Regulation of Prescription Drug Promotion

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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

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FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC)

Mission Statement:

To protect the public health by assuring prescription drug information is truthful, balanced, and accurately communicated

Objectives

- Ensure that prescription drug promotion is not false or misleading
- Ensure that complete picture of drug is conveyed
- Get more useful information about drugs and diseases to the American public

Mechanisms for Meeting Objectives

- Comprehensive surveillance and enforcement program
- Voluntary compliance
  - Guidance documents
  - Request for comments
  - Educational efforts

Federal Food, Drug and Cosmetic Act (FFD&C Act)

- FDA regulates promotional activities done by or on behalf of sponsor
- Code of Federal Regulations (CFR)
  - 201 - Prescription Drug Labeling
  - 202 - Prescription Drug Advertising

Code of Federal Regulations (CFR)

- Consistent with the approved product labeling or package insert (PI)
- Claims must be substantiated by adequate and well-controlled clinical studies
- Not be false or misleading
- Have fair balance
- Not promote uses not in product labeling

Prescription Drug Promotion

- Advertising
- Labeling

Advertising

- Published journals, magazines, newspapers, and other periodicals
- Broadcast through media such as radio, television, and telephone
- Disseminated with “Brief Summary”

Labeling

- Audio, visual, or printed matter including brochures, booklets, mailing pieces, exhibits, slides, etc.
- Supplied or disseminated by the manufacturer, distributor, packer, or any party acting on behalf of the sponsor
- Disseminated with the PI

FDA's Jurisdiction

	Rx	OTC
LABELING	FDA	FDA
ADVERTISING	FDA	FTC

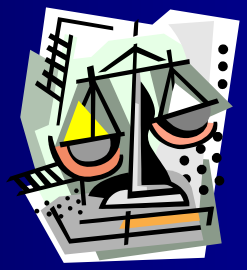
Advice to Industry

- Provide advisory comments on draft promotional materials
  - Product launches
  - Professional promotional materials
  - Direct-to-consumer (DTC)
  - Non-launch
- Usually voluntary submission
  - Pre-submission required for certain drugs (e.g., Subpart H “accelerated approval”)

Advice Within FDA

- Provide consultation
  - Draft labeling for new drug products and supplements
  - Cartons
  - Dear Healthcare Provider Letters

Enforcement



Surveillance

- Disseminated materials are submitted to FDA at time of initial use
  - Post-marketing reporting requirements (Form 2253)
  - Promotional materials DO NOT have to be submitted prior to use
- Conference attendance
- Complaints
  - Competitors, practitioners, consumers

Enforcement Actions

- Untitled letters/Notice of Violation (NOV)
- Warning Letters (WL)
- Injunctions/Consent Decrees
- Seizures
- Criminal actions

http://www.fda.gov/cder/warn/index.htm

Examples of Violations

- Unsubstantiated claims of safety
- Minimization of risk information
- Unsubstantiated claims of efficacy
- Unsubstantiated comparative claims
- Promotion of unapproved uses or drugs

Duragesic Warning Letter

- Professional File Card

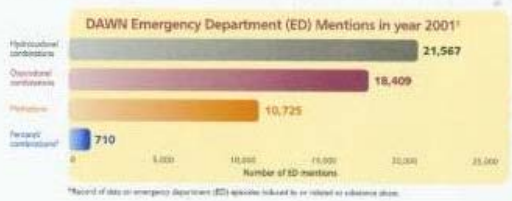
Duragesic Warning Letter

- False or Misleading Safety Claims
  - "Low reported rate of mentions in DAWN data"
  - Drug Abuse Warning Network (DAWN) data comparing the number of mentions
    - Fentanyl/combinations (710 mentions)
    - Hydrocodone/combinations (21,567 mentions)
    - Oxycodone/combinations (18,409 mentions)
    - Methadone (10,725 mentions)

