Learn More About Product Labeling

Product label

The product label is developed during the formal process of review and approval by regulatory agencies of any medicine or medical product. There are specific regulations concerning what must be included in a medicine label regarding its content, and how it works, as well as its proper administration and handling, its side effects, and its proven effectiveness and safety. The content and presentation of any medicine's specific labeling—originally drafted and submitted by the manufacturer—are reviewed and approved by regulatory agencies, which may require changes or additions to the label before approving the use of the medicine.

In the U.S., the complete label of a prescription medicine is made up of several documents that are approved and required by the Food and Drug Administration (FDA)—some professionally oriented and some intended for patients and consumers. The first and most comprehensive of these documents is always the professional Prescribing Information. Others may include Patient Counseling Information and a patient-oriented Medication Guide. Each of these components is described in more detail below.

Prescribing information (PI)

This document includes a great deal of technical medical detail intended to inform health care professionals who might prescribe or dispense a medicine. The PI of any approved medicine is publicly available and anybody may obtain it (from the manufacturer or from the FDA, for example), but a PI is written for a professional audience. Whatever your level of scientific and/or mathematical training, reading the PI cannot substitute for a discussion with a health care professional regarding the risks and benefits and appropriateness of a medicine in your individual circumstances.

Manufacturers typically make the PIs of their medicines available on the Web, and must include the PI as a printed "package insert" with any medicine that is sold in a box or other type of package. Note that a package insert may also include other material in addition to the PI (although you may see the terms "package insert" and "prescribing information" referred to interchangeably in general discussion).

Given the large amount of information to be provided, newer medicines must now have a two-part PI to make it easier to find and review the information. The first part, titled *Highlights of the Prescribing Information*, usually takes up less than one page, but may be longer, depending on the complexity and extent of the relevant information. This section excludes much of the technical detail, charts/graphs, and less broadly applicable information about the medicine. The second part is the full PI, with specifically labeled and numbered sections.

Although PIs for the older products cover the same types of information as for new products, some of the sections are arranged and labeled a bit differently. For instance, in PIs of older medicines, the topics *Medicine Interactions*, *Use in Special Populations*, and *Patient Counseling Information* are subsections of a separate *Precautions* section. In PIs of newer medicines, each of these three topics is presented as a separate section, and *Precautions* is part of a combined *Warnings and Precautions* section, rather than being its own section.

The table on the following page presents the required sections of the PI for newer and older products, as specified in FDA regulations. For medicines approved between 2001 and 2006, FDA regulations require the use of the new PI format on a schedule phased in over time. So, not all medicines approved during that time period will be in the new PI format yet, but will be by 2013.

Some of the more important sections of the PI relating to the safe and effective use of a medicine are described below.

Indications

The *Indications* section states what diseases or conditions a medicine should be used for, by which patients, and in what situations.

An indication will specify:

- The recognized ***disease or condition*** for which the medicine's use is approved, or the ***important manifestation*** of a disease or condition, such as:
  - Hypertension.
  - Edema in patients with congestive heart failure.
- Whether the medicine is approved to ***treat***, ***prevent***, or ***diagnose*** the disease or condition, or to ***relieve the symptoms*** associated with a disease or syndrome, such as:
  - Penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci.
  - Barium sulfate is indicated for use as a contrast agent in X-ray diagnosis of gastrointestinal disease
  - Chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis.
- Whether the medicine may be used ***by itself*** (often referred to as "monotherapy"), should be used as the ***primary therapy*** (i.e., without first trying another medicine) versus secondary/tertiary therapy (i.e., used only if another medicine has been found not to be sufficiently effective or to have unacceptable side effects), or in conjunction with another mode of therapy (such as surgery, diet, etc.—often referred to as "adjunctive therapy") or in combination with another medicine.
- Whether the medicine is only approved for certain ***subgroups of patients*** with the disease or symptom, such as:
  - Patients with mild disease.
  - Patients in certain age groups.
- Whether use of the medicine should be ***reserved for certain situations***, such as:
  - Cases where other therapy has not been effective (often referred to as "refractory" to other therapy).
  - Patients who are not able to tolerate the adverse effects they experience with another therapy or medicine.

