



# **Novel and Adaptive Labeling Approaches: PLR and Beyond**

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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.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

# **2006: A BANNER YEAR!!!**



**In 2006, FDA published  
Physician Labeling Rule (PLR)!!!**



# 2006 TRIVIA!!!



# QUESTION 1

**1. In 2006, which baseball team won the World Series?**

- a) St. Louis Cardinals
- b) Detroit Tigers
- c) Chicago White Sox
- d) Boston Red Sox



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- b) Detroit Tigers
- c) Chicago White Sox
- d) Boston Red Sox



## QUESTION 2

**2. In 2006, which was the most popular movie (i.e., top grossing movie)?**

- a) Star Wars: Episode III
- b) Harry Potter and the Goblets of Fire
- c) Pirates of the Caribbean: Dead Man's Chest
- d) Spider-Man 3



## QUESTION 2

2. In 2006, which was the most popular movie (i.e., top grossing movie)?

- a) Star Wars: Episode III
- b) Harry Potter and the Goblets of Fire
- c) **Pirates of the Caribbean: Dead Man's Chest**
- d) Spider-Man 3





## QUESTION 3



**3. In 2006, what was the price of a postage stamp?**

- a) 37 Cents
- b) 39 Cents
- c) 44 Cents
- d) 49 Cents

## QUESTION 3



**3. In 2006, what was the price of a postage stamp?**

a) 37 Cents

**b) 39 Cents**

c) 44 Cents

d) 49 Cents

# QUESTION 4



**4. In 2006, the most popular social network was?**

- a) Facebook
- b) Twitter
- c) MySpace
- d) Friendster

# QUESTION 4



**4. In 2006, the most popular social network was?**

- a) Facebook
- b) Twitter
- c) MySpace**
- d) Friendster

# QUESTION 5



**5. In 2006, FDA published which of the following FINAL guidances concerning the content and format for human prescription drug labeling?**

- a) WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING Sections of Labeling Guidance
- b) ADVERSE REACTIONS Section of Labeling Guidance
- c) CLINICAL STUDIES Section of Labeling Guidance
- d) A and B
- e) B and C

# QUESTION 5



**5. In 2006, FDA published which of the following FINAL guidances concerning the content and format for human prescription drug labeling?**

- a) WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING Sections of Labeling Guidance
- b) ADVERSE REACTIONS Section of Labeling Guidance
- c) CLINICAL STUDIES Section of Labeling Guidance
- d) A and B
- e) B and C**



## QUESTION 6

FDA

### **6. The 2006 PLR Final Rule:**

- a) Set minimal graphical requirements for labeling
- b) Revised current regulations for prescription drug labeling of older products by clarifying certain requirements
- c) Required that all FDA-approved patient labeling be reprinted with or accompany the prescribing information
- d) A and C
- e) All of the Above



## QUESTION 6

FDA

### 6. The 2006 PLR Final Rule:

- a) Set minimal graphical requirements for labeling
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- c) Required that all FDA-approved patient labeling be reprinted with or accompany the prescribing information
- d) A and C
- e) All of the Above**



# PLR: 2006-Present



- Major goal of PLR: Revise content/format of labeling to make it easier for healthcare providers to access, read, and use prescription drug\* information
- Challenge: Deciding when and how to label information not discussed in guidance and/or regulation
  - PLR regulations/guidances could not possibly cover all topics
  - Medical/drug development/technologic advances

\*The term *drug* refers to both human drugs and biological products.

# Novel/Adaptive Labeling Approaches



What are some options to consider for labeling content that may not be specifically discussed in guidance?



# When to Consider Novel/Adaptive Labeling Approaches....

Determine whether the information is:

- Pertinent to the safe and effective use of the drug
- Best communicated in the prescribing information.....