Proven clinical experience

Low reported rate of mentions in DAWN data*

Source: Drug Abuse Warning Network (DAWN) database



- Data do not distinguish between IV, transdermal, transmucosal, or illicit fentanyl analogs
- DAWN only captures drug abuse events that result in ED admission
- No data on severity of adverse events or hospital admissions

www.duragesic.com

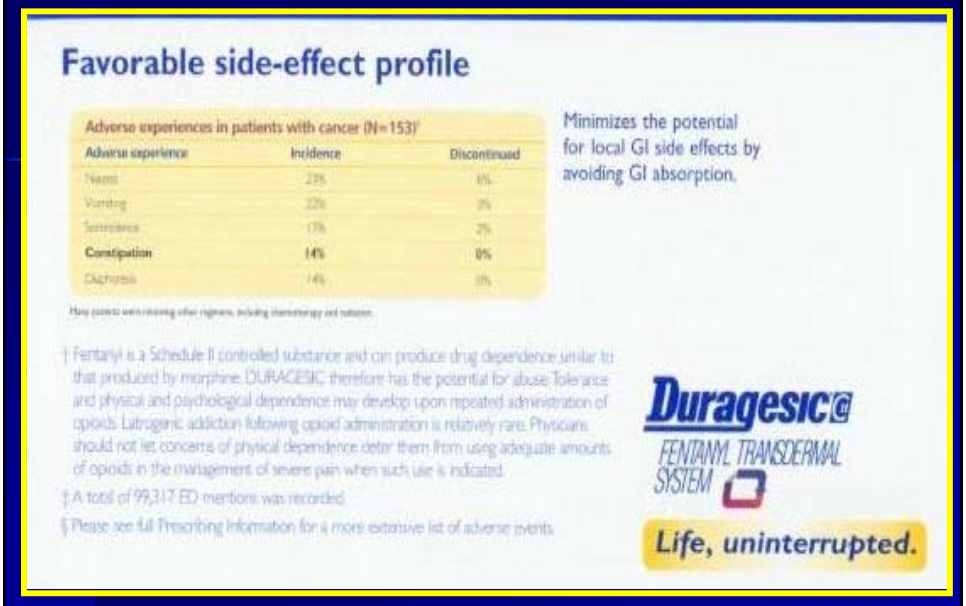
Please see important safety information, including Boxed Warning, on pages 13-14.

Duragesic Warning Letter

- No substantial evidence
  - DAWN data cannot provide the basis for a valid comparison among the products
  - DAWN - National public health surveillance system that monitors drug-related emergency department visits and death
  - Duragesic is not as widely prescribed as other opioid products
  - Lower mentions could be attributed to the lower frequency of use

Duragesic Warning Letter

- False or Misleading Safety Claims
  - "Favorable side-effect profile"
  - "Minimizes the potential for local GI side effects by avoiding GI absorption"
  - "Adverse experiences in patients with cancer" with a 14% rate of constipation for Duragesic and 0% discontinuation rate because of constipation



Duragesic Warning Letter

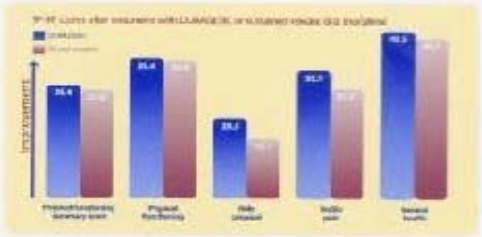
- Claims suggest that Duragesic is associated with less constipation, nausea, and vomiting than oral opioids, which are absorbed by the GI tract
- No substantial evidence to support the comparative claim

Duragesic Warning Letter

- Unsubstantiated Effectiveness Claims: improve patient outcomes and social or physical functioning or work productivity
  - "Significant improvement in social functioning"
  - "Work, uninterrupted"; "Life, uninterrupted"; "Game, uninterrupted"
  - "Chronic pain relief that supports functionality"
  - "Helps patients think less about their pain"
  - "Improvements in physical and social functioning"

