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FDA U.S. FOOD & DRUG ADMINISTRATION

Overdosage Information in Prescription Drug Labeling

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Disclaimer

- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.

Roundtable #1 Presentation

Some Types of Prescription Drug Labeling

Medication Guide[1] (a type of FDA-approved patient labeling)

MEDICATION GUIDE
DRUG-X [drug x]
(drugoxide injection)
for intramuscular use

What is the most important information I should know about DRUG-X? …
What is DRUG-X? …
Who should not take DRUG-X? …
Before taking DRUG-X, tell your healthcare provider about all of your medical conditions, including if you: …
How should I take DRUG-X? … If you take too much DRUG-X (overdose), get medical help, contact a Poison Help Line right away at 1-800-222-1222, or visit poisonhelp.org.
What should I avoid while taking DRUG-X? …
What are the possible side effects of DRUG-X? … Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store DRUG-X? …
General information about the safe and effective use of DRUG-X. Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use DRUG-X for a condition for which it was not prescribed. Do not give DRUG-X to other people, even if they have the same symptoms that you have. It may harm them. You can ask your health care provider for information about DRUG-X that is written for health care providers.
What are the ingredients in DRUG-X? …
Pharmaceutical company name and address

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: MM/YYYY

According to Medication Guide regulations, the “How should I take DRUG-X?” heading may include a statement of what patients should do in case of a drug overdosage

[1] See 21 CFR 208 available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-208.

Prescribing Information[1]

Written for **healthcare practitioners** and must:

- Contain a summary of essential scientific information needed for safe and effective use of the drug
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular
- Be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading

[1] Applies to Physician Labeling Rule (PLR) labeling and "old" (non-PLR) format labeling; 21 CFR 201.56(a) available at https://www.ecfr.gov/current/title-21/part-201/section-201.56#p-201.56(a)

Prescribing Information

"Old" Format Labeling Rule (1979)

- BOXED WARNING
- DESCRIPTION
- CLINICAL PHARMACOLOGY
- INDICATION AND USAGE
- CONTRAINDICATIONS
- WARNINGS
- PRECAUTIONS
  - General
  - Information for Patients
  - Carcinogenesis, Mutagenesis, Impairment of Fertility
  - Pregnancy subsection
  - Labor and Delivery
  - Nursing Mothers
  - Pediatric Use
  - Geriatric Use
- ADVERSE REACTIONS
- DRUG ABUSE AND DEPENDENCE
- **OVERDOSAGE**
- DOSAGE AND ADMINISTRATION
- HOW SUPPLIED

"Physician Labeling Rule" Format (2006)

- BOXED WARNING
- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
- 6 ADVERSE REACTIONS
- 7 DRUG INTERACTIONS
- 8 USE IN SPECIFIC POPULATIONS
- 9 DRUG ABUSE AND DEPENDENCE
- **10 OVERDOSAGE**
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
- 13 NONCLINICAL TOXICOLOGY
- 14 CLINICAL STUDIES
- 15 REFERENCES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

How Prescribing Information Is Developed and Reviewed

Development and Review of Prescribing Information

- Pharmaceutical company (company):
  - May start developing draft labeling as soon as the drug is determined suitable for first-in-human use
  - May ask FDA to comment on aspects of draft labeling *before* they submit an application or supplement
  - Submits draft labeling as part of an application or supplement
- FDA reviews draft labeling upon submission and throughout review cycle
- FDA and company:
  - Develop final labeling
  - Must agree to wording in labeling prior to approval

FDA Staff Who May be Involved in Prescribing Information Review[1]

CDER Staff and Groups that Typically Review Prescribing Information	Additional CDER Staff and Groups that Review Prescribing Information
Division management	Office management (e.g., for novel drugs)
Clinical (physicians)	Division Deputy Director for Safety
Associate Director for Labeling	Clinical microbiologists (antimicrobial products)
Office of Clinical Pharmacology (includes Labeling and Health Communications staff)	Labeling Policy Team
Division of Pediatric and Maternal Health	Office of Biotechnology Products labeling reviewer (for biological products)
Office of Pharmaceutical Quality	Division of Risk Management
Divisions of Medication Error Prevention and Analysis	Division of Pharmacovigilance
Pharmacology/toxicology	Controlled Substance Staff (controlled substances)
Office of Prescription Drug Promotion	Office of Regulatory Policy
Division of Medical Policy Programs (patient labeling reviewers)	Center for Devices and Radiological Health (device information in drug labeling)
Regulatory Project Managers	
Office of Biostatistics	

