

***Abuse-Deterrent Opioids:
Where is the Real Value?***

An Interview with:

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December 11, 2008

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- Dr. Heit is board certified in internal medicine (diplomat) and gastroenterology (diplomat). He is also certified in addiction medicine by the American Society of Addiction Medicine (ASAM) and is certified as a medical review officer (MRO). He is a fellow of the American College of Physicians and the American Society of Addiction Medicine. Dr. Heit is also a member of the American Pain Society and the American Academy of Pain Medicine and its annual scientific meeting planning committee. Dr. Heit was co-section coordinator, author and an editor on "Pain Management and Addiction Medicine" for ASAM's textbook *Principles of Addiction Medicine, Second and Third Edition*. He also co-authored two chapters in Bonica's *Management of Pain- Fourth Edition*. Dr. Heit served as chair of ASAM's scientific program "Common Threads: Pain & Addiction," from 2000 to 2005.
- Dr. Heit is a founding board member and treasurer of the International Association for Pain and Chemical Dependency. He is the recipient of the Marie Nyswander Award, which is given at the International Pain and Chemical Dependency Conference to an individual who has helped to build a bridge between pain and addiction and who has been a spokesperson for the compassionate and humane treatment of patients with pain.
- Dr. Heit was also instrumental in forming the Liaison Committee on Pain and Addiction of the American Society of Addiction Medicine, the American Academy of Pain Medicine, and the American Pain Society. The mission of this committee is to encourage collaboration between pain specialists and addiction specialists on issues of common interest.
- From 1990-1996, Dr. Heit served as medical addictionologist for Alcohol and Drug Services for Fairfax County. Dr. Heit is an assistant clinical professor of medicine at Georgetown University School of Medicine. He has lectured and published extensively on the interface of pain and addiction medicine.

The Topic of Today's Discussion

- On November 13 and 14, the joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee discussed the NDA for **King Pharmaceuticals' (NYSE: KG) and Pain Therapeutics' (NasdaqGM: PTIE) Remoxy (oxycodone hydrochloride controlled-release capsule) as well as Alpharma's (NYSE: ALO) abuse-deterrent formulation of morphine, Embeda.**
- Via an 11-8 informal vote, the advisory committee concluded that the data for Remoxy demonstrates tamper-resistance advantages over Purdue's Oxycontin. The committee recommended FDA approval of Remoxy with a suggested recommendation for specific label language for tamper resistance. Negotiations over an acceptable risk management plan are likely to delay Remoxy approval beyond the 12/11 FDA review deadline, perhaps into Q1/09.
- The advisory committee also concluded, via a 16-2 informal vote, that Alpharma's Embeda demonstrates tamper/abuse-resistance advantages over traditional extended release morphine. However, the advantages were considered modest. This relatively favorable review came shortly before King and Alpharma finally announced a \$1.6 billion merger agreement on November 24 after a protracted period of negotiation.

A Very Recent Update

Dec 11, 2008 /PRNewswire

PTIE Pain Therapeutics/King (KG) receive complete response letter from FDA for Remoxy

Pain Therapeutics has received a Complete Response Letter from the FDA for its NDA for Remoxy, an abuse-resistant controlled-release form of oxycodone.

Based on its review, the FDA has determined that **the NDA is not approved in its present form.**

The FDA believes additional non-clinical data will be required to support the approval of REMOXY. The FDA has not requested or recommended additional clinical efficacy studies prior to approval.

Pain Therapeutics and its partner King Pharmaceuticals and outside technical advisors are evaluating the FDA Complete Response Letter, will discuss the Letter with the FDA, and will provide an update when appropriate.

Pain Therapeutics and King Pharmaceuticals remain diligently committed to their strategic alliance to develop and commercialize REMOXY and other abuse-resistant pain medications.