## Prescribing Information (PI)

- Contains a **summary of the essential scientific information** needed for safe and effective use of a prescription drug\*
- Other communication resources may be appropriate for disseminating prescription drug information

\* 21CFR 201.56(a)(1)

# TOPICS



**Omitting Misleading and/or Clearly Inapplicable Labeling Content**

**Labeling Complex Dosing or Administration Information**

**Misfit Labeling Information**

# OMITTING MISLEADING AND/OR CLEARLY INAPPLICABLE LABELING CONTENT



# Pertinent Labeling Regulations

- Labeling must not be misleading:  
(21CFR 201.56(a)(2))
- Omit clearly inapplicable sections, subsections, or specific information:  
(21 CFR 201.56(d)(4))



# FULL PRESCRIBING INFORMATION: CONTENTS\*

## 1 INDICATIONS AND USAGE

## 2 DOSAGE AND ADMINISTRATION

## 4 CONTRAINDICATIONS

## 5 WARNINGS AND PRECAUTIONS

## 6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

## 7 DRUG INTERACTIONS

## 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of  
Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

## 9 DRUG 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

\*Sections or subsections omitted from  
the full prescribing information are not  
listed.





# FDA's Approach to Labeling

- FDA strives to approve all labeling that meets all labeling requirements
- In exceptional cases, FDA has approved labeling that omits required content when information is considered **misleading and/or clearly inapplicable** (21CFR 201.56(a)(2) and/or 21 CFR 201.56(d)(4))
  - Exceptions that are considered on a case-by-case basis

# Pregnancy and Lactation Labeling Rule (PLLR): Published 2014

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

## PRE - PLLR

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

## PLLR

~~NEW LABELING~~  
(effective June 30, 2015)

8.1 Pregnancy  
includes Labor and Delivery

8.2 Lactation  
includes Nursing Mothers

**NEW**

8.3 Females and Males of  
Reproductive Potential

# Omission of Labeling Content

- PLLR provides a new opportunity to consider the omission of required labeling content if the content is misleading and/or clearly inapplicable
- This policy is not new to PLR and has been communicated in the FDA Guidance: *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements*

## 8.1 Pregnancy

Pregnancy Exposure Registry

Risk Summary

Clinical Considerations

*Disease-Associated Maternal and/or Embryo/Fetal Risk*

*Dose Adjustments During Pregnancy and the Postpartum Period*

*Maternal Adverse Reactions*

*Fetal/Neonatal Adverse Reactions*

*Labor or Delivery*

Data

*Human Data*

*Animal Data*

## 8.2 Lactation

Risk Summary

Clinical Considerations

Data

## 8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Contraception

Infertility

**PLLR  
Labeling\***

\*21CFR 201.57(c)(9)(i)-(iii)

# PLLR Labeling Requirements

PLLR regulations are prescriptive and have generally more required content and specific format requirements compared with most other parts of PLR labeling; Requirements include:

- Headings/subheadings within subsections
- Specific statements (e.g., risk and benefit lactation statement)
- Noting absence of available data as well as available data

# MYDRUG (Fictitious Drug)



- **INDICATIONS AND USAGE:**

MYDRUG is indicated for:

- the treatment of erectile dysfunction
- as an adjunct to other diagnostic tests in the diagnosis of erectile dysfunction

(MYDRUG is not indicated for use in females)

## ***Pregnancy Subsection*** **If PLLR Requirements Met**

### **8.1 Pregnancy**

#### Risk Summary

There are no data concerning the use of MYDRUG in pregnant women. In animal reproduction studies, administration of drugazide to .....(see *Data*).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

# MYDRUG

## *Lactation Subsection*

### If PLLR Requirements Met

#### 8.2 Lactation

##### Risk Summary

There is no information regarding the presence of drugazide in human milk, the effects on the breastfed infant, or the effects on milk production.

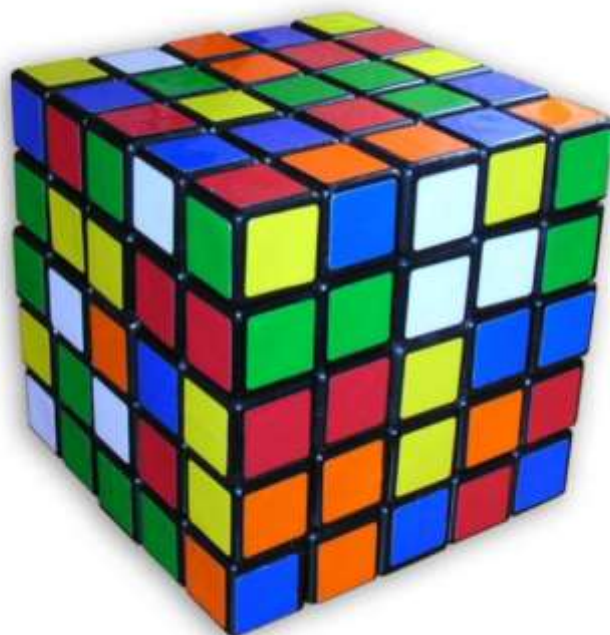
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MYDRUG and any potential adverse effects on the breast-fed child from MYDRUG or from the underlying maternal condition.