[1] Review of prescription drug labeling regulated in CDER; involvement depends on labeling type, complexity, product type, and other factors

Prescribing Information (PI) Approval and Post-Approval Changes

www.fda.gov

- Final PI is approved by FDA and attached to approval letter
- PI uploaded to Drugs@FDA[1]
- After approval (within 14 days), company submits PI electronically[2] and PI is posted on other websites (e.g., DailyMed)
- After approval, PI is updated:
  - Pharmaceutical company submits new supplement
  - FDA may contact pharmaceutical company to request update to PI or require update to PI

[1] For CDER-approved drugs, labeling posted to Drugs@FDA (www.fda.gov/drugsatfda) as a PDF file (for CBER-approved drugs, labeling posted to CBER's webpage (https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year))

[2] Posted electronically as a Structured Product Labeling (SPL) file

OVERDOSAGE Section of the Prescribing Information

Full Prescribing Information Sections

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
13 NONCLINICAL TOXICOLOGY
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

OVERDOSAGE Section Must* Include the Following Overdosage Information: (1 of 2)[1]

www.fda.gov

- Signs, symptoms, laboratory findings, and complications (e.g., organ toxicity, delayed acidosis)
- Concentrations of drug in biologic fluids associated with toxicity
- Physiologic variables influencing drug excretion
- Factors that influence dose response

* Refer to Slide #22 for required overdosage treatment information in the OVERDOSAGE section

[1] 21 CFR 201.57(c)(11). Available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-B/section-201.57#p-201.57(c)(11). The OVERDOSAGE section of labeling regulations for PLR format and "old" format labeling are very similar with minor changes (e.g., regulations for PLR format do not include the requirement to include the oral LD_{50} of the drug in animals) .

OVERDOSAGE Section Must* Include the Following Overdosage Information: (2 of 2)[1]

www.fda.gov

Amount of drug in a single dose that is:

- Ordinarily associated with symptoms of overdosage
- Likely to be life-threatening

The OVERDOSAGE section must be based on human data but if human data are unavailable, appropriate animal and in vitro data may be used

* Refer to Slide #22 for required overdosage treatment information in the OVERDOSAGE section

[1] 21 CFR 201.57(c)(11). Available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-B/section-201.57#p-201.57(c)(11). The OVERDOSAGE section of labeling regulations for PLR format and "old" format labeling are very similar with minor changes (e.g., regulations for PLR format do not include the requirement to include the oral LD_{50} of the drug in animals) .

Certain Information in Labeling is Omitted

- Omit clearly inapplicable sections, subsections, or specific information from labeling[1]
- Omit inaccurate, false, or misleading information from labeling[2]

[1] 21 CFR 201.56(d)(4) available at https://www.ecfr.gov/current/title-21/part-201/section-201.56#p-201.56(d)(4)
[2] 21 CFR 201.56(a)(2) available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-B/section-201.56(a)(2)

FDA updating warnings to improve safe use of prescription stimulants used to treat ADHD and other conditions

www.fda.gov

Serious risks with misuse, abuse, addiction, and sharing these drugs

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en Español

Chinese

Drug Safety Communication (PDF - 394 KB)

05-11-2023 FDA Drug Safety Communication

Content current as of:
06/13/2023

- **What safety concern is FDA announcing?**
- **What is FDA doing?**
- **What is a prescription stimulant and how can it help me?**
- **What should health care professionals do?**
- **What should patients and caregivers do?**
- **What did FDA find?**
- **What is my risk?**

See https://www.fda.gov/drugs/drug-safety-and-availability/fda-updating-warnings-improve-safe-use-prescription-stimulants-used-treat-adhd-and-other-conditions