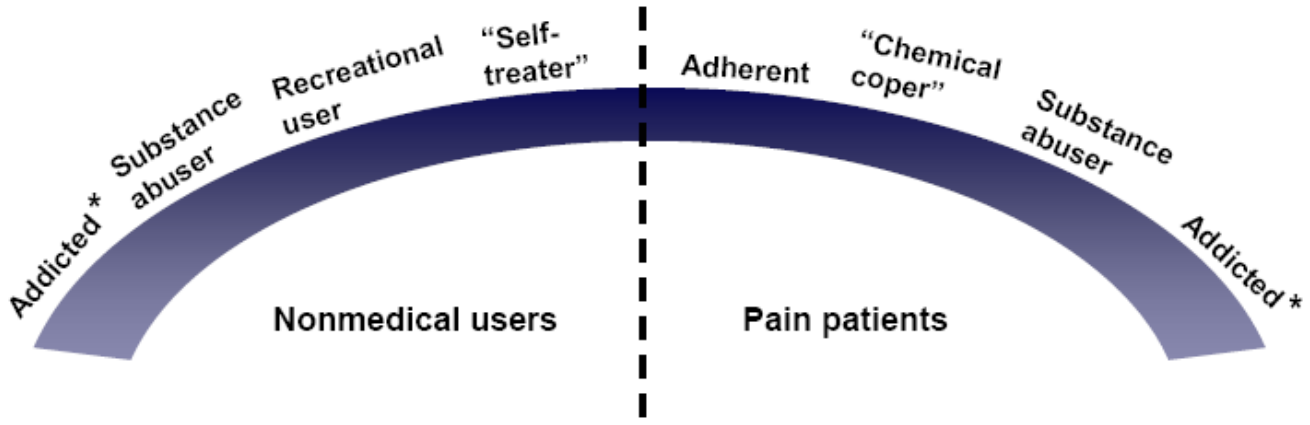
Definition of Terms

- **ABUSE:** Maladaptive pattern of opioid use leading to clinically significant impairment or distress, occurring in any of the following areas within a 12-month period: (American Psychiatric Association 2000)
 - Failure to fulfill major obligations at work, school, or home
 - Recurrent opioid use in hazardous situations, such as driving or operating heavy machinery while impaired
 - Opioid-related legal problems
 - Social and interpersonal problems caused, or exacerbated, by opioid use
- **ABUSE LIABILITY:** The potential of a drug to be abused, misused and diverted. It encompasses the risks associated with abuse, misuse or diversion of drug demonstrated to lead to tolerance, dependence or addiction.
- **DIVERSION:** Transfer of a controlled substance from a lawful to an unlawful channel of distribution or use. (Section 3303.(12) of the New York State Public Health Law)
- **MISUSE:** Use of legal medicines in a way not recommended by the doctor or the manufacturer; taking medicines in very large quantities that are dangerous to one's health.
- **OPIOID DEPENDENT:** A state of adaptation to opioid that is manifested by drug class-specific signs and symptoms produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist.
- **OPIOID TOLERANT:** A physiologic state resulting from regular use of an opioid in which an increased dosage is needed to produce a specific effect, or a reduced effect is observed with a constant dose over time.

