

***New and Innovative
Pharmacologic Strategies
to
Treat Pain***

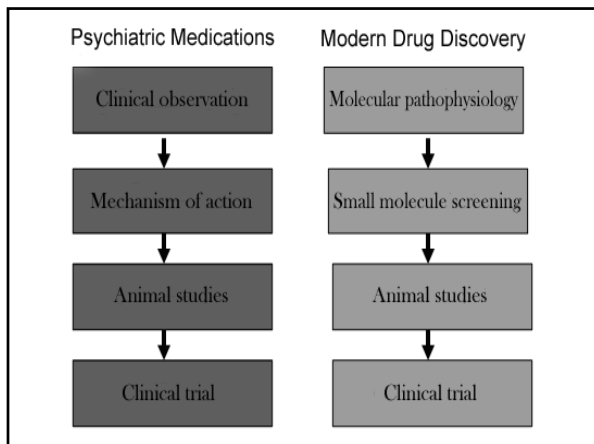
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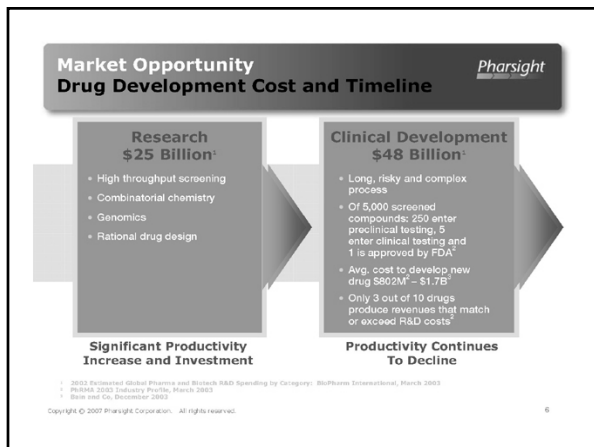
Objectives

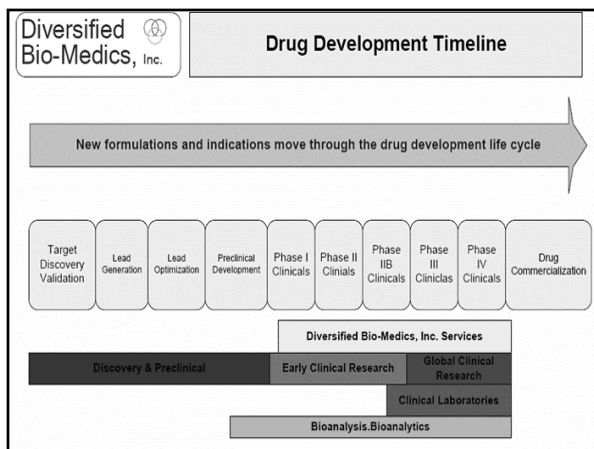
- Describe the evolution in pain management prescribing that necessitates new and innovative pharmacologic strategies.
- Identify trends in pharmacologic therapies utilized in advancing pain management.

Pain in America

- Highlights from a Gallup Survey 2000
- More than 26 million American (15%) who suffer pain monthly, have severe pain.
- 64% of pain sufferers will see a doctor only when they cannot stand the pain any longer.







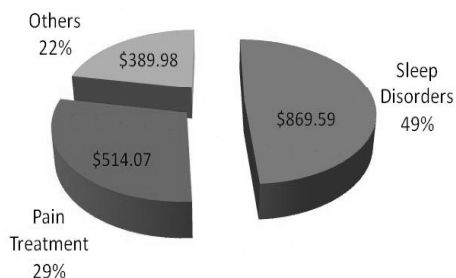
Commercial and Pipeline Insight: Opioid Report 2008

- Opioid market currently valued at \$7.7 B
- Short acting opioid market to triple in value over next 10 years, ex. Fentora, Nucynta
- Long acting opioid market valued at \$3 B in 2007 and due to grow until the patent expiry of Oxycontin in 2011
- After a short decline, the market will be stimulated with the launch of anti-abuse formulations, est. \$1 B market

Commercial & Pipeline Insight cont.

- Topical market, an opportunity for growth underserved market
- Despite J & J, Duragesic, facing generic opposition since 2005, sales remain strong due to brand strength. 12 mcg/hr.