CNS Stimulants: Changes to OVERDOSAGE Section[1]

www.fda.gov

Table 4. Overdosage	
Former*	**New** (reordered information)
~~Manifestations of amphetamine overdose include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia, and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Serotonin syndrome has been reported with amphetamine use.~~	**Clinical Effects of Overdose** **Overdose of CNS stimulants is characterized by the following sympathomimetic effects:** **•Cardiovascular effects including tachyarrhythmias, and hypertension or hypotension. Vasospasm, myocardial infarction, or aortic dissection may precipitate sudden**
~~Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.~~ ~~Remove all transdermal systems immediately and cleanse the area(s) to remove any remaining adhesive. The continuing absorption of dextroamphetamine from the skin, even after removal of the transdermal system, should be considered when treating patients with overdose.~~ Dextroamphetamine is not dialyzable. (*moved to Overdose Management*)	**cardiac death. Takotsubo cardiomyopathy may develop.** **•CNS effects including psychomotor agitation, confusion, and hallucinations. Serotonin syndrome, seizures, cerebral vascular accidents, and coma may occur.** **•Life-threatening hyperthermia (temperatures greater than 104°F) and rhabdomyolysis may develop.**

[1] See https://www.fda.gov/media/168050/download?attachment

Thousands of Prescription Drugs Have OVERDOSAGE Sections of Labeling

www.fda.gov

- 77% of Prescribing Information include an OVERDOSAGE section of labeling according to an FDA analysis[1]
- Prescription drugs that treat, prevent, or diagnose a multitude of diseases or conditions have an OVERDOSAGE section of labeling (e.g., allergic, anesthesiology, cardiac, critical care, dermatologic, endocrine, gastroenterology, gynecologic, hematologic, hepatic, infectious, neurologic, nutritional, oncologic, psychiatric, pulmonary, renal, rheumatologic, urologic)

We look forward to your perspectives on developing the OVERDOSAGE section for a variety of FDA-approved drugs approved to treat, prevent, or diagnose a wide range of diseases

[1] This analysis included a small percentage of Prescribing Information (PI) for "new" drugs approved since June 2001 and certain PI for drugs approved before June 2001 (e.g., drugs approved for new uses after June 2001). All these prescription drugs are approved under a new drug application (NDA) or biologics license application (BLA). This analysis does not include PI for generic drugs, repackaged drugs, or relabeled drugs.

Human Data Sources for Prescribing Information[1]

www.fda.gov

- Adequate and well-controlled studies
- Epidemiological or surveillance studies
- Human pharmacokinetic and pharmacodynamic studies
- Adverse event reports from literature and spontaneous reports

Although most of the human data sources for the Prescribing Information are from patients who received the drug under the approved conditions of use, this is typically NOT the case for overdosage data

[1] Examples of human data sources for the Prescribing Information are not exhaustive. This list does not include non-clinical data sources (e.g., animal studies, animal models, product quality data).

Roundtable #2 Presentation

OVERDOSAGE Section Must* Include Following Overdosage Treatment Information:[1]

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- Whether drug is dialyzable
- Recommended general treatment procedures
- Specific measures for support of vital functions (e.g., proven antidotes, gastric lavage, forced diuresis, or as per Poison Control Center)
- Such recommendations must be based on data available for the specific drug or experience with pharmacologically related drugs

Unqualified recommendations for which data are lacking for the specific drug or class of drugs must not be stated

* Refer to Slides #16 and 17 for other required overdosage information in the OVERDOSAGE section

[1] 21 CFR 201.57(c)(11). Available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-201/subpart-B/section-201.57#p-201.57(c)(11). The OVERDOSAGE section of labeling regulations for PLR format and "old" format labeling are very similar with minor changes (e.g., PLR format regulations included the Poison Center example but removed the induced emesis example for overdosage treatment).