Learn More About Product Labeling (cont'd)

Medicines Approved in U.S. After June 2006	Medicines Approved in U.S. Before June 2001
Highlights of Prescribing Information • Product Names, Other Required Information • Boxed Warning (if required) • Recent Major Changes • Indications and Usage • Dosage and Administration • Dosage Forms and Strengths • Contraindications • Warnings and Precautions • Adverse Reactions • Drug Interactions • Use in Specific Populations	For an older medicine, the PI does not include a "Highlights" section
Full Prescribing Information Boxed Warning (if required) 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 – 8.1 Pregnancy – 8.2 Labor and delivery – 8.3 Nursing mothers – 8.4 Pediatric use – 8.5 Geriatric use 9. Medicine Abuse and Dependence – 9.1 Controlled substance – 9.2 Abuse – 9.3 Dependence 10. Overdosage 11. Description 12. Clinical Pharmacology – 12.1 Mechanism of action – 12.2 Pharmacodynamics – 12.3 Pharmacokinetics 13. Nonclinical Toxicology – 13.1 Carcinogenesis, mutagenesis, impairment of fertility – 13.2 Animal toxicology and/or pharmacology 14. Clinical Studies 15. References 16. How Supplied/Storage and Handling 17. Patient Counseling Information	• Product Names • Boxed Warning (if required) • Description • Clinical Pharmacology • Indications and Usage • Contraindications • Warnings • Precautions • Adverse Reactions • Drug Abuse and Dependence • Overdosage • Dosage and Administration • How Supplied • Animal Pharmacology and/or Animal Toxicology • Clinical Studies

An "indication" for a medicine refers to a specific use of that medicine, as approved by a regulatory agency such as the FDA, based on its review and analysis of all the medical evidence on the benefits and risks of the medicine from laboratory and clinical testing.

Contraindications

By contrast, a "contraindication" for a medicine refers to a specific situation in which the medicine should NOT be taken or administered—defined as circumstances under which using the medicine entails a substantial risk of harm that clearly outweighs any possible therapeutic benefit. Put another way, the *Contraindications* section describes the kinds of cases where patients would have a substantial risk of being harmed by a medicine without the potential for sufficient benefit to make that risk acceptable. The *Warnings* section of the PI will also include a brief mention of any contraindications (with cross-references to this section), and will provide more detail about any specific adverse reaction that is involved.

Various criteria can be considered for determining when a medicine is contraindicated:

- Patient ***age*** (especially infants or young children, or elderly individuals, for whom the demonstrated effectiveness might be less, or the risk of harmful adverse reactions greater, than for other ages).
- Patient ***gender*** (a risk may be higher, or the effectiveness of the medicine less, for male compared with female individuals).
- ***Concomitant therapy*** (other medicines or treatments already being taken might lead to harmful adverse reactions if this medicine were taken at the same time).
- ***Disease state*** (the risk-benefit relationship might be different for different severities or stages of the disease to be treated).
- ***Other condition*** (a specific coexisting disease or the general condition of a patient might make use of a medicine potentially more hazardous, or less effective against a disease).
- Patient ***hypersensitivity*** to the medicine.

A contraindication is a judgment by regulators—after reviewing the available medical evidence—about the benefit-risk relationship of using that medicine under specific circumstances. For example, a medicine may be approved for treatment of advanced stages of a life-threatening disease, despite a known risk of serious adverse reactions, if a sufficient level of effectiveness has been demonstrated and no safer effective treatment options exist. In contrast, that same medicine may be contraindicated for patients in whom the same treated disease is less advanced, if it can be treated with other medicines that are equally effective but have a lower risk of serious side effects. It is important to remember that whether a medicine is right for you, at the right time, and for your condition, is always a decision ultimately made by you and your doctor. Note that, according to FDA regulations, contraindications are issued regarding medicine hazards that are known—because they have been demonstrated in studies and/or clinical experience—not for hazards that are simply theoretically possible.

