Patient Labeling 101

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Patient Labeling

Consists of:

- Medication Guides (MG)
- Patient Package Inserts (PPI)
- Instructions for Use (IFU)
MG required if FDA determines one or more circumstances exist:

1. patient labeling could help prevent serious AEs
2. serious risks: could affect patient’s decision to use
3. patient adherence to directions crucial to effectiveness
Medication Guides

FDA-approved patient labeling and a component of REMS

- Primarily for outpatient Rx products with serious & significant public health concerns
- Based on (not in conflict with) Professional Information (PI)
- Format and content
  - At least 10 point font
  - Written in nontechnical language
  - Specified section headings (Q & A)
    - relevant to drug product
Medication Guides

Distribution Requirements

- Mfrs must provide sufficient #s of MGs or means for the dispenser to produce
- Dispenser required to provide MG when product is dispensed
Medication Guides

- In the past, a Medication Guide was approved and considered only part of labeling.
- Now, any drug that requires a new Medication Guide is considered to have a REMS.
  - Some drugs with existing MGs may convert to a REMS if FDA determines that there is new safety information.
Consumer Medication Information (CMI):

- is information that is developed by third party companies, such as First Databank Wolters Kluwer Health, and others.
- is not part of FDA-approved labeling and is not reviewed by the Agency.
Patient Labeling Review Process

- A collaborative effort between OND and OSE/DRISK
- DRISK is generally consulted by OND
- DRISK provides a formal review of patient labeling with recommended revisions
- DRISK works with OND to negotiate Patient Labeling with Applicants
Package Insert (PI)

MG = Medication Guide
PPI = Patient Package Insert
PIFU = Patient Instruction for Use

- Patient Labeling Reviewers rely on the PI to provide the basis for information that is included in patient labeling (PPI, MG, or PIFU)

- Review goal for PPI, MG, PIFU:
  - should be scientifically accurate, specific, and comprehensive, and should not conflict with PI information
  - weight given to and placement of information within patient labeling must be consistent with the weight given to and placement of information in the PI
Enhancing Readability of Patient Labeling Materials

General approaches to enhance readability:

- Patient labeling should be written at a 6 to 8th grade reading level
- Use of certain fonts: Verdana, Arial, or APHont size 11 or greater for better visibility
- Use of text boxes, bold font, and underlining to highlight important concepts
- Good use of white space, chunking, and bulleted formatting to enhance cognition
We appreciate the questions that were forwarded to us for consideration.
Many of the questions fall outside the scope of the Patient Labeling Team and should be addressed with OND. Examples:

- The PRO Guidance
- Inclusion of patient input regarding labeling
- Inclusion of quality of life issues in labeling
- Ensuring timely posting of updated labeling materials on the FDA web site, or timely distribution of updated printed materials
Questions from Patient Representatives:

- Several Patient Representatives asked about including percentages of side effects and clinical trials statistics in patient labeling.
“Many of the materials are printed in pt. 2 type (or smaller!). Can FDA force the providers to make them legible w/o magnifying glasses?”
“Most patients do not read the labels if their doctor explained the drug and the side effects. Is there a way to print the label in such a way that it is attractive to the reader?”
“Simply keeping track of the nomenclature (brand name, trade name, generic name, proprietary name, chemical name, etc.) is very confusing, even to professionals. FDA is making a real effort to remove such conflicts, but patients feel overwhelmed at times. Has any thought been given to creating some new system?”
“…how does this new drug I am about to start taking interacts with drugs I am already taking? In other words you should not take this drug with drugs X, Y, and Z.”
“...I think it would be good to know, definitively, the process these pieces of information go through, the intended audience for each piece of information and then, ultimately how or if PRs (or anyone, for that matter) can weigh in and advocate for changes to be made to these informative pieces. ...in my field of interest, asthma, there are PPIs which exist where there is no consistency whatsoever. In one paragraph, this word or that phrase is used and in the very next paragraph, a different word or different phrasing is used. While this is not so difficult for one who is immersed in this disease and in the lingo, I know that this would be difficult for the average person to try and follow when the words and phrases change over and over w/in the same document. Not to mention those persons when English is not their first (or second) language.”
Thank you for your attention!
Prescription Drug Information