CNS Stimulants: Changes to OVERDOSAGE Section[1]

www.fda.gov

Table 4. Overdosage	
Former*	**New** (reordered information)
Management of Overdose Consult with ~~a Certified~~ Poison ~~Control Center~~ (1-800-222-1222) ~~for up-to-date guidance and advice on the management of overdosage with methylphenidate~~. ~~Provide supportive care, including close medical supervision and monitoring.~~ Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug ~~overdosages~~. ~~Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures. Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses~~.	**Overdose Management** Treatment **for CNS stimulant overdose** should consist of those general measures employed in the management of overdose with any drug. Consider the possibility of multiple drug **ingestion. [[for amphetamines state: D-amphetamine is not dialyzable] [for methylphenidate state: Because methylphenidate has a large volume of distribution and is rapidly metabolized, dialysis is not useful]]**. Consider contacting the Poison **Help line** (1-800-222-1222) **or a medical toxicologist for additional overdose management recommendations**.

[1] See https://www.fda.gov/media/168050/download?attachment

OVERDOSAGE Section: Some Challenges with Including Treatments for Drug Overdosage

- Only a handful of prescription drugs have been FDA-approved to treat overdosage (e.g., acetylcysteine, digoxin immune Fab, flumazenil, leucovorin, naloxone, uridine triacetate)
- There is generally a lack adequate and well-controlled trials that support approval of a prescription drug to treat a drug overdosage

OVERDOSAGE Section: What Type and Quantity of Evidence is Needed to Support the Use of Drug to Treat Overdosage of Another Drug?

www.fda.gov

[1] Following drugs are FDA-approved for treatment of overdosage of specific drugs: acetylcysteine, digoxin immune Fab, flumazenil, leucovorin, naloxone, uridine triacetate


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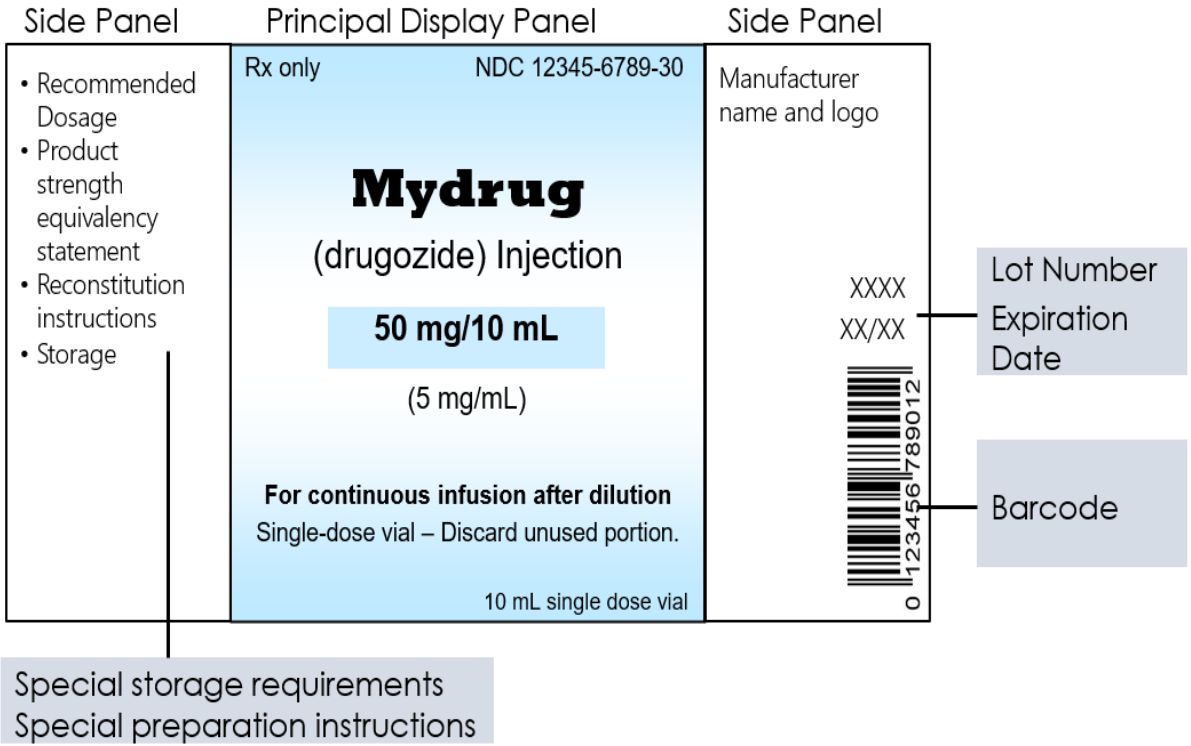
Extra Slides

Other Types of Prescription Drug Labeling

Container Label[1]

www.fda.gov



Cautionary or warning statements about overdosage may be included on carton and container labeling

[1] See guidance for industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022).