Warnings

Information about a medicine's important side effects and what to do about them is provided in the *Warnings* section, which now forms part of an integrated *Warnings and Precautions* section under the new PI labeling format. Clinically significant adverse events are described, along with other potential safety hazards, limitations in the medicine's use due to those reactions and hazards, and steps to take if they occur. The defining criterion for inclusion under *Warnings* is that a reasonable association must have been established between the adverse event or risk and the medicine—although a definitive causal relationship need not be established.

The *Warnings* section may also provide information about nonapproved uses of the medicine. This would be the case either if the medicine has been commonly used for a condition or if there is a common belief that the medicine is effective for a condition, but the preponderance of evidence demonstrates that the medicine is not effective and that this usage of the medicine is associated with a clinically significant risk or hazard. Note that, because such situations involve nonapproved uses of the medicine, they would not be covered in other sections of the PI such as *Indications and Usage* or *Contraindications*.

Boxed warning

This term refers to a specially formatted warning that is the strongest level of safety warning that may be required by the FDA for an approved medicine. Specifically, a boxed warning gives a brief explanation of any contraindications or serious warnings that may be associated with death or serious injury, with a cross-reference to more detailed information covered in the *Warnings* and/or *Contraindications* sections of the PI. If a boxed warning is required, it will be found at the beginning of the PI, with the text surrounded by a thick black border, with the heading *WARNING*. For this reason, it is often referred to as a "black box" or "black box warning."

Precautions

In the old PI labeling format, actions required to make sure a medicine is properly and safely used were included under *Precautions* if not covered in other sections of the PI (for example, under *Warnings*, *Dosage and Administration*, *Indications and Usage*, or *Contraindications*). This type of information appears in an integrated *Warnings and Precautions* section under the new PI labeling format.

This section also may include information for the prescriber concerning certain laboratory tests that may be necessary or helpful to the practitioner to ensure the medication is being used safely or to help predict when possible adverse reactions might occur.

Precautions for health care professionals are covered separately from precautions for patients. For example, health care professionals might be instructed to ensure that certain preexisting medical conditions are treated prior to using the medicine because of the risk of the medicine

exacerbating those conditions, or to test the levels of certain enzymes in the patient that might affect the activity of the medicine.

Note: The *Information for Patients* subsection, within the *Precautions* section under the old labeling rules, has been deleted under the new PI labeling format. It may still appear in older labels, but not in the newer labels. That section has been replaced by the *Patient Counseling Information* section (see below).

Information for patients/Patient counseling information

This section explains to health care professionals the information about the medicine that they should discuss with their patients. Such information might include precautions about operating machinery when using the medicine, or instructions on when to take the medicine relative to mealtimes.

Note that this section may have different titles and locations within the product label according to when the medicine and/or its labeling was approved. Whether in the newer or older format, however, the same types of information are provided.

- *Information for Patients* is found in PIs for older medicines. You will find it as a subsection under the *Precautions* section near the middle of the PI.
- *Patient Counseling Information*, on the other hand, is a separate section at the very end of the PIs for newer medicines.

If a medication has information designed specifically for patients (*Patient Package Insert* or *Medication Guides*), that information would be contained in a separate document that may be printed at the end of the PI, or provided separately. That kind of labeling is not always necessary or required, so not all medications will have such a document.

Medication Guide

A *Medication Guide* or other patient labeling may be required for certain medicines. This printed document contains FDA-approved information that may be included at the end of the PI, but must be made available separately.

A *Medication Guide* or other patient labeling may provide:

- Certain information that is necessary to prevent serious side effects.
- Information about a known serious side effect with a medicine to help patients to make an informed decision about whether the benefits of taking the medicine outweigh the risks.
- Directions for the use of a product that are essential to its effectiveness.

A listing of products that have Medication Guides, with links to those Guides, is available on the FDA Web site at: *http://www.fda.gov/drugs/drugsafety/ucm085729.htm*.