Improved patient outcomes:
Open-label, crossover comparison study

Significant improvement in physical functioning summary score



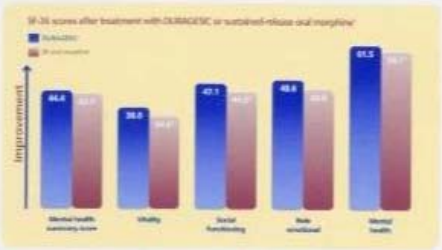
*p<0.05

Study received 256 patients who had chronic nonmalignant pain requiring patient opioids for 4 weeks prior and, by protocol, must have achieved moderate pain control with a stable dose of oral opioid for 7 days preceding the trial. Patients were given appropriate doses of DURAGESIC or sustained-release morphine over 8 weeks, followed by a crossover period in which patients were given the equivalent dose of the other therapy for 4 weeks. Within the trial, patient populations (1.1% of patients using DURAGESIC and 4% of patients using sustained-release oral morphine) withdrew due to adverse events. Among patients who were fentanyl- and morphine-naive, 1.1% using DURAGESIC and 5.6% using sustained-release oral morphine withdrew due to adverse events.*

www.duragesic.com

Please see important safety information, including Boxed Warning, on pages 13-14.

Significant improvement in social functioning



*p<0.05

Duragesic®
FENTANYL TRANSDERMAL SYSTEM

Life, uninterrupted.

Duragesic Warning Letter

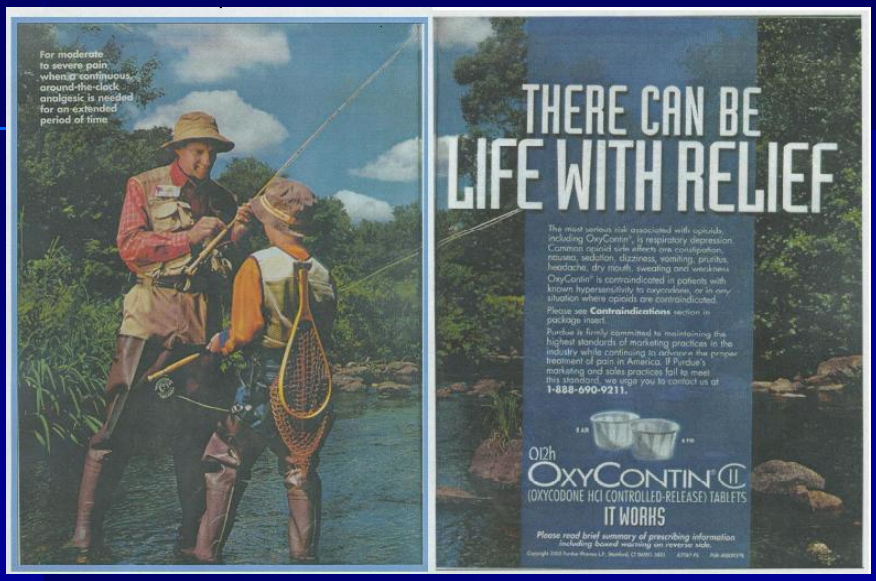
- Referenced study is inadequate to support the claims of improvement in physical or social functioning, or work productivity
  - Open-label study
  - No substantial evidence to support the claims

