ENGELBERG CENTER for Health Care Reform at BROOKINGS

April 20, 2012

Discussion Guide

Prescribing Information for Health Care Professionals

Workshop Background

Prescribing information (sometimes referred to as "PI," "package insert," "prescription drug labeling," and "professional labeling") is intended to provide health care professionals with information needed to aid in prescribing prescription drugs and biologics and counsel patients on their safe and effective use. Designed to be informative, accurate, and evidence-based, the prescribing information (PI) is an important tool for health care professionals, and opportunities to ensure the utility of the PI are of interest to the U.S. Food and Drug Administration (FDA).

PI was first standardized by FDA in 1979. In the decade following the introduction of this initial format, the PI became increasingly lengthy and complex, thus making their use burdensome for health care professionals. FDA subsequently began to explore new or improved formats to increase utility. As part of this exploration, opinions were gathered from health care professionals and other stakeholders through forums such as focus groups, public meetings, and national surveys.

These efforts resulted in the proposal of a new rule to govern PI content and format in December 2000. Intended to make the information in the PI more informative and accessible and to promote better risk communication and fewer medication errors, this proposed rule was modified based on public comment. In January 2006, FDA issued a final rule called the "Physician Labeling Rule" (PLR) and outlined a phased implementation schedule for manufacturers to comply with the new standards (Table 1). All new drug applications, biologics license applications, or efficacy supplements approved by FDA after June 30, 2001, are required to be in compliance with the PLR format by June 30, 2013; any such applications approved prior to 2001 are encouraged, though not required, to introduce PLR formatting.

PLR introduced multiple content and format revisions to the previous PI, which are detailed in tables 2 and 3, respectively. These revisions include a *Highlights* section that contains a concise, half-page summary of the important information contained in the Full Prescribing Information (FPI); introduction of a table of contents; the reordering of some information based upon the frequency of use; the regrouping of some information based upon the manner in which it is used; and creation of a *Patient Counseling Information* (PCI) section for health care professionals to use when communicating with patients about important uses and risks of a drug. Illustrative examples of the PI prior to PLR (Appendix 1), the PI in the PLR format (Appendix 2), and PCI sections (Appendix 3 and 4) are included with this discussion guide.

In addition to PLR, FDA published final regulations requiring that the content of labeling be submitted electronically in a form that FDA can process, review, and archive. Structured Product Labeling (SPL), the electronic format adopted by FDA, allows for the posting of up-to-date PIs free of charge on publically available websites such as FDA's online labeling repository and DailyMed (provided by the National Library of Medicine (NLM)). SPL provides a format for the exchange of information necessary for

initiatives associated with including the PI in electronic formats (e.g., electronic medical records and e-prescribing).

Workshop Objectives

Six years have passed since PLR was issued. While FDA is not considering changing the regulations, the Agency is interested in receiving feedback from key stakeholders that either develop or use PI. In addition, because regulatory requirements regarding the PCI section are not detailed, FDA has found that the content and format of this section varies considerably. This workshop, convened by the Engelberg Center for Health Care Reform at Brookings in cooperation with FDA, seeks to engage stakeholders in a discussion of the utility of the PI as a communication tool for health care professionals and to discuss which content in the PCI section is most useful for counseling patients. Comments and recommendations from the meeting will be considered as FDA develops strategies for improving PLR labeling.

Session I: Experience with PIs

This session will focus on experiences from everyday practice to illustrate ways in which the PI is accessed by health care professionals and discuss whether the PLR format, as currently implemented, is meeting health care professionals' needs. Discussion questions may include the following:

- What do recently published reviews of compliance to the PLR format show?
- How is labeling information typically accessed and used by health care professionals (e.g., electronically vs. paper, only used for newly approved products, only used to answer specific questions, etc.)?
- What are the benefits of the PLR format over the old format?
- Is the PI in the PLR format meeting the needs of prescribers and other health care providers?
    - How often do providers refer to the PI to get specific information?
    - When providers refer to the PI, what specific information are they seeking (e.g., dosing information, consult for newly approved drugs, risk information, etc.)?
    - How is the Highlights section currently being used?
    - Is the Highlights section meeting its intended goal of providing a concise summary of the most important prescribing information? Is it too short/too long?