Alpharma FDA Advisory Committee Briefing Package

Opioid Abuse: The Problem

Opioid Users are a Heterogeneous Population



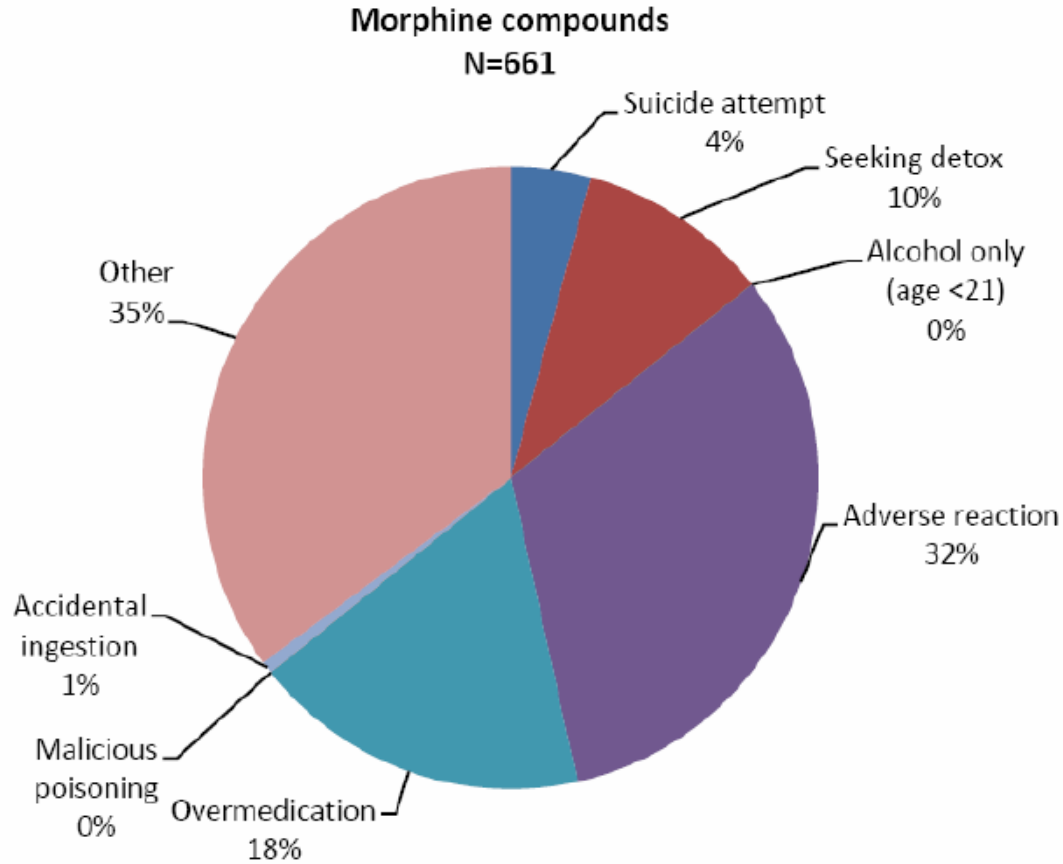
* Substance abuse disorder

Opioid Prescription misuse and abuse is not limited to non-medical users:
patients who take opioids for legitimate pain may also be at risk

Alpharma FDA Advisory Committee Briefing Package

Opioid Abuse: The Problem

Non-Medical Use of Morphine-Related Cases Reported in 2008



Alpharma FDA Advisory Committee Briefing Package

Opioid Abuse: The Problem

OxyContin: The Abuser's Drug of Choice

- In recent years, the DEA reports that OxyContin abuse has substantially increased.

“The introduction in 1996 of Oxycontin, commonly known on the street as OC, OX, Oxy, Oxycotton, Hillbilly heroin, and kicker, led to a marked escalation of its abuse as reported by drug abuse treatment centers, law enforcement personnel and health care professionals. Although the diversion and abuse of OxyContin appeared initially in the eastern US, it has now spread to the western US including Alaska and Hawaii”.

- Abusers can quickly and easily extract large amount of oxycodone by simply breaking or crushing OxyContin tablets. Doing so disrupts OxyContin's time release mechanism and allows an abuser to immediately ingest, snort or inject a large dose of oxycodone that was originally intended to be slowly released over 12 hours. Rapid increases in plasma levels of oxycodone (dose dumping) may lead to overdose, respiratory distress or death. The inherent vulnerability of the OxyContin formulation may also lead to accidental overdose by patients who may mistakenly cut or crush the tablets.

NDA 22-234 Remoxy Advisory Committee Briefing

Remoxy (Pain Therapeutics, King Pharmaceuticals)

- Remoxy is a unique, long-acting formulation of oral oxycodone for moderate to severe chronic pain, designed to resist common methods of prescription drug misuse and abuse.



Remoxy employs Durect's Oradur technology in a sustained release oral gel-cap. Remoxy's gelatinous formulation allows for the controlled release of the active pharmaceutical ingredient and may deter abuse of the drug.

NDA 22-234 Remoxy Advisory Committee Briefing

Remoxy: Reduction of Abuse Potential?