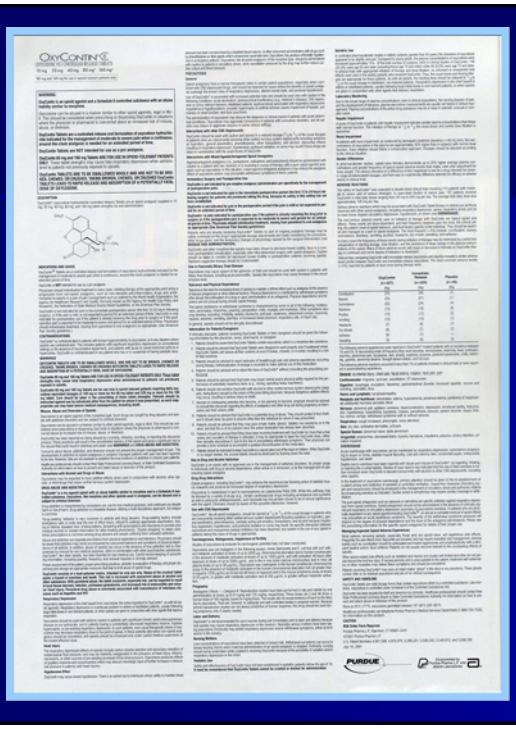
OxyContin Warning Letter

- Professional Journal Advertisement

OxyContin Warning Letter

- Claims of effectiveness for pain relief, “There can be life with relief”
- Omission of material facts related to abuse liability and fatal risks
  - No information relating to potential for abuse
  - No facts related to potentially fatal risk
  - No disclosure of limitations of use





OxyContin Warning Letter

- Minimization of risk in information presented
  - "The most serious risk with opioids, including OxyContin, is respiratory depression"
  - Statement suggests that there are no specific safety considerations for OxyContin related to respiratory depression
  - Fails to warn that this risk can be a fatal one

OxyContin Warning Letter

- Overbroadening of Indication
  - Partial language from the PI: “For moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time”
  - Fails to communicate the actual indication and suggests its use for pain relief in a much broader range of patients

IMPORTANT CORRECTION

PURDUE

Purdue Pharma L.P.

January 2003

Dear Healthcare Practitioner,

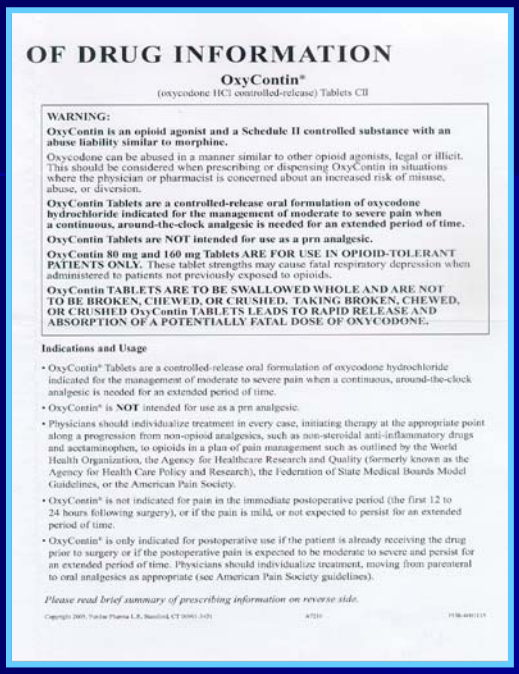
Earlier publications of this journal contained advertisements for OxyContin® (oxycodone HCl controlled-release) Tablets that were the subject of a Warning Letter from the U.S. Food and Drug Administration in January 2003, stating that the advertisements violated provisions of the drug advertising and promotion regulations.

The Warning Letter stated that information concerning important risks associated with OxyContin® Tablets that appears in the boxed warning of the OxyContin® Prescribing Information was not presented in the main body of the advertisements. This information concerns potentially fatal risks associated with the use of OxyContin® and the abuse liability of OxyContin®. In addition, the Warning Letter stated that the body of the advertisements did not present important information regarding limitations on the indicated use of OxyContin®.

Consequently, we direct you to the information on safety, risks, and indications for OxyContin® Tablets, including the boxed warning, located on the adjacent page.

Sincerely,

Robert F. Reder, MD
Vice President,
Medical Affairs and Worldwide Drug Safety



OF DRUG INFORMATION

OxyContin®

(oxycodone HCl controlled-release) Tablets CII

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Indications and Usage

- OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
- OxyContin® is **NOT** intended for use as a prn analgesic.
- Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.
- OxyContin® is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time.
- OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (see American Pain Society guidelines).

Please read brief summary of prescribing information on reverse side.