## *Pregnancy and Lactation* subsections: Omitted



# **LABELING COMPLEX DOSING OR ADMINISTRATION INFORMATION**



# Complex Dosing or Administration Information



- DOSAGE AND ADMINISTRATION\* section includes dosage (e.g., recommended dose, interval between doses) administration, and preparation information
- For complex directions, flowcharts, diagrams, or tables are recommended and commonly used
- However, other options could be considered.....

\*See 21 CFR 201.57(c)(3) and FDA Guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products-Content and Format*

# Consider Creating an “Overview” Subsection



## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosage Overview

Administer PEGASYS by subcutaneous injection once weekly in the abdomen or thigh for the treatment of:

- Adult patients with chronic hepatitis C (CHC) without or with HIV coinfection [*see Dosage and Administration (2.2)*]; and
- Pediatric patients with CHC [*see Dosage and Administration (2.3)*]; and
- Adult patients with chronic hepatitis B (CHB) [*see Dosage and Administration (2.4)*].

For treatment of CHC, use PEGASYS in combination with other HCV antiviral drugs. For information about the recommended dosage and administration and the safe and effective use of these other HCV antiviral drugs, refer to their prescribing information. PEGASYS monotherapy is only indicated in the treatment of CHC if there are contraindications to or significant intolerance to other HCV antiviral drugs.

For dosage modifications in patients with CHC or CHB:

- Due to neutropenia, thrombocytopenia, ALT elevation, and depression [*see Dosage and Administration (2.5)*].
- In patients with severe renal impairment (creatinine clearance less than 30 mL/minute) and in patients with creatinine clearance between 30 and 50 mL/minute [*see Dosage and Administration (2.5)*].

# Consider Including

## *Instructions for Use* for Healthcare Providers

- *Instructions for Use* are typically a form of patient labeling; developed for products with complicated or detailed patient-use instructions
- DOSAGE AND ADMINISTRATION section of the PI should summarize information necessary for healthcare providers to safely and effectively dose and administer drugs
- In certain instances, information may be too complex to adequately convey in the PI alone [e.g., drug administered by healthcare providers (as opposed to patients) using some devices]

## *Instructions for Use Considerations*

- Summarize key dosage and administration in the DOSAGE AND ADMINISTRATION section
- Include a cross-reference and hyperlink in DOSAGE AND ADMINISTRATION to the Instructions for Use *[see Instructions for Use]* for more detailed information
- Consider entitling the document to differentiate it from an Instructions for Use for Patients (e.g., *Healthcare Provider Instructions for Use*)