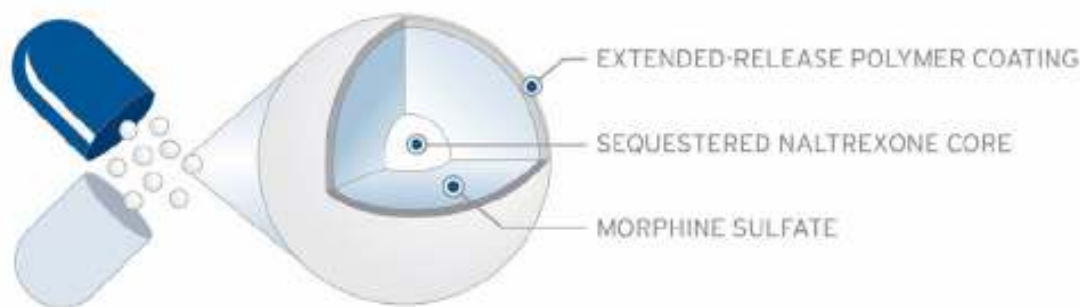
- At the advisory meeting, the FDA presented their interpretation of the Remoxy in vivo tamper resistance data. This included the trials aimed at demonstrating that the extended release properties of Remoxy could not be altered by physical manipulation and extraction, chewing, buccal delivery, and co-ingestion with alcohol.
- The FDA's analysis focused exclusively on the comparative C_{max} (maximum concentration levels in the bloodstream) between Remoxy and OxyContin. Based upon this analysis, they argued that the extended release properties of Remoxy could be defeated in all of the methods that were tested.
- Pain Therapeutics countered that the C_{max}/T_{max} ratio is the key parameter, as the goal of the Remoxy formulation is to prevent very rapid release of the oxycodone (dose dumping).
- In Pain Therapeutics' analysis, there was a clear difference between Remoxy and Oxycontin with Remoxy demonstrating a lower 0-2 hour AUC than Oxycontin post tampering.
- This topic was the source of much debate among the panelists, but the final voice vote implies that Pain Therapeutics argument prevailed.

NDA 22-234 Remoxy Advisory Committee Briefing

ALO-01 (Alpharma): Delivery System Design

- ALO-01 is a capsule comprised of individual pellets containing morphine sulfate with a sequestered naltrexone hydrochloride inner core. When ALO-01 is taken as prescribed, morphine is released in an extended-release profile to provide relief of moderate-to-severe chronic pain for up to 24 hours, when around-the-clock pain relief is needed. While the morphine is being released, naltrexone, an opioid antagonist, remains adequately sequestered in the core of each pellet.
- However, upon crushing, or complete chewing of the pellets, both the morphine and naltrexone would be available and if taken orally, absorbed as an immediate-release dosage form.
- Uniquely, the released and absorbed naltrexone would:
 - mitigate the liking and euphoric effects of the morphine; and
 - minimize the potential for abuse of morphine.

