



# Considerations for Best Labeling Practices

***Melissa Beaman  
Director, Global Regulatory Affairs  
Labeling, GlaxoSmithKline***

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## ***Disclaimer***

***The views and opinions expressed in the following PowerPoint and accompanying oral presentation should not be construed as official or unofficial FDA position.***

# Agenda

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- Background
- Best Labeling Practices
- Editing Issues
- Summary



# Background

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- GSK interacts with many FDA review Divisions and reviewers (CDER and CBER)
- All Labeling Teams (GSK & FDA) have style preferences
- GSK has developed standards/ best labeling practices



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## **“Best Labeling Practices”**

**For purposes of this presentation, “Best Labeling Practices” are standards/guiding principles GSK has adopted. These may be based on regulations, guidances, feedback from FDA review of labeling, and/or internal preferences or procedures.**

# Best Labeling Practices

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- Prescribing Information Version/Dating
- Patient Information Version/Dating
- Cross References
- Avoid Being Too Specific
- Recent Major Changes
- Highlights
- Full Prescribing Information
- Other General Tips



# Prescribing Information Version/Dating



- Date on PI for CBE submission is date of submission
- When CBE submission is approved
  - If there are *no edits to the submitted CBE content*
    - Date remains *date of submission*
  - If edits to CBE content have been made
    - Change date to *date of FDA approval*



# Patient Information Version/Dating

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- Considered separate documents from Prescribing Information (PI)
- Therefore should have separate dates/versioning
- Format: “Revised: May 2017” or “Revised 5/2017”
- Update revision date (month/year)
  - at end of FDA-approved “Patient Package Inserts” and/or FDA-approved “Instructions for Use” only when content changes





# Cross References

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- Cross referencing is encouraged (and may be required)
- Reduces the need to repeat detailed information
- Cross references are particularly helpful in Section 17 Patient Counseling Information
- Only use cross reference if additional information is provided



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# Cross References (cont.)



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## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

### Immunizations

Inform patients that they should not receive live vaccines while taking TRADENAME. Response to vaccinations could be impaired by TRADENAME *[see Warnings and Precautions (5.7)]*.

### 5.7 Immunization

Live vaccines should not be given for 30 days before or concurrently with TRADENAME as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving TRADENAME or the effect of TRADENAME on new immunizations. Because of its mechanism of action, TRADENAME may interfere with the response to immunizations.

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# Avoid Being Too Specific



- Avoid specifying number of cases when discussing post-marketing adverse reactions or overdose (e.g., REACTION was/has been reported in 2 subjects)



Two cases of JC virus-associated PML resulting in neurological deficits have been reported in patients with SLE receiving immunosuppressants, including TRADENAME.

- State it was/has been reported



Cases of JC virus-associated PML resulting in neurological deficits have been reported in patients with SLE receiving immunosuppressants, including TRADENAME.

- Eliminates need to update labeling if additional cases reported

- In FPI capture all information under a subsection heading
- Recommend not including information between Section 2 and subsection 2.1

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Recommended Dosage in Adults**

- Not applicable when listing clinically significant adverse reactions between Section 6 (ADVERSE REACTIONS) and subsection 6.1 (Clinical Trials Experience)

# Tips to Reduce Highlights Length

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- Summarize information – complete sentences not necessary
- Use active voice. Instead of “Live vaccines should not be given....”, state “Do not give live vaccines....”
- Use tables (multiple dosage regimens, etc.)
- Use bulleted lists
- Ensure margins are ½ inch
- Shorten space between bullets and beginning text
- Avoid repeating Highlights Boxed Warning(s) in Highlights Warnings and Precautions

# Recent Major Changes



- List multiple changes in order they appear in FPI
- List most recent date if more than 1 change in same section/subsection
- If changes to more than 1 subsection in a section, list separately if space permits

If keeping Highlights to less than ½ page is an issue:

- Consider only listing the main section heading, with the date of the most recent change

See next slide

# Recent Major Changes



## ➤ If space in Highlights is an issue

### -----RECENT MAJOR CHANGES-----



Boxed Warning	09/2017
Dosage and Administration, Recommended Dosage (2.2)	09/2017
Dosage and Administration, Dosage Recommendation with Certain Concomitant Medications (2.3)	08/2017
Dosage and Administration, Not Recommended Due to Lack of Dosage Adjustment (2.4)	09/2017
Contraindications (4)	09/2017
Warnings and Precautions, Hypersensitivity Reactions (5.1)	09/2017



### -----RECENT MAJOR CHANGES-----

Boxed Warning	09/2017
Dosage and Administration, Recommended Dosage (2)	09/2017
Contraindications (4)	09/2017
Warnings and Precautions, Hypersensitivity Reactions (5.1)	09/2017

## Other General Tips



- Prescribing Information and FDA-Approved Patient Labeling changes may affect container labeling.  
**Always check!**
- Check website links – are websites still active?
- Check phone numbers - still active and applicable?
- Do numbers in tables agree with numbers in text (if appropriate)?
- Do TOC headings match FPI headings?
- Are section references accurate?
- Checklist may be helpful



# Editing/Format Issues

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Im not obsessed  
i'm an editor!