Revenues by Therapeutic Areas in 2007 (millions of USD)



**Risk
Evaluation &
Mitigation
Strategies**

What is a REMS?

- Strategies for managing a known or potential serious risk associated with a drug or biological product
- Required if FDA deems it necessary to ensure product's benefits outweigh its risks
- May be required by FDA before or after a product has been approved for marketing
 - If FDA becomes aware of new safety information after original approval, agency can require a REMS

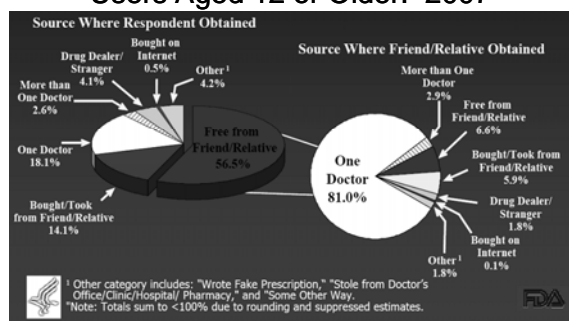
**The FDA's
Rationale for a
Classwide REMS
on Controlled-
Release Opioids**

Why is a Classwide REMS necessary?

- According to the FDA:
 - Prescription opioids “are at the center of a major public health crisis of addiction, misuse, abuse, overdose and death.”
 - The scope of the problem with prescription opioids has grown since 2000 and continues to worsen
 - Strategies used thus far have not adequately addressed prescription opioid misuse and abuse
 - “The risks must be addressed.”

Source: REMS for Opioid Analgesics: How Did We Get Here? Where are We Going? Presented by Bob A. Rappaport, M.D., Director, CDER, FDA on March 3, 2009.

Source of Pain Relievers for Most Recent Nonmedical Use, Past Year Users Aged 12 or Older: 2007



What are the Goals of the REMS?

- Ensure the benefits of the drugs outweighs the risks
- Ensure health care providers, dispensers, and patients are aware of and understand the risks as well as the appropriate use of controlled-release opioids
- Maintain access to prescription opioids for legitimate patients
- Reduce prescription opioid misuse, abuse, addiction, and overdose deaths

Why can FDA impose a REMS?

- Title IX of 2007 Food and Drug Administration Act Amendments (FDAAA) authorizes FDA to require the development of a REMS

- Elements to Assure Safe Use may be used to restrict distribution

Risk management and the FDA

- Risk management tools were used before “risk management” became an official process in 2007
- FDA views risk management as an iterative process of:
 - Assessing a product’s benefits and risks
 - Developing and implementing tools as interventions to minimize risks while preserving benefits
 - Evaluating effectiveness of those tools and reassessing the benefit-risk balance
 - Adjusting the tools, when needed, for continuous risk minimization

FDA begins requiring REMS under FDAAA

- **September 2008 – FDA deems 16 products as having existing REMS**
 - ACAM 2000, Accutane, Actiq, Clozaril, Ionsys, Letairis, Lotronex, Mifeprex, Plenaxis, Revlimid, Soliris, Thalomid, Tracleer, Tikosyn, Tysabri, Xyrem
 - All had elements to assure safe use
- **December 2008 – FDA requires antiepileptics REMS**
 - Risk is increased risk of suicidal thoughts and behavior
 - Only REMS requirement is Med Guide
- **February 2009 – FDA requires class-wide REMS for controlled release opioids**
 - Applies to fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone
 - Risks are misuse, abuse, accidental overdose

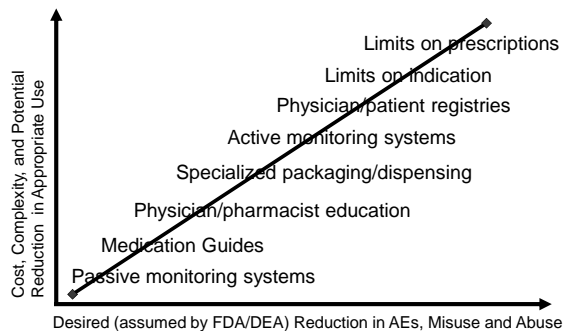
Elements that may be included in a REMS

- Medication Guide (MedGuide)
- Patient Package Insert
- Communication Plan
- Elements to Assure Safe Use (ETASU)
- Implementation System
- Special Labeling Requirements
- Postapproval Studies
- A timetable for assessment of the REMS must be included