PATIENT INFORMATION
DRUG-X [drug X]
(drugoxide-a and drugoxide-b tablets)
for oral use

What is DRUG-X? …
Do not take DRUG-X if you: …
Before taking DRUG-X, tell your health care provider about all of your medical conditions, including if you: …
How should I take DRUG-X? **…** If you take too much DRUG-X (overdose), get medical help, contact a Poison Help Line right away at 1-800-222-1222, or visit poisonhelp.org.
What should I avoid while taking DRUG-X? **…**
What are the possible side effects of DRUG-X? … Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store DRUG-X? …
General information about the safe and effective use of DRUG-X. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DRUG-X for a condition for which it was not prescribed. Do not give DRUG-X to other people, even if they have the same symptoms that you have. It may harm them. You can ask your health care provider for information about DRUG-X that is written for health care providers.
What are the ingredients in DRUG-X? …
Name of pharmaceutical company and address

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: MM/YYYY

Patient Package Insert[1]

(another type of FDA-approved patient labeling)

[1] Oral contraceptives see 21 CFR 310.501
Estrogen-containing products see 21 CFR 310.515.

Patient Medication Information: Proposed Rule[1]

www.fda.gov

In May 2023, FDA proposed a new rule for Patient Medication Information (PMI). If finalized, PMI would:

- Require pharmaceutical companies to create a new type of labeling for patients (or their caregivers) for prescription drugs used, dispensed, or administered on an outpatient basis
- Be a one-page document with standardized format and content and written in non-technical language
- Be submitted to FDA for approval
- Require authorized dispensers to provide PMI to patients (or their caregivers) each time a prescription drug (for which an FDA-approved PMI exists) is used, dispensed, or administered on an outpatient basis

[1] *Medication Guides: Patient Medication Information* proposed rule. For more information about PMI, see https://www.fda.gov/drugs/cder-conversations/patient-medication-information-2023-proposed-rule-help-patients-understand-their-prescription

Updating Labeling

Updating Labeling

www.fda.gov

Pharmaceutical Company's Responsibilities

- Should review labeling at least annually for outdated information[1]
- Labeling must be updated when new information becomes available that causes labeling to become inaccurate, false, or misleading[2]
  - "a drug … shall be deemed to be misbranded .. (i)f its labeling is false or misleading in any particular"[3]

Labeling Update Opportunities

Encourage updates in multiple labeling type submissions (e.g., PLR conversions, efficacy supplements)

[1] Guidance for industry: *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013)
[2] 21 CFR 201.56(a)(2)
[3] FD&C Act [section 352(a) of the U.S.C.]

Toxicities in Clinical Studies with Dosages Greater Than Maximum Recommended Dosage

Toxicities in Clinical Studies with Dosages Greater Than Maximum Recommended Dosage

www.fda.gov

- In phase 1 studies of an investigational drug (DRUG-X), a single 100 mg dose resulted in dizziness, somnolence, mental status changes, and nausea and vomiting
- These adverse reactions were not seen after administration of 10 mg of DRUG-X once daily in 12-week adequate and well-controlled studies
- Subsequently, DRUG-X is approved for use with a recommended dosage of 10 mg once daily

Do you consider specific toxicities that have only occurred in clinical studies at dosages greater than the maximum approved recommended dosage to be an overdosage and should this information be described in the OVERDOSAGE section of labeling?

Prescription Drug Labeling Review Resources

Drugs@FDA[1]

[1] www.fda.gov/drugsatfda

FDA's Labeling Resources for Human Prescription Drugs

For Industry

www.fda.gov

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FDA's labeling resources for human prescription drugs are primarily directed to industry staff who develop human prescription drug labeling. Human prescription drug labeling:

- Contains a summary of the essential scientific information needed for the safe and effective use of the drug; and
- Includes the Prescribing Information, FDA-approved patient labeling (Medication Guides, Patient Package Inserts, and/or Instructions for Use), and/or carton and container labeling.