Handwritten red annotations include:

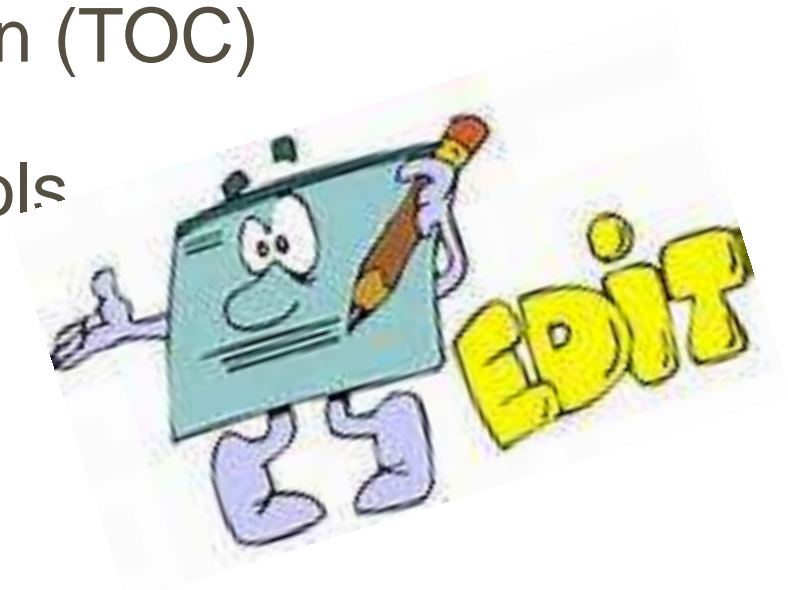
- A circled "wf" above the word "not".
- A circled "cap" to the left of the word "i'm".
- A circled "s" above the word "obsessed".
- A circled "ed" above the word "editor".
- Red arrows pointing to the apostrophe in "Im", the apostrophe in "i'm", and the 'e' in "editor".
- A red arrow pointing to the 's' in "obsessed".
- A red arrow pointing to the 'e' in "editor".

# Editing/Format Issues

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- Product Title in Highlights
- Highlights Boxed Warning
- Font Style for Headings and Subheadings
- Table of Contents section (TOC)
- Use of Signs and Symbols
- Abbreviations



# Product Title in Highlights



- Product title should appear on one line in HIGHLIGHTS



**BENLYSTA (belimumab)  
for injection, for intravenous use**



**BENLYSTA (belimumab) for injection, for intravenous use**

- Use lowercase for dosage form and route of administration



**EPIVIR (lamivudine) Tablets, for oral use  
EPIVIR (lamivudine) Oral Solution**



**EPIVIR (lamivudine) tablets, for oral use  
EPIVIR (lamivudine) oral solution**

## Highlights - Boxed Warning § 201.57(a)(4)

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- Center title and “***See full prescribing information for complete boxed warning.***”
- All text within the box must be in bold
- Recommend using bullets
- Concise summary
- Add carriage return in black box in Highlights to add more white space

**Summarize!**



# Highlights - Boxed Warning § 201.57(a)(4) (cont.)



Centered,  
bold text



## **WARNING: SUICIDAL THOUGHTS AND BEHAVIORS**

*See full prescribing information for complete boxed warning.*

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)**

White  
space



Bullets



# Font Style for Headings and Subheadings

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- Font style/placement can be important
- Especially in 6.1 Clinical Trials Experience, 8.1 Pregnancy, and 12.3 Pharmacokinetics
- *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*
- Use title case and underlining **or** *italics* (not both) for subsection headings
  - The key is to be **consistent** throughout the labeling



# Font Style for Headings and Subheading (cont.)

## GSK Standard



Specific Populations

Heading (underlined)  
on line by itself

*Patients with Renal Impairment:* The pharmacokinetic properties of XXX have been determined in healthy adults and in adults with impaired renal function, with and without hemodialysis.

$T_{\max}$  was not significantly affected by renal function. Based on these observations, it is recommended that the dosage of XXX be modified in patients with renal impairment [see *Dosage and Administration (2.4)*].

*Patients with Hepatic Impairment:* The pharmacokinetic properties of XXX in adults with hepatic impairment are shown in Table 6. Subjects were stratified by severity of hepatic impairment.

Pharmacokinetic parameters were not altered by diminishing hepatic impairment. Safety and efficacy of XXX have not been established in the presence of decompensated liver disease [see *Indications and Usage (1)*].