Examples of Elements to Assure Safe Use

- Labeling and product packaging
- Education of health care providers
- Prescriber training, experience, special certification
- Special certification of practitioners, pharmacies, or health care settings that dispense the drug
- Drug dispensation limited to certain settings, such as hospitals or prescribers' offices
- Drug dispensation limited to patients with evidence/documentation of safe use conditions, such as laboratory tests (e.g. not pregnant)
- Patients subject to monitoring
- Patient enrollment in a registry

Levels of REMS Restrictions





NUCYNTA™
tapentadol

Tapentadol is a new centrally acting oral analgesic. It has two mechanisms of action, combining mu-opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol tablets have been approved in 50 mg, 75 mg and 100 mg doses.



A New Spin on Old Favorites

Fentanyl

Oral Transmucosal System (OTS™) Drug Delivery Technology

ACTIQ uses OTS technology to deliver fentanyl



ACTIQ® 400 mcg ACTIQ® fentanyl
ACTIQ oral transmucosal system (OTS™)

ACT 221

FENTORA™



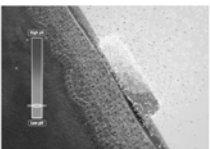

We have liftoff
With new OraVescent™ Technology, drug delivery is taking off at effervescent speed

- A breakthrough drug delivery platform
- Effervescent for enhanced dissolution and absorption
- Rapid, efficient delivery across the buccal mucosa
- Potential applications with highly lipophilic compounds


Cephalon

Characteristics of Buccal Mucosa



- Large surface area
- Uniform temperature
- High permeability
- Well vascularized



FENTORA™
fentanyl buccal tablet ©

Onsolis™

fentanyl buccal soluble film ©



BEMA Film Placement

Because fentanyl is subject to abuse and misuse, Onsolis was approved with a Risk Evaluation and Mitigation Strategy, or REMS, which is a required plan for managing risks associated with a drug or biological product.

Fentanyl Sublingual Spray

- Fentanyl Sublingual Spray in Treating Patients With Breakthrough Cancer Pain
- This study is currently recruiting participants.
- Verified by National Cancer Institute (NCI), October 2008
- First Received: October 1, 2007 Last Updated: July 15, 2009
- **Sponsored by: Insys Therapeutics Inc**
Information provided by: National Cancer Institute (NCI)
ClinicalTrials.gov Identifier: NCT00538850

Fentanyl Nasal Spray (Nasalfent)

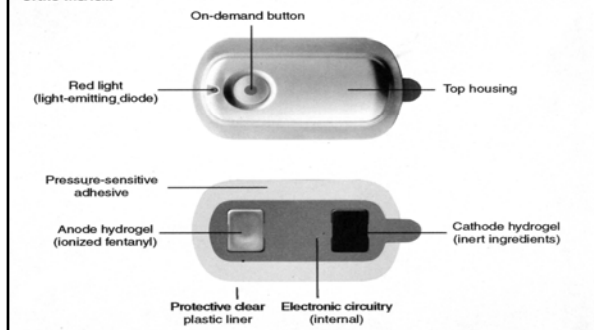
- Intranasal Fentanyl for the Treatment of Breakthrough Pain in Cancer Patients (FT-017-IM)
- This study has been completed.
- First Received: June 26, 2006
Last Updated: February 26, 2008
- **Sponsored by: Nycomed**
Information provided by: Nycomed
ClinicalTrials.gov Identifier: NCT00345735

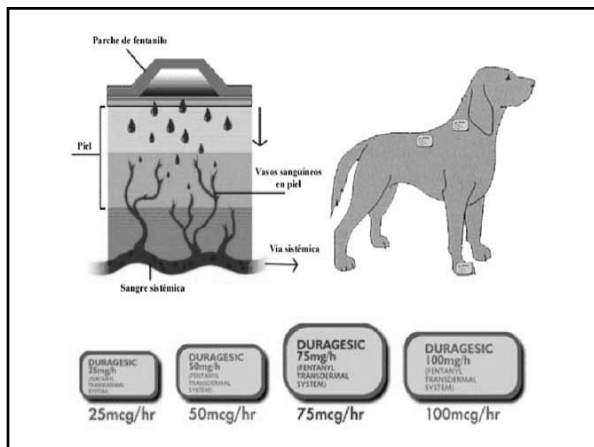
Evolution of Transdermal Fentanyl

- FDA approval August 1990 with limited use
- Low dose only
- Widespread use
- Disposal issues
- Diversion issues
- Moderate dosing
- Late 2004, 12 mcg/hr dose introduced
- 2005 goes generic
- 2008 lonsys pending (PCTS), post-op med, device, medication, both
- 2009 lonsys scrapped