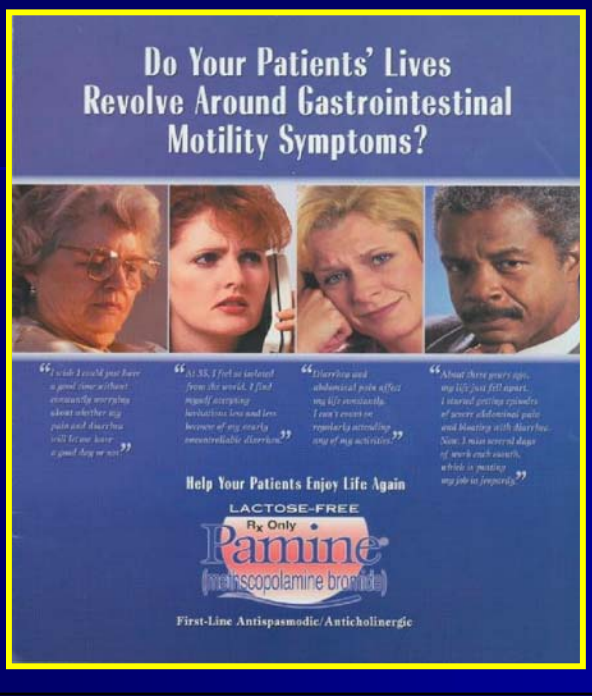
A7210

Pamine Warning Letter

- Professional detail aid
- Patient brochure
- Website

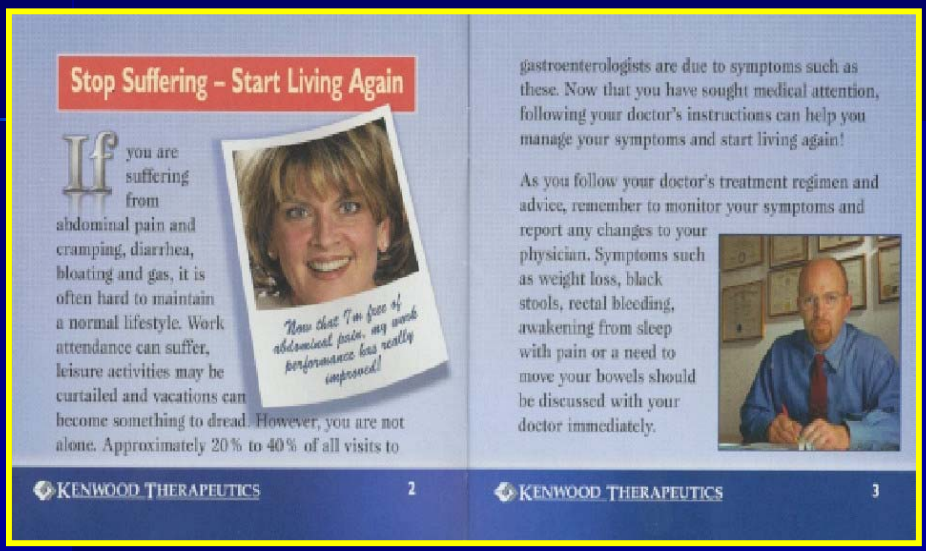
Pamine Warning Letter

- Unsubstantiated Effectiveness Claims
  - "Do Your Patient's Lives Revolve Around Gastrointestinal Symptoms?"
  - "At 35, I feel so isolated from the world. I find myself accepting invitations less and less because of my nearly uncontrollable diarrhea."
  - "About three years ago, my life just fell apart. I started getting episodes of severe abdominal pain and bloating with diarrhea. Now, I miss several days of work each month, which is putting my job in jeopardy."



Pamine Warning Letter

- Unsubstantiated Effectiveness claims
  - "If you are suffering from abdominal pain and cramping, diarrhea, bloating and gas, it is often hard to maintain a normal lifestyle. Work attendance can suffer, leisure activities may be curtailed and vacations can become something to dread."