*Pregnant Women:* The pharmacokinetics of XXX in patients with HBV or HIV-1 infection and in healthy volunteers were similar at similar doses. XXX pharmacokinetics were studied in 36

Subheadings (italics)  
Followed by colon and text follows  
on same line

# Table of Contents section (TOC)

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- Two-column format
- Columns evenly spaced
- Columns aligned
  - Align first entry of the second column with the first *entry* of the first column; not with “FULL PRESCRIBING INFORMATION:CONTENTS\*”
  - Columns approximately the same length
  - Section numbers and headings aligned
  - Subsection numbers and subheadings aligned



# Table of Contents section (TOC)



FULL PRESCRIBING INFORMATION: CONTENTS*		Aligned
<b>1 INDICATIONS AND USAGE</b>		
<b>2 DOSAGE AND ADMINISTRATION</b>		
2.1 Intravenous Preparation and Dosing Instructions		
2.2 Subcutaneous Dosing Instructions		
<b>3 DOSAGE FORMS AND STRENGTHS</b>		
<b>4 CONTRAINDICATIONS</b>		
<b>5 WARNINGS AND PRECAUTIONS</b>		
5.1 Mortality		8.2 Lactation
5.2 Serious Infections		8.3 Females and Males of Reproductive Potential
5.3 Hypersensitivity Reactions, including Anaphylaxis		8.4 Pediatric Use
5.4 Infusion Reactions		8.5 Geriatric Use
5.5 Depression		8.6 Renal Impairment
5.6 Malignancy		8.7 Hepatic Impairment
5.7 Immunization		8.8 Racial Groups
5.8 Concomitant Use with Other Biologic Therapies or Intravenous Cyclophosphamide		<b>10 OVERDOSAGE</b>
<b>6 ADVERSE REACTIONS</b>		<b>11 DESCRIPTION</b>
6.1 Clinical Trials Experience with Intravenous Administration		<b>12 CLINICAL PHARMACOLOGY</b>
6.2 Clinical Trials Experience with Subcutaneous Administration		12.1 Mechanism of Action
6.3 Postmarketing Experience		12.2 Pharmacodynamics
6.4 Immunogenicity		12.3 Pharmacokinetics
<b>7 DRUG INTERACTIONS</b>		<b>13 NONCLINICAL TOXICOLOGY</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>		13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
8.1 Pregnancy		<b>14 CLINICAL STUDIES</b>
		14.1 Clinical Trials Experience with Intravenous Administration
		14.2 Clinical Trials Experience with Subcutaneous Administration
		<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
		16.1 Intravenous Infusion
		16.2 Subcutaneous Injection
		<b>17 PATIENT COUNSELING INFORMATION</b>

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

Section numbers aligned

Generally same length

Subsection numbers and headings aligned

# Signs/Symbols in Labeling

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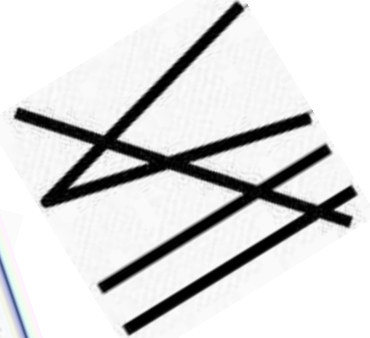
$>$  = Greater than  
 $\geq$  = Greater than or equal to  
 $<$  = Less than  
 $\leq$  = Less than or equal to



$\nabla$

GREATER  $>$

LESS  $<$



# Use of Signs/Symbols in Labeling



- “When should symbols (e.g., /, >, <, ≥, ≤) or spelled-out words be used?”

Which to use?

- Consider if symbols will create potential for errors in:
  - Prescribing the medication
  - Administering the medication
- Especially important in Dosage and Administration



# Use of Signs/Symbols in Labeling (cont.)



- Use of slash (“/”)
  - Consider the intent
  - Ensure it is not confusing
- Commonly used symbols may be preferable in some contexts:
  - Those with minimal risk of medication errors
  - Would replacement of symbols by words make understanding difficult (see examples next slide)



# Use of Signs/Symbols in Labeling (cont.)



“ALT greater than 3 times ULN to less than or equal to ALT 5 times ULN”



“ALT >3 times ULN to ≤5 times ULN”  
(e.g., in a listing of liver enzyme elevations of varying severity in the ADVERSE REACTIONS section; or in a table of dosage modification criteria in the DOSAGE AND ADMINISTRATION section)



“CrCl 30 mL per minute to 50 mL per minute”



“CrCl 30 mL/minute to 50 mL/minute”



“5 mg per kg per day”



“5 mg/kg/day”

- Define in Highlights
- Redefine at first use in Full Prescribing Information section
- Express uncommon routes of administration in full (e.g., intradermal, intrathecal)
- Helpful reference:  
*List of Error-Prone Abbreviations, Symbols, and Dose Designations*, Institute for Safe Medication Practices



## Tips for Industry

- Know and apply Guidances and Regulations
- Keep note of FDA comments
- Apply learnings to other PIs
- Adapt standards to accommodate consistent FDA comments
- Create a checklist
- **Be consistent!**





# References



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Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format

Implementing the PLR Content and Format Requirements (PDF - 527KB)

Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format (PDF - 144KB)

Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements

Guidance for Industry: SPL Standard for Content of Labeling Technical Questions and Answers

Institute for Safe Medicine Practices <http://ismp.org/>