Ionysis

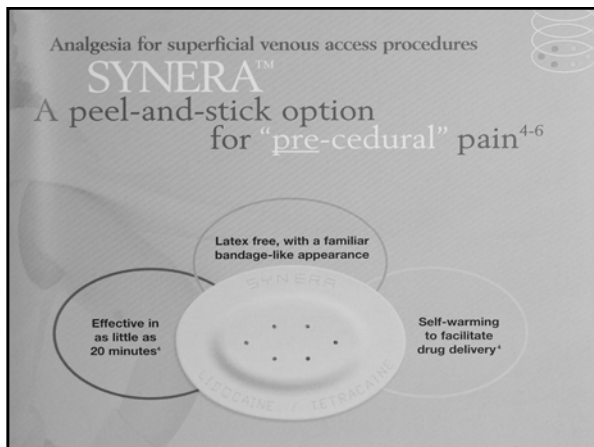
Figure 1. Fentanyl hydrochloride patient-controlled transdermal system. The unit weighs 15 g and is 3.3 in long, 1.9 in wide, and 0.39 in high. Reprinted with permission from Ortho-McNeil.





Local Anesthetics





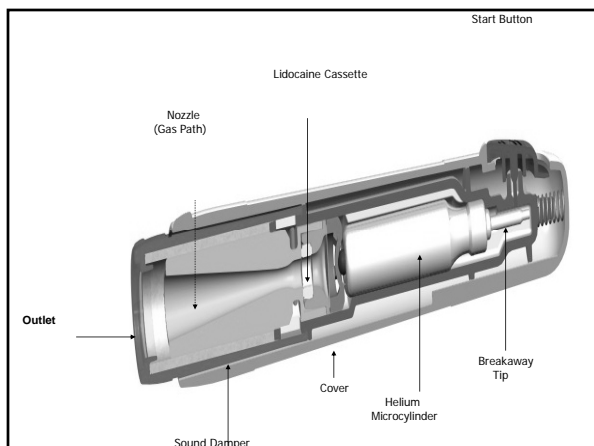
Zingo™

- The powder intradermal injection system delivers lidocaine hydrochloride monohydrate into the skin
- Provides local analgesia within 1 to 3 minutes of application
- Analgesia diminishes within 10 minutes of treatment
- Contraindicated in patients with a known history of sensitivity to local anesthetics
- Zingo is a ready-to-use, sterile, single-use, disposable, needle-free delivery system

Zingo™

- Provides local analgesia within 1 to 3 minutes of application
- Delivers local analgesia without requiring a prolonged application time
- Demonstrated efficacy for children 3-18 years of age
- Safety and tolerability established in > 1700 patients
- Easily incorporated into healthcare setting





Naltrexone

Subcutaneous Methylnaltrexone

- New Drug Application filed 5/30/07, FDA approved 4/2008
- For treatment of opioid-induced constipation in patients receiving palliative care
- Peripherally acting opioid receptor antagonist
- Without interfering with pain relief
- No other approved medication for this population

Wyeth

Abuse-Resistant & Deterrent Technologies

- *For many Americans, drug abuse is a painful fact of life. And pain is often the cause. By one estimate, more than 33 million Americans have abused prescription pain killers.*

Embeda

- Block reward/induce aversive effects if crushed or dissolved
- FDA APPROVES EMBEDA™ FOR MANAGEMENT OF MODERATE TO SEVERE CHRONIC PAIN
- BRISTOL, Tenn., August 13, 2009 /PRNewswire/ — King Pharmaceuticals®, Inc. (NYSE:KG) today announced that the U.S. Food and Drug Administration (FDA) has approved EMBEDA™ (morphine sulfate and naltrexone hydrochloride) Extended Release Capsules for oral use. EMBEDA™ is the first FDA-approved long-acting opioid that is designed to reduce drug liking and euphoria when tampered with by crushing or chewing.

Embeda



Elite

- Elite is preparing to commence Phase III clinical trials for ELI-216, the only once daily oxycodone containing naltrexone (an opioid antagonist) which provides a superior barrier to abuse compared to the other oxycodone formulations."