- Human Prescription for Drug and Biological Products
- A prescription drug product label is a compilation of information about a product written by the manufacturer and approved by FDA
- Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products became effective in June 2006
Adverse Event Reporting

Adverse Event Reports Comes IN to FDA

MedWatch

Safety Information Goes OUT to the Public
MedWatch History

FDA Safety Information and Adverse Event Reporting Program
1993 to 2009

1993 - MedWatch, The FDA Adverse Event Reporting Program

1998 - MedWatch, The FDA Medical Products Reporting and Safety Information Program

2009 - MedWatch, The FDA Safety Information and Adverse Event Reporting Program


“Our goal is to…more widely disseminate information of the FDA’s actions that have resulted from adverse event and product problem reporting.”
FDA Website
www.fda.gov/medwatch
MedWatch Safety Information Out
MedWatch-issued product specific alerts

- FDA website
  - “your Internet gateway for timely safety information....”
- MedWatch Safety Alerts
  - Product-specific, timely and actionable alerts for drugs, biologics, devices and special nutritional products
- Monthly Drug Safety Labeling changes
  - 40-50 drugs with 80-100 changes/month to Boxed Warnings, Warning, Contraindications, Precautions, Adverse Reactions, Medication Guides
Monthly Safety Labeling Changes

- Clinically important safety labeling updates, including changes to the following labeling sections:
  - Boxed Warnings
  - Contraindications
  - Warnings and Precautions
  - Adverse Reactions
  - Patient Package Insert & Medication Guide

- In 2008:
  - 1157 safety changes
  - 561 PI’s
  - 56 boxed warnings
  - 60 Medication Guides
### Monthly Safety Labeling Changes

#### January 2009

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>BW</th>
<th>C</th>
<th>W</th>
<th>P</th>
<th>AR</th>
<th>PPI/MG</th>
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<tbody>
<tr>
<td><strong>Celexa (citalopram hydrobromide) tablets</strong>&lt;br&gt;<strong>Celexa (citalopram hydrobromide) solution</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Levoatri (sotalol) oral solution</td>
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<tr>
<td>Effexor XR (venlafaxine HCl) Extended-Release Capsules and Effexor (venlafaxine HCl) Tablets</td>
<td>X</td>
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<tr>
<td>Hydopen (hydrocodone and homatropine) Tablets</td>
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**Celexa (citalopram hydrobromide) tablets January 2009**

**Detailed View: Safety Labeling Changes Approved by FDA Center for Drug Evaluation and Research (CDER) — January 2009**

The detailed view includes drug products with safety labeling changes to the BOXED WARNING, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, or PATIENT PACKAGE INSERT/MEDICATION GUIDE sections. Deletions or editorial revisions made to these sections are not included in this summary. Read about the new physician labeling format.

#### Summary View

<table>
<thead>
<tr>
<th>Sections Modified</th>
<th>Summary of Changes to Contraindications and Warnings</th>
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<tbody>
<tr>
<td><strong>WARNINGS</strong></td>
<td><strong>WARNINGS</strong></td>
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<tr>
<td>Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions</td>
<td>The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Celexa treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists...</td>
</tr>
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</table>
Xenical (orlistat) capsules

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – May 2010

Summary View

PRECAUTIONS

General

There have been rare postmarketing reports of severe liver injury with hepatocellular necrosis or acute hepatic failure in patients treated with orlistat with some of these cases resulting in liver transplant or death. Patients should be instructed to report any symptoms of hepatic dysfunction promptly and obtain medical advice.

Patient Package Insert

What are the possible risks of XENICAL?

Xenical has been shown to reduce the absorption of certain vitamins. You should take a multivitamin containing vitamins D, E, K, and beta-carotene once a day at least 2 hours before or after the administration of Xenical, such as at bedtime.

