Tufts Health Care Institute
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Abuse Resistance: Labeling Considerations

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Overview

- Requirements for labeling
- Types of drug abuse descriptive statements in labeling
- Examples of drug abuse statements in labeling

Requirements for Labeling

- Each statement must be justified by data and results submitted in the NDA/BLA
- FD&C ACT 502- drug product is misbranded if its "labeling is false or misleading in any particular [502(a)] " and fails to have "adequate directions for use [502(f)]"
- 21 CFR 201.56 (General) and 201.57 (Specific) describe the content and format requirements for labeling information

21 CFR 201.56

- General requirements on content and format of labeling
  - Information for safe and effective use
  - Informative and accurate
  - Neither promotional in tone nor false or misleading
  - Based on data derived from human experience (whenever possible)

21 CFR 201.57

- Specific requirements on content and format of labeling for human prescription drugs:
  - (a) Description
  - (b) Clinical Pharmacology
  - (c) Indications and Usage
  - (d) Contraindications
  - (e) Warnings
  - (f) Precautions
  - (g) Adverse Reactions
  - (h) Drug Abuse and Dependence
  - (i) Overdosage
  - (j) Dosage and Administration
  - (k) How Supplied
  - (l) Animal Pharmacology and/or Toxicology
  - (m) Clinical Studies and References
- The labeling may omit any section or subsection of labeling format if clearly inapplicable. (21 CFR 201.56)

Draft Guidance for Industry: Clinical Studies Section of Labeling

Intended to help applicants decide:

(1) What studies should be included in CLINICAL STUDIES section

(2) How to describe individual studies

(3) How to present study data, including data in graphs and tables

Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format. May 2001

Draft Guidance for Industry: Clinical Studies Section of Labeling

Include:

- Concise, accurate summary of evidence supporting effectiveness
- Adequate and well-controlled efficacy studies for approved indications
  - Not intended to describe all available efficacy
- Study results inconsistent with overall conclusions
  - Absence, limitations, dose response or effects in population subsets

Don't include:

- Unapproved indications
- Comparative safety or efficacy claims without substantial evidence
- Studies not adequate and well-controlled

Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics—Content and Format. May 2001

21 CFR 201.57(h)- Drug Abuse and Dependence Section of Labeling

Shall contain the following subsections as appropriate:

- *Controlled Substance*
  - Stated if controlled by DEA schedule
- *Abuse*
  - Primarily based on human data & pertinent animal data
  - State types of abuse, adverse events associated, susceptible patient populations
- *Dependence*
  - Effects from psychological and physical dependence
  - Quantity of drug that may lead to tolerance or dependence
  - Adverse effects of chronic abuse and abrupt withdrawal
  - Procedures to diagnose and treat effects of abrupt withdrawal

Types of Drug Abuse Resistance Statements in Labeling

ePDR® Search Results

- Drug Abuse and Dependence Sections= 163
- Drug Abuse and Dependence Section (Opioids)= 30
  - Dependence = 30/30 (100%)
  - Controlled Substance = 23/30 (77%)
    - DEA Schedule information in other places in label
  - Abuse = 17/30 (57%)
    - Abuse information often in Warnings and Precautions
- No specific drug abuse liability studies for opioids identified in labeling
- Occasional drug dependence and withdrawal data

PDR Electronic Library™. Thompson Micromedex. http://www.thomsonhc.com/pdrel/librarian/. Accessed October 20, 2005.

Where are descriptive statements in labeling regarding abuse potential?

√ Drug Abuse and Dependence

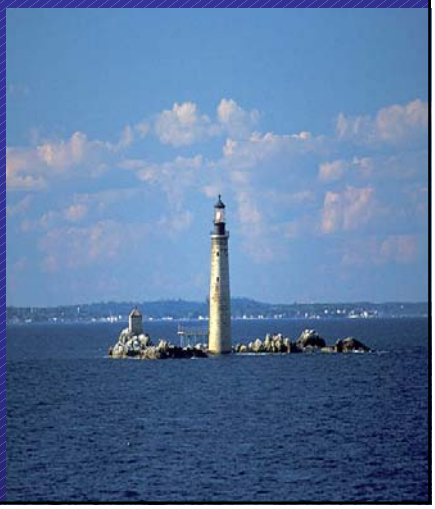
√ Warnings, Precautions, Black Box

√ Description

? Clinical Pharmacology

? Clinical Trials

? Indications and Usage



Examples of Abuse-Resistant Statements In Labeling

Strategies Referenced in Labeling

- Formulation intended to reduce/prevent abuse
  - Lomotil® (Atropine component)
- Different structure and pharmacodynamic effects than other drugs of abuse
  - Lunesta®
- Labeling with human studies regarding abuse potential
  - Marinol®
  - Strattera®
  - Amerge®