PHARMACOLOGIC CORE TECHNOLOGY

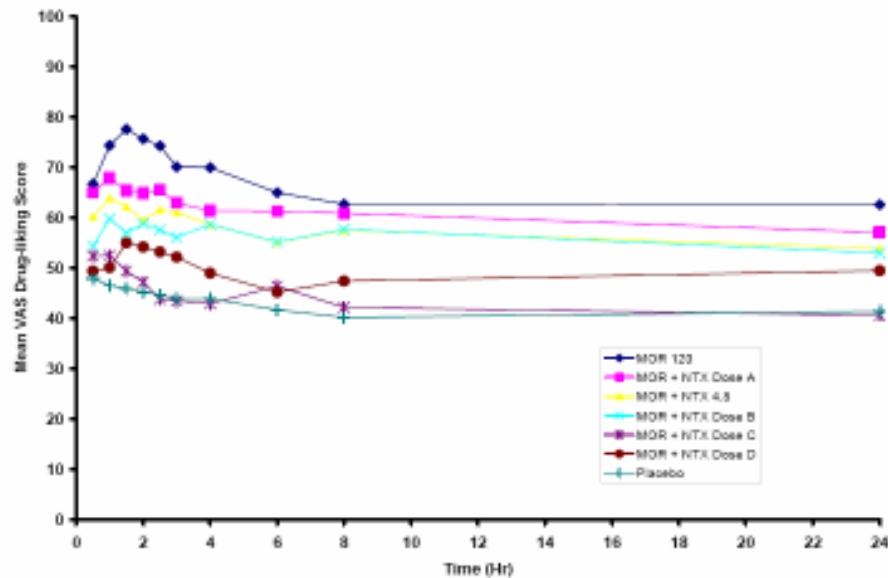


Alpharma FDA Advisory Committee Briefing Package

ALO-01 (Alpharma): Reduction of Abuse Potential

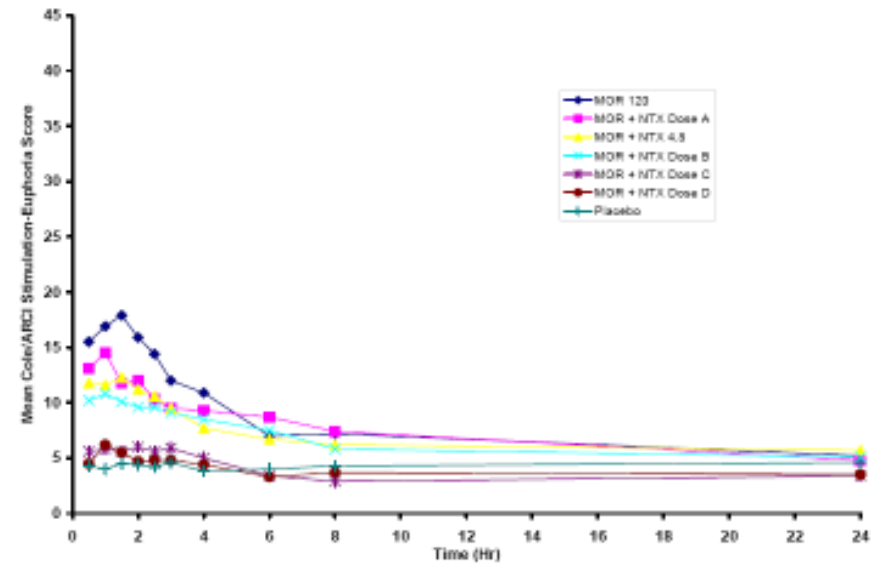
- Intravenous morphine plus IV naltrexone, given in the same proportion as the ALO-01 capsule formulation, reduced drug liking and euphoria compared to IV morphine alone.
- The study suggests that the selected naltrexone to morphine ratio (1:25) provides an adequate reduction of abuse potential.

Figure 21: VAS DEQ Drug Liking Results: Study ALO-KNT-201



MOR=morphine sulfate immediate-release, NTX=naltrexone HCl

Figure 22: Cole/ARCI Stimulation-Euphoria Results: Study ALO-KNT-201



MOR=morphine sulfate immediate-release, NTX=naltrexone HCl

Alpharma FDA Advisory Committee Briefing Package

ALO-01 (Alpharma): Efficacy & Safety

- The efficacy of ALO-01 Capsules has been evaluated in three clinical trials (ALO-KNT-202, ALO-KNT-301, and ALO-KNT-302) in patients with chronic moderate to severe pain.
- These studies showed that ALO-01 is effective for the treatment of chronic pain as expected based on its morphine pharmacokinetics similar to KADIAN®. The studies also showed that the sequestered naltrexone in ALO-01 performed as designed and did not alter the safety or efficacy of ALO-01.