Some patients taking Xenical may develop an increased risk for the development of kidney stones. Promptly report any symptoms of back pain or blood in the urine.

Some patients prescribed Xenical may already be at increased risk for the formation of gall stones. Weight loss with Xenical can increase the risk of gall stones. Promptly report any symptoms of pain in the upper right portion of the abdomen. The pain may be accompanied by nausea and vomiting.

There have been rare reports of severe liver injury in patients taking Xenical. Promptly discontinue Xenical and contact your healthcare provider if you develop symptoms suggestive of liver impairment, such as loss of appetite, itching, yellowing of the skin, dark urine, light colored stools, or right upper quadrant pain.
Label and Approval History

Drug Name(s)          ZETIA (Brand Name Drug)
FDA Application No.   (NDA) 021445
Active Ingredient(s)  EZETIMIBE
Company               MSP SINGAPORE

Label Information

What information does a label include?
Note: Not all labels are available in electronic format from FDA.

View the label approved on 07/21/2009 (PDF) for ZETIA, NDA no. 021445
• To see older, previously-approved labels, go to the "Approval History" section of this page. Older labels are for historical information only and should not be used for clinical purposes.

Approval History
NDA 021445

Note: Not all reviews are available in electronic format from FDA. Older labels are for historical information only, and should not be used for clinical purposes. Approval dates can only be verified from 1984 to the present.

Click on a column header to re-sort the table:

<table>
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<th>Action Date</th>
<th>Supplement Number</th>
<th>Approval Type</th>
<th>Letters, Reviews, Labels, Patient Package Insert</th>
<th>Note</th>
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<td>026</td>
<td>Labeling Revision</td>
<td>[Label (PDF)] [Letter (PDF)]</td>
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<td>[Label (PDF)] [Letter (PDF)]</td>
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<td>025</td>
<td>Package Change</td>
<td>[Label (PDF)] [Letter (PDF)]</td>
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</tr>
</tbody>
</table>
Other FDA-approved safety information

- DailyMed Current Labeling
  - An FDA/National Library of Medicine collaboration
Patient Medication Information
( PMI – aka CMI )
The Single-Document Solution
PMI — Giving Patients the Information They Need

- Patients need easy access to prescription medication information (PMI) that is clear, concise, current, accurate, actionable, and accessible

- 2008 Evaluation of Consumer Medication Information
  - 94% consumers received information with new prescriptions
  - 75% met the criteria for usefulness
  - Demonstrating the PMI need is not being met
Current System

- **Patient Package Inserts (PPI)** - prescription information developed by manufacturers, approved by FDA and dispensed with specific products, e.g. oral contraceptives, estrogen-containing products.

- **Consumer Medication Information (CMI)** - prescription drug information developed by pharmacies or an outside company, voluntarily distributed to consumers by pharmacies.

- **Medication Guides** - prescription drug information for certain medications that “pose a serious and significant public health concern,” developed by the manufacturer, approved by FDA, and required to be distributed to consumers each time the medication is dispensed.
A New Paradigm —
The Single-Document Solution

- Over 22,000 marketed products requiring PMI
- Eliminate PPIs, CMI, and Medication Guides
- FDA will propose a new regulation
  - Require all prescription drugs to have a single PMI document
  - Describe the content and format
  - Define evaluation criteria and standards
  - Require manufacturers to consumer-test
- Source of PMI document — FDA approved professional labeling
- Manufacturers must develop, test, and submit PMI to an electronic repository
PMI Activities

- Feature *Rheutopia*, fictitious drug for RA and other conditions
  - Multiple indications and multiple serious risks
  - Unique administration (injection)

- Myriad of issues to be addressed, including:
  - Design Quality Management System for monitoring/evaluation with enforcement authority
  - Processes for evaluation
  - Submission and distribution
  - PMI repository and access
  - Interim solutions for phased-in implementation strategy
DRAFT PROTOTYPE 1

PATIENT INFORMATION
Rheupia™ [Roo-toh-piej-ah] (also known as arthralgia)

Important Warning: Serious Infections
- Rheupia affects the immune system. It can lower your ability to fight infections. Do not use Rheupia if you have an active infection.
- People taking Rheupia have gotten serious infections including tuberculosis (TB) and infections caused by viruses, fungi, or bacteria. Some people have died from these infections.