Lomotil® (Diphenoxylate/Atropine)

- Description
  - "A subtherapeutic amount of atropine sulfate is present to discourage deliberate overdosage"
- Drug Abuse and Dependence
  - "In doses used for the treatment of diarrhea, whether acute or chronic, diphenoxylate has not produced addiction. Diphenoxylate is devoid of morphine-like subjective effects at therapeutic doses. At high doses it exhibits codeine-like subjective effects. The dose which produces antidiarrheal action is widely separated from the dose which causes central nervous system effects. The insolubility of diphenoxylate hydrochloride in commonly available aqueous media precludes intravenous self-administration."

LOMOTIL® Prescribing Information. G.D. Searle LLC. (Pharmacia Corp) (Pfizer Inc.). September 2001

Lunesta® (Eszopiclone)- Clinical Pharmacology (Pharmacodynamics)

"Eszopiclone is a nonbenzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties."

Lunesta® Prescribing Information. Sepracor, Inc. December 15, 2004

Lunesta®- Drug Abuse and Dependence

- Abuse liability study in individuals with history of benzodiazepine abuse
  - Doses 2-4 fold greater than max. resulted in dose-related increase in amnesia and hallucinations for both LUNESTA and diazepam 20mg
- "No development of tolerance to any parameter of sleep measurement was observed over six months"
  - Placebo-controlled study based on 4-week objective and 6-week subjective assessments
  - Placebo-controlled study for 6 months based on subjective assessments
- "Clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome"

Lunesta® Prescribing Information. Sepracor, Inc. December 15, 2004

Marinol® (Dronabinol)- Drug Abuse and Dependence

"In an open-label study in patients with AIDS who received MARINOL Capsules for up to five months, no abuse, diversion, or systematic changes in personality or social functioning were observed despite the inclusion of a substantial number of patients with a past history of drug abuse."

MARINOL® Prescribing Information. Solvay Pharmaceuticals, Inc. September 2004.

Strattera ® (Atomoxetine HCl)- Drug Abuse and Dependence

"In a randomized double-blind, placebo-controlled abuse-potential study in adults comparing effects of STRATTERA and placebo, STRATTERA was not associated with a pattern of response that suggested stimulant or euphoriant properties."

"Clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200 adults with depression showed only isolated incidents of drug diversion or inappropriate self-administration associated with STRATTERA. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome."

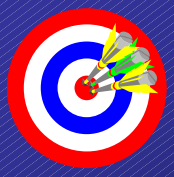
Strattera® Prescribing Information. Eli Lilly and Company. July 13, 2005

Amerge® (Naratriptan)- Drug Abuse and Dependence

"In one clinical study enrolling 12 subjects, all of whom had experience using oral opiates and other psychoactive drugs, AMERGE Tablets produced less intense subjective responses ordinarily associated with many drugs of abuse than did codeine (30 to 90 mg)."

Amerge® Prescribing Information. GlaxoSmithKline. May 2003.

"Begin with the end in mind"



- Target Product Profile (TPP)
  - FDA-PhRMA workgroup developed template
  - Summary of drug development program described in terms of labeling concepts to facilitate communication
  - *Dynamic* summary that changes as knowledge of the product increases
- Voluntarily prepared and submitted by the sponsor
- NOT an obligation to develop according to TPP
- http://www.fda.gov/cder/tpi

  (New website coming!)

Summary

- Drug abuse-resistant methodologies (and studies) may result in fact-based labeling statements in some cases
- Opportunities to modify statements required in labeling with appropriate documentation
- Identification of desired labeling statements early in development can be beneficial
  - Consider using a Target Product Profile (TPP)

Thank you!