Remoxy

Physical Abuse resistance, Remoxy™

REMOXY, an investigational drug, is a unique, long-acting oxycodone formulation for moderate-to-severe chronic pain designed to reduce potential risks of unintended use. In mid-2008, an NDA for REMOXY was accepted by the FDA and was granted Priority Review. In December 2008, Pain Therapeutics received a Complete Response Letter from the FDA. Subsequent to the receipt of the Complete Response Letter, King assumed full control of all activities related to the development of REMOXY(r).

To be resubmitted in 2010.



www.clinicaltrial.gov

- Pain Management specialty
- 1727 studies reviewed
- Phase I
- Phase II
- Phase III
- Phase IV

www.clinicaltrials.gov

- A Study of Extended-Release Hydrocodone/Acetaminophen (Vicodin CR®) in Subjects With Acute Pain Following Bunionectomy
- This study has been completed.
- First Received: November 20, 2006 Last Updated: October 24, 2007
- Sponsored by: Abbott
- Information provided by: AbbottClinicalTrials.gov Identifier: NCT00402792

Clinical trials cont.

- **CYTRAM (Cytochrome P450, Tramadol)**
- **This study is not yet open for participant recruitment.**
- Verified by University Hospital, Caen, August 2009
- First Received: August 3, 2009 Last Updated: August 10, 2009
- **Sponsored by: University Hospital, Caen**
Information provided by: University Hospital, Caen ClinicalTrials.gov Identifier:
NCT00952159 **Purpose**
- Many methods to detect CYP2D6 poor metabolizers have been validated. Some of them are based on phenotyping (metabolism of dextromethorphan or debrisoquine) and some others on genotyping. Up to now, CYP2D6 pharmacogenetics has been restricted to the field of research, in spite of poor metabolizer profile concerns 5 to 10 % of caucasian population. Nevertheless, the polymorphism of CYP2D6 is responsible for the metabolism of many drugs, particularly of two opioids involved in **pain management**: codeine and tramadol, their metabolites representing the most effective part of the drug effect. So prescribing codeine or tramadol in a patient poor metabolizer for the CYP2D6 is likely to be ineffective in **pain management**. O-demethyl-tramadol, the metabolite of tramadol via CYP2D6, is important to consider because its analgesic effect is 2 to 4 times more potent than tramadol. The investigators propose to phenotype CYP2D6 in post-operative patients treated by tramadol by monitoring serum concentrations of O-demethyl tramadol and tramadol to make a ratio in comparison with genotype, and to find a threshold to determine poor metabolizers.

Oh, those NSAIDs!

Diclofenac



Biatain - Ibu

- Manufacturer by Coloplast
- Combines absorbent foam with release of ibuprofen as the dressing comes into contact with wound fluid.
- Foam base can absorb large amts. of exudate to reduce leakage & maceration while continuously releasing ibuprofen in wound.
- Awaiting FDA approval in US



Clinical trials

Etoricoxibe - Preemptive and Postoperative Analgesia for Abdominal and Thoracic Surgery (EPPA)

- This study is currently recruiting participants.
 - Verified by Ludwig-Maximilians - University of Munich, April 2009
 - First Received: July 15, 2008 Last Updated: April 27, 2009
 - **Sponsors and Collaborators: Ludwig-Maximilians - University of Munich**
MSD Sharp and Dohme
 - **Information provided by:** Ludwig-Maximilians - University of Munich **ClinicalTrials.gov Identifier:** NCT00716833
- Pain Abdominal Surgery, Thoracic Surgery
Drug: Etoricoxibe
Drug: Placebo
Phase III

NSAIDS clinical trials

KRYSTAL- Ketoprofen IYsinate Sore Throat Lozenges

This study is currently recruiting participants.