What Does Rheupia Treat?
- Rheumatoid arthritis in adults. Rheupia reduces painful and swollen joints, slows joint damage, and improves mobility and the ability to do physical activities.
- Polymyalgia rheumatica in adults in people older than 5 years of age who did not have good results from other medicines. Rheupia reduces pain, improves mobility, and decreases the number of painful joints.
- Ankylosing spondylitis. Rheupia reduces back pain, swelling, and improves mobility.
- plaque psoriasis in adults who may benefit from taking medicine or receiving phototherapy (using ultraviolet light). Rheupia improves or clears up areas of skin with psoriasis.

What Should I Tell My Doctor?
Before using Rheupia, tell your doctor if you:
- have an infection, are being treated for an infection, or think you have an infection (such as a cold, flu, or skin infection).
- have TB or have been near someone who has TB.
- lived in or traveled to other countries.
- have any nervous system or heart problems.
- are taking the medicine Kineret (anakinra).
- are scheduled to receive a vaccination (including a flu shot). You should not get a vaccination while taking Rheupia.

When Should I Call My Doctor?
Stop using Rheupia and tell your doctor right away if you develop:
- fever, cough, flu-like symptoms, skin infection (red, warm, painful skin or open sores).
- numbness, tingling, weakness, vision problems, or dizziness.
- chills, swollen lymph nodes, night sweats, fever, or weight loss.
- bruising, bleeding, and pale skin.
- shortness of breath, swelling of ankles or feet, or sudden weight gain.
- chest discomfort or pain, shortness of breath, joint pain or a rash on your cheeks or arms.

What Are Some Common Side Effects?
- Redness, rash, swelling, itching or bruising where the shot was given.
- Headache
- Runny nose
Tell your doctor about any side effect that does not go away in a few days or gets worse.

How Do I Use Rheupia?
- Rheupia is an injection (shot). Do not use Rheupia until you have been shown how to give a shot.
- Store Rheupia in the refrigerator. Do not shake or freeze.
- If you forget to take a dose, take it as soon as you remember. Take your next dose at your regularly scheduled time.
- Your doctor will tell you how often to use Rheupia. Do not use Rheupia more often than prescribed.

Where Can I Get More Information?
- Visit www.fda.gov
- Call 1-800-(manufacturer).
DRAFT PROTOTYPE 2
PATIENT INFORMATION
Rheutopia™ (Roo-toh-pee-ab) (also known as arizatate)

Important Warning: Serious Infections
- Rheutopia affects the immune system. It can lower your ability to fight infections. Do not use Rheutopia if you have an active infection.
- People taking Rheutopia have gotten serious infections including tuberculosis (TB) and infections caused by viruses, fungi, or bacteria. Some people have died from these infections.

What Does Rheutopia Treat?
- Rheumatoid arthritis in adults. Rheutopia reduces painful and swollen joints, slows joint damage, and improves mobility and the ability to do physical activities.
- Polycystic juvenile rheumatoid arthritis (JRA) in people older than 4 years of age who did not have good results from other medicines. Rheutopia reduces pain, improves mobility, and decreases the number of painful joints.
- Ankylosing spondylitis. Rheutopia reduces back pain, swelling, and improves mobility.
- Plaque psoriasis in adults who may benefit from taking medicine or receiving phototherapy (using ultraviolet light). Rheutopia improves or clears up areas of skin with psoriasis.