Session II: Opportunities to Encourage Clinicians' Use of PIs

This session will discuss opportunities and strategies for encouraging use of the PI as a primary means of communicating drug information to health care professionals. Discussion questions may include the following:

- Would clinicians prefer to have more or all PIs in the PLR format?
- What sections (or specific information) of the PI could be more helpful or are difficult to use?
- What are some ideas for encouraging use of the PI as a primary resource for prescription drug information for clinicians?

Session III: Experiences with Patient Counseling Information and Opportunities to Encourage its Use

Specifically focusing on the PCI section of the PI, this session will discuss the information that health care professionals find most important in communicating about drugs with patients. Discussion questions may include the following:

- When counseling patients on a newly prescribed drug, what information do prescribers typically discuss and emphasize?
- What level of detail is most helpful to present in the PCI section? For example, which of the following should the PCI accomplish:

- Identify issues to discuss, with cross-references to the fuller discussions elsewhere in the PI?
- Fully present each topic without the need for referencing other parts of the PI?
- Balance the first two options.

- If the drug has FDA-approved patient labeling (e.g., patient package insert, Medication Guide, Instructions for Use), how much information from the patient-directed document should be included in the Patient Counseling Information section (e.g., administration instructions, unique storage/handling requirements)?

Table 1: Implementation Timeline for PI in the PLR Format

Qualifying Date for NDA, BLA, or efficacy supplement*	Date that NDA/BLA applicants must submit proposed labeling in PLR format
Submitted 6/30/06 or after	At the time of submission
Pending on 6/30/06 Approved between 6/30/05 and 6/30/06	By 6/30/09
Approved between 6/30/04 and 6/29/05	By 6/30/10
Approved between 6/30/03 and 6/29/04	By 6/30/11
Approved between 6/30/02 and 6/29/03	By 6/30/12
Approved between 6/30/01 and 6/29/02	By 6/30/13
Approved prior to 6/30/01	Voluntary and encouraged compliance

**The PLR format applies to New Drug Applications (NDAs), Biologics License Applications (BLAs), and efficacy supplements.*

Table 2: Overview of Content Revisions in PLR

Section	Revision Details
Highlights	- Introduces half-page summary of most important prescribing information - Located at the beginning of the PI - References FPI for further information - Includes pharmacological class
Recent Major Changes in *Highlights*	- Summarizes labeling changes made within the previous 12 months to *Indications and Usage*, *Dosage and Administration*, *Boxed Warning*, *Contraindications*, and *Warnings and Precautions* sections - Located in *Highlights* with corresponding notation in margin of FPI
Contents	- Provides standardized order for FPI and orients prescriber - Allows for hyperlinks in electronic formats
Boxed Warning	- Included in *Highlights* (up to 20 lines of text) - Included as full text in FPI
Contraindications	- Includes only known hazards - Includes only patient groups in which risk clearly outweighs potential benefit
Adverse Reactions	- Includes only reactions with some basis for causal relationship to drug - Separates adverse reactions collected during clinical trials from those received from spontaneous reports - Generally pools adverse reactions from all trials - Contains contact information for reporting suspected adverse reactions (*Highlights*)
Patient Counseling Information	- Expands information from previous *Precautions* section - Provides key information for prescribers when communicating with patients - References FDA-approved patient labeling which is appended to end of PI

Table 3: Overview of Format Revisions in PLR

Section or Category	Revision Details
Indications and Usage; *Dosage and Administration*	- Relocated to allow most frequently utilized information to come first in FPI - Includes limitations and conditions of use in *Indications and Usage*
Warnings and Precautions	- Consolidates and reorganizes information from previous *Precautions* and *Warnings* sections into one section
Drug Interactions; *Use in Specific Populations*	- Introduced to reorganize information from previous *Precautions* section into separate sections
Clinical Studies; *Nonclincial Toxicology*	- Required to be included in FPI (formerly optional)
Dosage Forms and Strengths	- Selected information from *How Supplied* section now presented earlier in FPI - Moves *How Supplied* toward the end of FPI
Typeface and presentation	- Sets minimum font size at 8 point - Standardizes bold headers, tables, bullets, and white space

Appendix 1: PI Example prior to introduction of PLR format, Maxalt (rizatriptan benzoate)*
Product example used to demonstrate format only.

