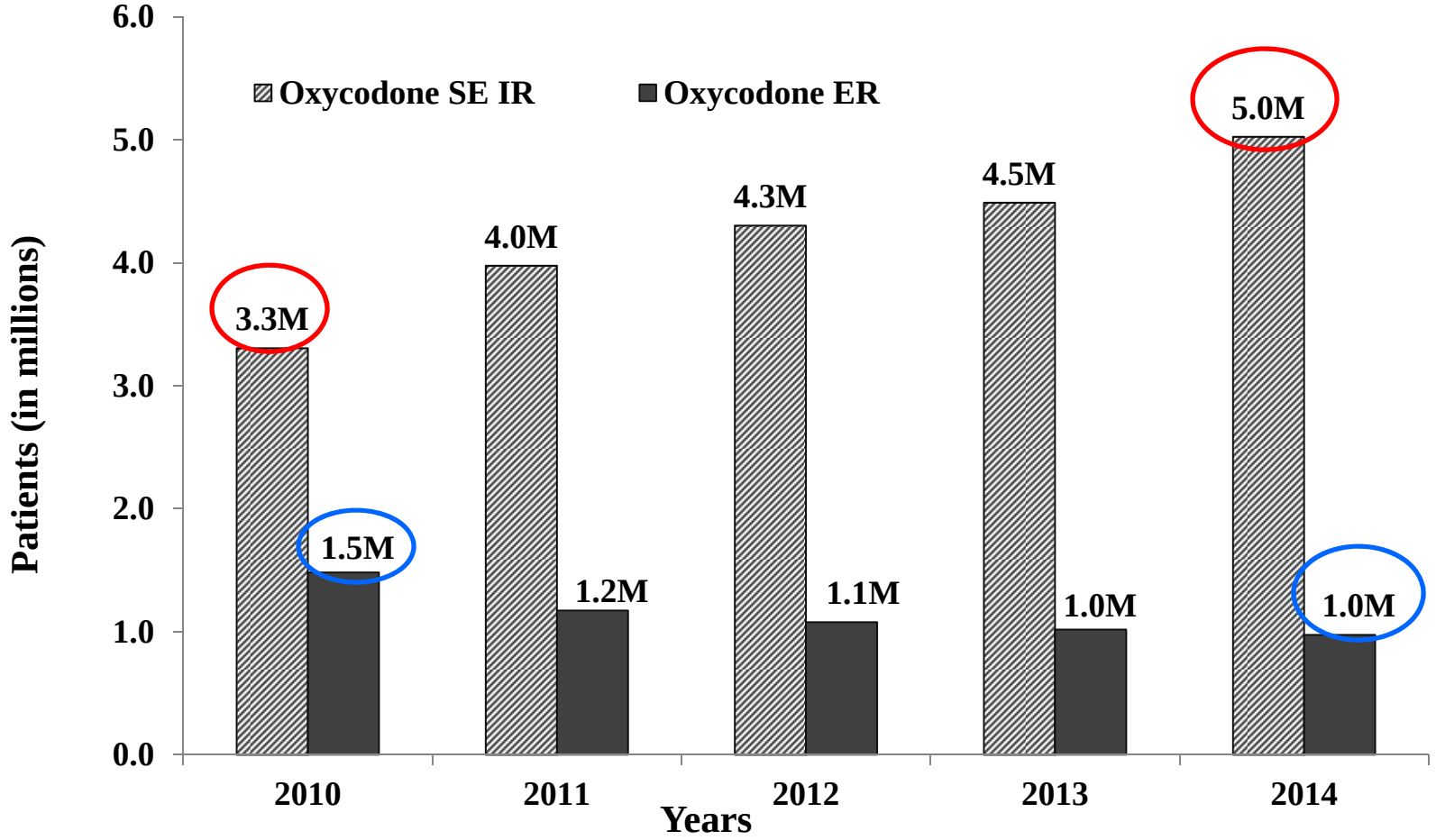
Source: IMS Health, National Prescription Audit ™ Extracted May 2015

Patient Level Data
U.S. Outpatient Retail Pharmacies, 2010-2014

Unique Patient Utilization:
Outpatient Retail Pharmacy Settings

- IMS Health, Total Patient Tracker(TPT)
- Captures U.S. adjudicated prescription activity
  - Across all payment types
- Data are nationally projected to the outpatient pharmacy retail setting
  - Receives >1.9 billion prescription claims per year
  - 158 million unique patients

Oxycodone SE IR and ER Unique Patient Data



Nationally estimated number of patients who received dispensed prescriptions for oxycodone single entity (SE) immediate-release (IR) or oxycodone extended-release (ER) products from U.S. outpatient retail pharmacies, 2010-2014

Source: IMS Health, National Prescription Audit ™ Extracted May 2015

Label Instructions for Administration of Opioids

Extended- and Immediate-release Opioid Analgesics

- Generally labeled to take without regard to food, e.g., no significant food effect
- Opana ER (oxymorphone ER) and Opana (oxymorphone IR) are labeled to take on an empty stomach due to food effect (Cmax increased by 50% in fed state compared to fasted, slight increase in AUC)

Concern

Because most opioids are labeled to take without regard to food, prescribers and patients may not comply with labeling for this product based on long-standing behaviors

Clinical Implications of AVRIDI's Food Effect

Pharmacokinetics

In the fed state:

1. The absorption of oxycodone from AVRIDI is substantially delayed (median Tmax ~ 4 h; range 1- 9h) as compared to Roxicodone (median Tmax ~1.5 h; range 0.5 - 4 h)

2. The partial AUC's over 4-6 h dosing interval for AVIRIDI are lower compared to Roxicodone

3. AVRIDI takes longer to achieve comparable systemic exposure compared to Roxicodone

Efficacy and Safety Implications

- Efficacy
  - Concern whether patients will be able to comply with dosing instructions and take medication on an empty stomach every 4-6 hours
  - Variability in absorption of oxycodone due to administration without regard to food or in the fed state alone may result in variable or delayed efficacy.

- Safety
  - Patients may take extra doses if analgesia not adequate, possibly resulting in adverse events
  - Risk of accidental overdose with all opioids; food effect for this product adds another factor that contributes to this risk

Summary

- There is extensive use of ER and IR oxycodone products
- The majority of products are labeled to take without regard to food
- AVRIDI has a significant food effect such that it must be administered without food
- Inability to comply with dosing instructions or administration of AVRIDI without regard to food may result in patients taking additional doses and increased risk of adverse events and accidental overdose
- Because most opioids are labeled to take without regard to food, prescribers and patients may not comply with labeling for this product based on long-standing behaviors

Acknowledgements

CDER, Office of Surveillance and Epidemiology, Division of Epidemiology II

Jennie Wong, Pharm D, Drug Utilization Analyst

Rajdeep Gill, Pharm D, Drug Utilization Data Analysis Team Leader

Back Up Slides Shown

Simulation of Overdose Vs. Steady-State With OCI Under Fed Condition