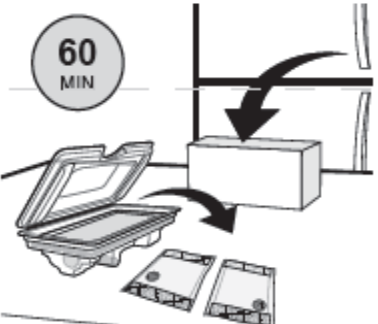


## Instructions for Use

**You must read these complete instructions before you administer SUSTOL for the first time.**

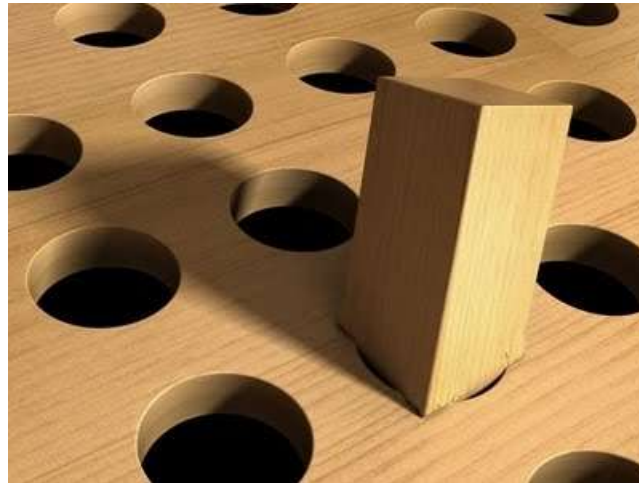
**SUSTOL must be administered by a healthcare provider.**



<b>What is SUSTOL?</b>	<p>SUSTOL is a subcutaneous injection that provides long-acting antiemetic medication to patients receiving chemotherapy. SUSTOL contains a highly viscous polymer that provides sustained release of granisetron.</p> <p>SUSTOL is supplied as part of an administration kit.</p>				
<b>When should you administer SUSTOL?</b>	<p>Administer SUSTOL at least 30 minutes before chemotherapy on Day 1 of chemotherapy treatment and not more frequently than once every 7 days, because of the extended release properties of the formulation.</p>				
<b>Before you begin to prepare SUSTOL Injection</b>	<p><b>Read these critical instructions.</b></p> <p><i>Do not substitute any of the components from the kit for administration.</i></p> <p>Check to make sure the SUSTOL kit contains:</p> <ul style="list-style-type: none"> <li>• One sterile single-dose glass syringe which contains 10 mg granisetron</li> <li>• One sterile 18G x 5/8" administration needle</li> <li>• Two sodium acetate warming pouches</li> <li>• One Point-Lok® needle protection device</li> <li>• Instructions for Use, Package Insert and Medication Guide</li> </ul>				
<p><b>Bring SUSTOL to room temperature</b></p> 	<table border="1"> <thead> <tr> <th>STEP</th><th>To bring SUSTOL to room temperature:</th></tr> </thead> <tbody> <tr> <td>1</td><td> <p>Remove SUSTOL kit from refrigeration. Open carton and remove tray. Open tray and unpack warming pouches. Wait a minimum of <b>60 minutes</b> prior to use to allow SUSTOL and the warming pouches to warm to room temperature.</p> <p>SUSTOL may be left out at room temperature overnight, and for up to 7 days, before it must be discarded. SUSTOL may be re-refrigerated if not used within the 7 day period.</p> <p>Warming SUSTOL prior to injection decreases the viscosity and makes administration easier. Bringing SUSTOL to room temperature prior to warming with the sodium acetate warming pouch will facilitate warming of SUSTOL to body temperature.</p> </td></tr> </tbody> </table>	STEP	To bring SUSTOL to room temperature:	1	<p>Remove SUSTOL kit from refrigeration. Open carton and remove tray. Open tray and unpack warming pouches. Wait a minimum of <b>60 minutes</b> prior to use to allow SUSTOL and the warming pouches to warm to room temperature.</p> <p>SUSTOL may be left out at room temperature overnight, and for up to 7 days, before it must be discarded. SUSTOL may be re-refrigerated if not used within the 7 day period.</p> <p>Warming SUSTOL prior to injection decreases the viscosity and makes administration easier. Bringing SUSTOL to room temperature prior to warming with the sodium acetate warming pouch will facilitate warming of SUSTOL to body temperature.</p>
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# MISFIT LABELING INFORMATION

(information that doesn't quite fit into an established section/subsection)





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### **4 CONTRAINDICATIONS**

### **5 WARNINGS AND PRECAUTIONS**

### **6 ADVERSE REACTIONS**

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

### **7 DRUG INTERACTIONS**

### **8 USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of  
Reproductive Potential

8.4 Pediatric Use

8.5 Geriatric Use

### **9 DRUG ABUSE AND DEPENDENCE**

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

**Required Sections/Subsections based  
on 21CFR 201.56(d)**

### **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

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Pharmacology

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### **15 REFERENCES**

### **16 HOW SUPPLIED/STORAGE AND HANDLING**

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\*Sections or subsections omitted from the  
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**Additional nonstandard subsections  
and/or headings within subsections  
used to enhance labeling organization,  
presentation, or ease of use  
can be added**

**17 PATIENT COUNSELING  
INFORMATION**

\*Sections or subsections omitted from the full prescribing information are not listed.