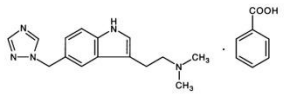
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA 9652502

MAXALT®
(RIZATRIPTAN BENZOATE)
TABLETS
MAXALT-MLT®
(RIZATRIPTAN BENZOATE)
ORALLY DISINTEGRATING TABLETS

DESCRIPTION

MAXALT* contains rizatriptan benzoate, a selective 5-hydroxytryptamine$_{1B/1D}$ (5-HT$_{1B/1D}$) receptor agonist.

Rizatriptan benzoate is described chemically as: *N,N*-dimethyl-5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indole-3-ethanamine monobenzoate and its structural formula is:



Its empirical formula is $C_{15}H_{19}N_5 \cdot C_7H_6O_2$, representing a molecular weight of the free base of 269.4. Rizatriptan benzoate is a white to off-white, crystalline solid that is soluble in water at about 42 mg per mL (expressed as free base) at 25°C.

MAXALT Tablets and MAXALT-MLT* Orally Disintegrating Tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 mg or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate.

Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rizatriptan binds with high affinity to human cloned 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors. Rizatriptan has weak affinity for other 5-HT$_1$ receptor subtypes (5-HT$_{1A}$, 5-HT$_{1E}$, 5-HT$_{1F}$) and the 5-HT$_7$ receptor, but has no significant activity at 5-HT$_2$, 5-HT$_3$, alpha- and beta-adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors.

Current theories on the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of vasoactive and pro-inflammatory peptides from sensory nerve endings in an activated trigeminal system. The therapeutic activity of rizatriptan in migraine can most likely be attributed to agonist effects at 5-HT$_{1B/1D}$ receptors on the extracerebral, intracranial blood vessels that become dilated during a migraine attack and on nerve terminals in the trigeminal system. Activation of these receptors results in cranial vessel constriction, inhibition of neuropeptide release and reduced transmission in trigeminal pain pathways.