Verified by Sanofi-Aventis, June 2009

First Received: June 29, 2009 No Changes Posted

Sponsored by: Sanofi-Aventis

Information provided by: Sanofi-Aventis **ClinicalTrials.gov Identifier:** NCT00929877

Pain

Drug: KETOPROFEN(RP19583)

Drug: Placebo

Phase III

Sativex

- Randomized, double-blind study, placebo-controlled, parallel group trial in 66 patients with MS and related central neuropathic pain
- Patients received Sativex spray as adjunctive analgesic treatment
Each spray=2.7 mg THC + 2.5 mg cannabidiol
Patients self-titrated up to a max of 48 sprays over 24 hours

Sativex


- A Study of Sativex® for Pain Relief in Patients With Advanced Malignancy. (SPRAY)
- This study is currently recruiting participants.
- Verified by GW Pharmaceuticals Ltd., February 2009
- First Received: September 13, 2007 Last Updated: July 27, 2009
- **Sponsors and Collaborators: GW Pharmaceuticals Ltd.**
Quintiles
Information provided by: GW Pharmaceuticals Ltd. **ClinicalTrials.gov Identifier:** NCT00530764 Purpose
- The purpose of this study is to determine the effective dose range and to demonstrate a non-effective dose range of Sativex in patients with advanced cancer, who experience inadequate pain relief even though they are on optimized chronic opioid therapy.
- **Condition Intervention Phase** Palliative Care
Pain
Cancer
Drug: GW-1000-02
Phase II

Sativex

- A Study of Sativex® for Pain Relief of Peripheral Neuropathic Pain, Associated With Allodynia
- This study has been completed.
- First Received: July 3, 2008 No Changes Posted
- **Sponsored by: GW Pharmaceuticals Ltd.**
Information provided by: GW Pharmaceuticals Ltd. **ClinicalTrials.gov Identifier:** NCT00710554 Purpose
- The purpose of this study is to evaluate the efficacy of Sativex® compared with placebo in relieving peripheral neuropathic pain associated with allodynia.
- **Condition Intervention Phase** Pain
Peripheral Neuropathy
Drug: Sativex
Drug: Placebo
Phase III

New Delivery Devices


MOD™ – Security Features



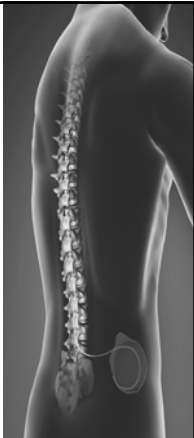
- MOD™ only responds to patient's RFID wristband and nursing smart card
- MOD™ lock and unlock to replace the med tray is via software program
- MOD™ locks into its special tray with IV pole lock
- Meds visible through clear top
- MOD™ memory retains patient data

Advances in Intrathecal Therapy

- Lighter, smaller, less expensive, MRI compatible, longer battery life devices
- Dual chamber devices??
- New player in the programmable market?



■ **"InSet Technologies is focused on developing better treatment options for the 75 million Americans in chronic pain, more than diabetes, heart disease, and cancer combined. Our first product for delivery of intrathecal medication, the Prometra® programmable implantable pump, is undergoing clinical trials. InSet is headquartered in Mount Olive, NJ."**



Patient Controlled Intrathecal Dosing




Topicals

- **New Topical Treatment for Continued Pain After Shingles**
- **This study has been completed.**
- First Received: September 10, 2007 Last Updated: October 8, 2008 [History of Changes](#)
- **Sponsors and Collaborators: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)**
Biomedical Development Corporation
The University of Texas Health Science Center, Houston
- **Information provided by: National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) ClinicalTrials.gov Identifier: NCT00566904 Purpose**
- Shingles is an outbreak of rash or blisters on the skin that is caused by the same virus that causes chicken pox.
- Some people experience continued **pain** even after the shingles rash and blisters have healed; this **pain** is known as postherpetic neuralgia. The purpose of this study is to evaluate the effectiveness of a new topical treatment for postherpetic neuralgia in adults.
- **Condition Intervention Phase** Postherpetic Neuralgia
Drug: Epikeia coatings with aspirin
Drug: Epikeia coatings with lidocaine
Other: Epikeia coatings alone
Phase I

Prevention

Alvimopan
Peripherally acting
mu opioid receptor
antagonist
Available for
management of
postoperative ileus
Give 30 minutes to 5
hours
Pre-op and then 12
mg. dose q 12
hours starting
POD #1.



Clinical trial

- Enteral Naloxone Versus a Traditional Bowel Regimen for the Prevention of Opioid Induced Constipation in Trauma Patients
- This study is currently recruiting participants.
- Verified by CAMC Health System, January 2009
- First Received: November 24, 2008
Last Updated: January 15, 2009
- **Sponsored by: CAMC Health System**
Information provided by: CAMC Health System
ClinicalTrials.gov Identifier: NCT00799201

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