## **“Misfit Information” Topics**

- Immunogenicity Data
- Juvenile Animal Data
- “Other” Specific Populations
- Patient Experience
- PATIENT COUNSELING INFORMATION Section

# IMMUNOGENICITY DATA



# Immunogenicity Assessments for Therapeutic Protein Products

- Studies that evaluate the immune response to therapeutic proteins and their potential to impact safety and/or efficacy
- Clinical implications associated with antibodies are discussed in appropriate sections of labeling (e.g., IgG antibodies associated with immune reactions are discussed in WARNINGS AND PRECAUTIONS)
- **Where are the immunogenicity data summarized?**

# Inclusion of Immunogenicity Data



- Location of Information: *Immunogenicity* subsection of ADVERSE REACTIONS section\*:

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

### 6.2 Immunogenicity

### 6.3 Postmarketing Experience

\*See FDA Draft Guidance: *Labeling for Biosimilar Products*

# ADVERSE REACTIONS Section: Immunogenicity Statement



- Include following standard statement or appropriate modification at beginning of Immunogenicity subsection preceding the immunogenicity data
  - "As with all therapeutic proteins\*, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to *[insert product's nonproprietary name]* in the studies described below with the incidence of antibodies in other studies or to other products may be misleading."
- \* If product is a peptide, an oligonucleotide, or a heparin, instead of including the words "therapeutic proteins" insert the word "peptides", "oligonucleotides", and "heparins", respectively.

# JUVENILE ANIMAL TOXICOLOGY DATA





# Juvenile Animal Toxicology Data

- Nonclinical toxicity studies in juvenile animals can provide useful information concerning the safety profile of a drug in immature systems and a drug's potential effects on the growth and development of pediatric patients....
- **Where and how should juvenile animal data be discussed in labeling?**

## ***Pediatric Use Subsection***

- Include a concise summary of clinically-relevant nonclinical juvenile animal toxicology data under a heading, *Juvenile Animal Data*, in the *Pediatric Use* subsection, following the information required under 21CFR 201.57(c)(9)(iv)
- In general, juvenile animal data should not be discussed in labeling when the data do not suggest an adverse signal

# Juvenile Animal Data:

## Focus on Clinical Relevance

Discuss juvenile animal data using relevant terms:

- human equivalent dose exposures;
- ages of animals studied and how they correlate with approximate human ages;
- organ systems affected (e.g., “central nervous system” instead of “excessive grooming” or “hindlimb splay”);
- duration of treatment of animals and relationship to clinical use;
- reversibility of the adverse effect; and,
- if applicable, developmental delay.

# **“OTHER” SPECIFIC POPULATIONS**



# USE IN SPECIFIC POPULATIONS

## Section\*

- Content requirements described for
  - 8.1 Pregnancy
  - 8.2 Lactation
  - 8.3 Female and Males of Reproductive Potential
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
- Additional subsections may be included, as appropriate, if sufficient data are available concerning the use of the drug in other specified subpopulations (e.g., renal or hepatic impairment)

\*See 21CFR 201.57(c)(9)

## “Other” Specific Population

What are examples of “Other” Specific Populations that could be considered for inclusion as a USE IN SPECIFIC POPULATIONS subsection (i.e., in addition to subsections pertinent to patients with renal or hepatic impairment)?



## “Other” Specific Population Example (1)\*

### 8.7 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizers had increased flibanserin exposures compared to CYP2C19 extensive metabolizers. Additionally, syncope occurred in a subject who was a CYP2C19 poor metabolizer [*see Adverse Reactions (6.1) and Clinical Pharmacology (12.5)*]. Therefore, increase monitoring for adverse reactions (e.g., hypotension) in patients who are CYP2C19 poor metabolizers. The frequencies of poor CYP2C19 metabolizers are approximately 2–5% among Caucasians and Africans and approximately 2–15% among Asians.