For assistance on how to navigate this webpage and the associated FDA labeling resource webpages for human prescription drugs see video.

If you are a healthcare professional, patient, or caregiver, visit Frequently Asked Questions about Labeling for Prescription Medicines.

- **Key Labeling Databases**
- **Additional Labeling Databases**
- **How May "Current" Labeling Be Different Than "FDA-Approved" Labeling**
- **Searchable Product Databases**
- **Imported-Drug Specific Labeling Resources**
- **Resources for Promotional Labeling and Other FDA-Regulated Products**

[1] FDA's Labeling Resources for Human Prescription Drugs webpage available at https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

Prescribing Information Resources

for Industry

www.fda.gov

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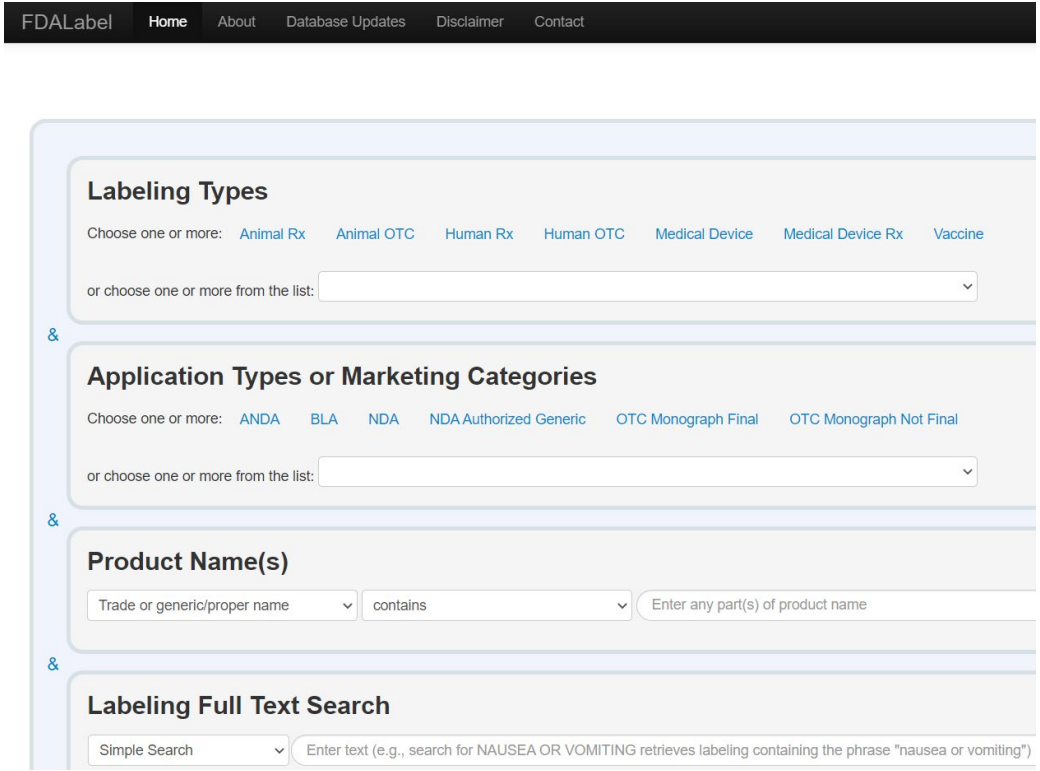
- Highlights of Prescribing Information
- Boxed Warning
- 1 Indications and Usage
- 2 Dosage and Administration
- 3 Dosage Forms and Strengths
- 4 Contraindictions
- 5 Warnings and Precautions
- 6 Adverse Reactions
- 7 Drug Interactions

[1] Prescribing Information Resources webpage available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

FDALabel: Full-Text Search of Labeling for Drugs for Human Use[1]

www.fda.gov



FDALabel and DailyMed generally have the same data

[1] NCTR's FDALabel searches "in use" labeling (Structured Product Labeling files) of (available at https://nctr-crs.fda.gov/fdalabel/ui/search) for prescription drugs and nonprescription drugs as well as other FDA-regulated products