Stop Suffering – Start Living Again

If you are suffering from abdominal pain and cramping, diarrhea, bloating and gas, it is often hard to maintain a normal lifestyle. Work attendance can suffer, leisure activities may be curtailed and vacations can become something to dread. However, you are not alone. Approximately 20% to 40% of all visits to

KENWOOD THERAPEUTICS 2

gastroenterologists are due to symptoms such as these. Now that you have sought medical attention, following your doctor's instructions can help you manage your symptoms and start living again!

As you follow your doctor's treatment regimen and advice, remember to monitor your symptoms and report any changes to your physician. Symptoms such as weight loss, black stools, rectal bleeding, awakening from sleep with pain or a need to move your bowels should be discussed with your doctor immediately.

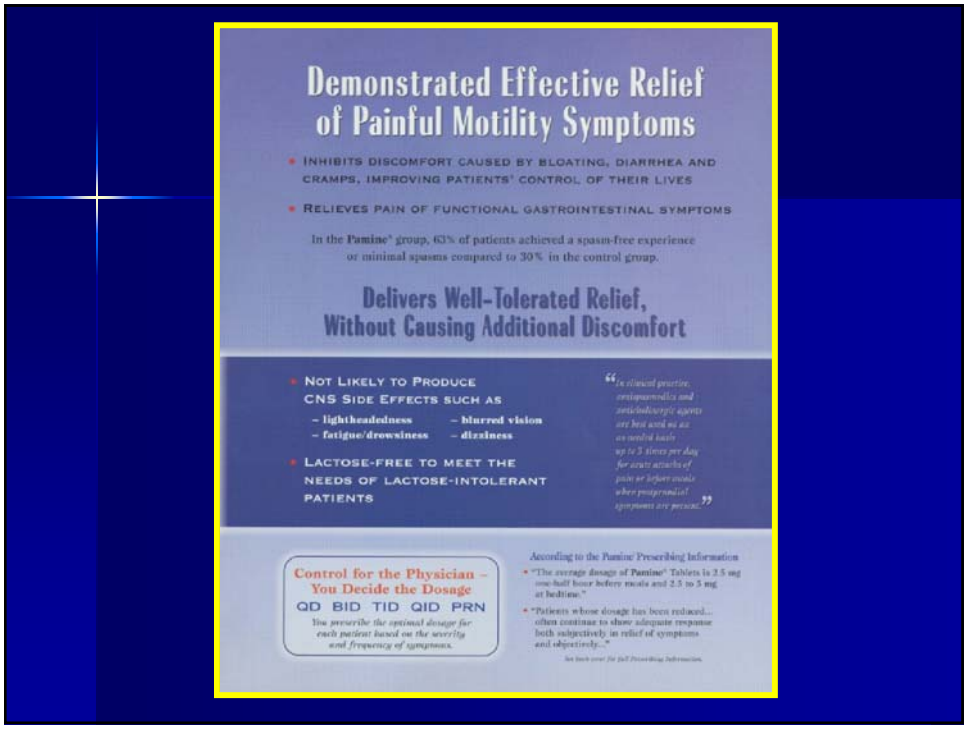
KENWOOD THERAPEUTICS 3

Pamine Warning Letter

- No substantial evidence to support claims
- Adverse Reactions section of the PI states “bloated feeling” has been associated with use of the drugs

Pamine Warning Letter

- Omission of risk information
- False or misleading safety claims
  - “Not likely to produce CNS side effects such as
    - Lightheadedness
    - Fatigue/drowsiness
    - Blurred vision
    - Dizziness”



Pamine Warning Letter

- Warnings section of the PI states that Pamine may produce drowsiness or blurred vision, and that the patient should be cautioned regarding activities requiring mental alertness such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug.

DDMAC Contact Information

- Website: www.fda.gov/cder/ddmac
- Address for regulatory submissions:
  - Food and Drug Administration
  - Center for Drug Evaluation and Research
  - Division of Drug Marketing, Advertising, and Communications
  - 5901-B Ammendale Road
  - Beltsville, MD 20705-1266
- Phone: 301-796-1200
- Fax: 301-796-9877