\*Derived from FDA-Approved PI for ADDYI: 8/2015

## “Other” Specific Population Example (2)\*

### 8.7 Smokers

Smoking causes induction of CYP1A2 levels. The exposure of tasimelteon in smokers was lower than in non-smokers and therefore the efficacy of HETLIOZ may be reduced in smokers [*see Clinical Pharmacology (12.3)*] .

\*Derived from FDA-Approved PI for HETLIOZ: 12/2014



# “Other” Specific Population Example (3)\*

- No adequate and well-controlled studies in adults
- Safety and efficacy was extrapolated to adults

## 1 INDICATIONS AND USAGE

VERMOX CHEWABLE is indicated for the treatment of patients one year of age and older with gastrointestinal infections caused by *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm).

## 8 USE IN SPECIFIC POPULATIONS

### 8.6 Adult Use

The safety and effectiveness of VERMOX CHEWABLE have been established in adults for the treatment of gastrointestinal infections by *T. trichiura* and *A. lumbricoides*. Use of VERMOX CHEWABLE in adults for these indications is supported by evidence from an adequate and well-controlled trial in pediatric patients ages 1 to 16 years [see *Clinical Studies* (14.1)], safety data in adults [see *Adverse Reactions* (6.1)], pharmacokinetic data in adults [see *Clinical Pharmacology* (12.3)]

\*Derived from FDA-approved PI for VERMOX CHEWABLE 500 mg tablets (slightly modified for presentation purposes) (6/13/2017)

# Patient Experience Data



**Efficacy**

**Safety**

**Other?**

# RITUXAN HYCELA:

## Patient Experience Data\*

### 14.4 Patient Experience

Previously untreated adult patients outside of the United States with CD20+ diffuse large B-cell lymphoma (DLBCL) or CD20+ follicular non-Hodgkin's lymphoma (FL) Grades 1, 2, or 3a were randomized to receive a standard chemotherapy regimen (CHOP, CVP, or bendamustine) and either RITUXAN HYCELA 1,400mg/23,400 Units at Cycles 2–4 (after the first cycle with intravenous rituximab) or a rituximab product by intravenous infusion at Cycles 1–4. After the fourth cycle, patients were crossed over to the alternative route of administration for the remaining 4 cycles. After Cycle 8, 477 of 620 patients (77%) reported preferring subcutaneous administration of RITUXAN HYCELA over intravenous rituximab and the most common reason was that administration required less time in the clinic. After Cycle 8, 66 of 620 patients (11%) preferred rituximab intravenous administration and the most common reason was that it felt more comfortable during administration. Forty eight of 620 patients (7.7%) had no preference for the route of administration. Twenty nine subjects of 620 (4.7%) received Cycle 8 but did not complete the preference questionnaire.

\*Derived from FDA-Approved Rituxan Hycela PI: 6/2017

# PATIENT COUNSELING INFORMATION

## Section

- Only in very rare instances will an entirely new concept be included in this section that does not have a related discussion elsewhere in labeling<sup>1</sup>
- Following are rare examples of when including a concept in PATIENT COUNSELING INFORMATION section without a related discussion elsewhere in PI could be considered. Statements direct healthcare providers to:
  - Inform patients about reversible discoloration of urine for drugs used to treat a serious disease
  - Advise patients to follow sharps disposal recommendations for self-administered injectable drugs for which disposal instructions are included in patient labeling
  - Advise patients about unintentional drug exposure to pets

# Summary



- PLR is the backbone (both format and content) for communicating prescription drug labeling information
- Although FDA will continue to publish guidance concerning specific labeling recommendations, when needed, there will always be new labeling questions that arise as medicine/drug development evolves



# Final Thoughts...

As we continue to identify labeling issues that require novel/adaptive approaches, consider:

- **Target Product Profile\*** to capture ultimate labeling goal
- **Early and frequent input from FDA**, especially when considering novel labeling approaches (i.e., approaches that are not captured in published guidance)
  - Throughout drug development
  - When finalizing draft labeling to submit to FDA (e.g., pre-NDA/BLA meetings) to allow sufficient time for focused early labeling discussions
- **Share experiences** in a precompetitive forum (e.g., Labeling Conferences)