Alpharma FDA Advisory Committee Briefing Package

The Label Challenge

- The FDA wants to differentiate the tamper-resistant opioids to encourage prescribing over the standard formulations, but does not want to allow these products to be promoted as abuse-resistant opioids.
- A false sense of security may lead to lax prescribing (and diversion) problems, particularly with primary care physicians.
- Alharma's suggested label:

4.4.2.2. Label Claim

Additionally, during drug development, DAARP confirmed to Alharma Pharmaceuticals LLC that a claim for reduced abuse potential in a product label is difficult to establish. The Division suggested that the development of a post-marketing program could be worthwhile to support such label claim. Alharma Pharmaceuticals is committed to perform post-marketing studies in partnership with the Agency. We are considering several alternatives to design epidemiologic studies that could collect, trend and analyze post-marketing data to demonstrate that ALO-01 represents a meaningful incremental reduction in abuse potential.

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Risk Management

- Risk management plan negotiations are likely to delay approval of both ALO-01 and Remoxy.
- There is concern over REMS plans to encourage physician education and prevent over-prescribing.
- The FDA will require King and Alharma to rigorously monitor post-marketing use of their products in order to gauge abuse levels. This is in the context of:
 - Significant challenges of abuse monitoring
 - Flaws with the tools currently available
- The likely data focus will be adverse events databases and hospitalization statistics.
- “Street value” may also be considered as a measure of abusability.
- These data ultimately may lead to stronger tamper-resistance labeling and perhaps even an abuse-resistance claim, but the prediction was that such claims are unlikely to be granted for at least 2-3 years post-launch.

Alharma FDA Advisory Committee Briefing Package

Where is the Real Value?

- Tamper-Resistant = Abuse-Deterrent?
- For which patient types?
- What are the implications for prescribing patterns.

- **Patient demographics / trends**

- High pain medication subscribing areas include rural Appalachia (KY, OH, TN, VA, WV)
- Diverted OxyContin widely available in Miami, New Orleans and Portland, ME
- Pain clinics often target of abusers

- **High-risk patient profile**

- Concentrated in urban areas / inner city
- History of drug abuse, recent or remote
- Consume prescription before it runs out; multiple providers; frequent ER visits
- Approximately 1-5% of oncology palliative care patients
- Pain but in the recovery of disease of addiction
- History of drug issues, addiction and pain

- **Low-risk patient profile**

- Oncology patients
- Chronic pain and no history of addiction

Office of National Drug Control Policy; Defined Health Research

The Future Marketplace

- How do the entry of abuse-deterrent opioids change the market for products with no such claim?

SELECT "ABUSE-DETERRENT" ORAL OPIOIDS IN DEVELOPMENT

Brand Name	Generic Name	Company	Stage
Oxycontin AR	Oxycodone ER	Purdue	Filed
Remoxy	Oxycodone ER	King/Pain Therapeutics	Filed
Embeda	Morphine Sulfate ER + Low Dose Naltrexone	Alpharma	Filed
Acurox	Oxycodone IR + niacin	King/Acura Pharma	Phase III
Oxytrex	Oxycodone + Low Dose Naltrexone	Pain Therapeutics	Phase III
ELI-216	Oxycodone ER + Low Dose Naltrexone	Elite Pharmaceuticals	Phase III
NRP-290	Hydrocodone CBD	Shire	Phase II
Oxycodone NT	Oxycodone ER + Low Dose Naltrexone	Alpharma	Phase II
TQ-1017	Tramadol CR	TheraQuest Biosciences	Phase I
PTI-202	Undisclosed	King/Pain Therapeutics	Phase I
Acuracet	Oxycodone IR/APAP/Niacin	King/Acura Pharma	Phase I
Vicavert	Hydrocodone/APAP/Niacine	King/Acura Pharma	Phase I
Hydromorphone/Niacin	Hydromorphone/Niacin	King/Acura Pharma	Phase I

Source: Company reports; Cowen and Company research

OxyContin: Branded → Generic → Branded → Generic

SG Cowen Therapeutic Categories Outlook Sept 2008

Questions?

Disclosure

Dr. Howard Heit has disclosed that he has received honoraria from Purdue Pharma L.P., Abbott Laboratories, Cephalon, Inc., Titan Pharmaceuticals, Inc., and King Pharmaceuticals, Inc. He has received consultant fees from Purdue, Abbott, Cephalon, Titan, King, Endo Pharmaceuticals, Alpharma Inc. and MEDA Pharmaceuticals Inc."

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