What Should I Tell My Doctor?
Before using Rheutopia, tell your doctor if you:
- have an infection, are being treated for an infection, or think you have an infection (such as a cold or flu skin infection).
- have TB or have been near someone who has TB. You may be tested and treated for TB.
- lived in or traveled to other countries. There is more risk for getting TB or other infections in certain countries.
- have any nervous system or heart problems.
- are taking the medicine Kineset (anakinra). The risk of serious infections increases when used with Rheutopia.
- are scheduled to receive a vaccination (including a flu shot). You should not get a vaccination while taking Rheutopia.

When Should I Call My Doctor?
Stop using Rheutopia and tell your doctor right away if you develop:
- Fever, cough, flu-like symptoms, skin infection (red, warm, painful skin or open sores). These can be symptoms of a serious infection.
- Numbness, tingling, weakness, vision problems, or dizziness. Symptoms of nervous system diseases, like multiple sclerosis, may develop or get worse.
- Chills, swollen lymph nodes, night sweats, fever, or weight loss. You may have a higher chance of getting lymph node cancer.
- Bruising, bleeding, and pale skin may not make enough blood cells. These are failure that may develop or get.
- Chest discomfort or pain, shortness of breath, swelling, sudden weight gain. These may be symptoms of an with lupus-like syndrome.

What Are Some Common
- Redness, rash, swelling, itching. the shot was given.
- Headache
- Runny nose

Tell your doctor about any side effects away in a few days or get worse.

Active ingredient: arizatate

Uses:
- Rheumatoid arthritis (adults and children older than 4): reduces painful swollen joints, slows joint damage and improves mobility.
- Ankylosing spondylitis: reduces back pain, swelling, and improves mobility.
- Plaque psoriasis in adults: clears up areas of skin with psoriasis.

Warnings:
- Important Warning: Serious Infections
- Do not use Rheutopia if you have an active infection. Rheutopia affects the immune system and can lower your ability to fight infection. Some people have died from an infection such as tuberculosis (TB) when using Rheutopia.
- No other uses.
- Act specialty:
- Ask the doctor before using if you have:
- have any signs of infection (fever, chills, flu-like signs), have a skin infection (red, warm, painful skin or open sores).
- Enrolled positive for tuberculosis (TB) or have been near someone who has TB.
- If your symptoms are new or get worse, return to your doctor.
- Your doctor will tell you how to use Rheutopia. Do not use doses prescribed.
- Take this daily for 1-2 days.
- You may report side effects to the manufacturer at (phone # and web address) or FDA at 1-4

You may report side effects to the manufacturer at (phone # and web address) or FDA at 1-4

FDA U.S. Food and Drug Administration Protecting and Promoting Public Health
PMI Activities, *cont.*

- Fall 2010 – Initiate public process on PMI Single-Document Solution
- Planned public workshop in conjunction with Brookings Institution
- Consumer Testing
  - FR Notice research protocol published 5/4/10; comment period closed 7/6/10
  - Initiate study following OMB approval Spring 2011
  - Test content compression, format and order of information
  - 150 face-to-face pre-screening encounters with consumers
  - Experimental design – 900 consumers with RA
  - Follow-up internet study – 200 consumers with RA
July 2010: Englewood Center for Health Care Reform at Brookings

http://www.brookings.edu/~/media/Files/events/2010/0721_CMI/Final%20CMI%20discussion%20guide%20071910.pdf accessed 8/30/2010
Moving Forward

- Access and distribution – preliminary recommendations
  - Central e-repository of up-to-date leaflets
  - Permit e-receipt by the pharmacy
  - Pharmacy cannot change content or format
  - Permit the option for patients to receive leaflet electronically or in paper form (or other formats?)

- Process
  - Public/private consortium
  - Interim pilot solutions
Development and Distribution of Patient Medication Information for Prescription Drugs

• Register for the public hearing
  – email registration information to PMIpublicmeeting@fda.hhs.gov.

• Submit electronic comments

• Submit written comments
  – Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852

• A live webcast of this hearing will be viewable at
  – September 27  https://collaboration.fda.gov/p15d109272010/
  – September 28  https://collaboration.fda.gov/p15d209272010/

[Docket No. FDA–2010–N–0437]