Pharmacokinetics

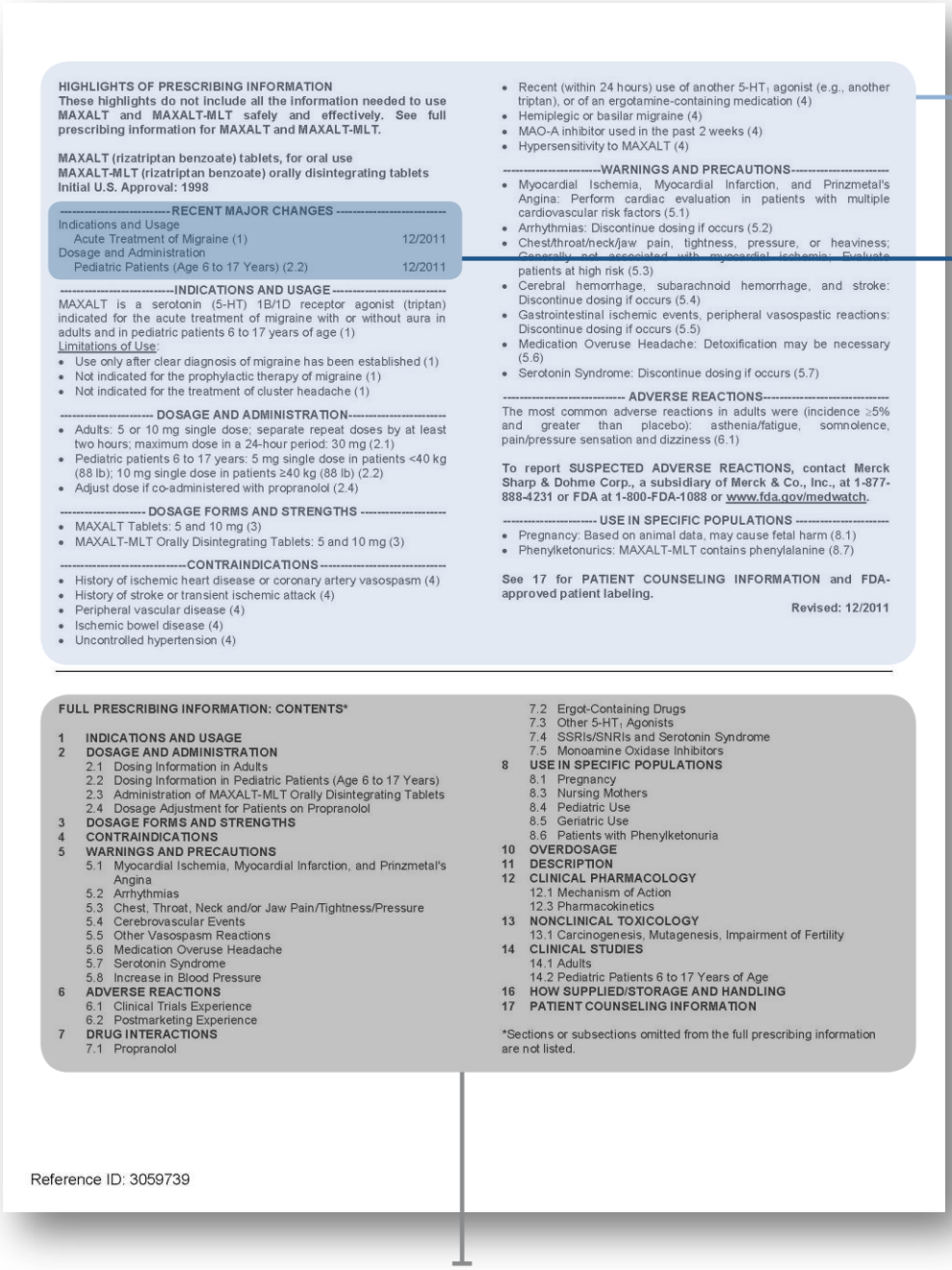
Rizatriptan is completely absorbed following oral administration. The mean oral absolute bioavailability of the MAXALT Tablet is about 45%, and mean peak plasma concentrations (C_{max}) are reached in

* Registered trademark of MERCK & CO., Inc.

1

Appendix 2: PI Example in PLR format, Maxalt (rizatriptan benzoate)

Product example used to demonstrate format only.



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MAXALT and MAXALT-MLT safely and effectively. See full prescribing information for MAXALT and MAXALT-MLT.

MAXALT (rizatriptan benzoate) tablets, for oral use
MAXALT-MLT (rizatriptan benzoate) orally disintegrating tablets
Initial U.S. Approval: 1998

----------RECENT MAJOR CHANGES ----------
Indications and Usage
Acute Treatment of Migraine (1) 12/2011
Dosage and Administration
Pediatric Patients (Age 6 to 17 Years) (2.2) 12/2011

----------INDICATIONS AND USAGE ----------
MAXALT is a serotonin (5-HT) 1B/1D receptor agonist (triptan) indicated for the acute treatment of migraine with or without aura in adults and in pediatric patients 6 to 17 years of age (1)
Limitations of Use:
- Use only after clear diagnosis of migraine has been established (1)
- Not indicated for the prophylactic therapy of migraine (1)
- Not indicated for the treatment of cluster headache (1)

---------- DOSAGE AND ADMINISTRATION----------
- Adults: 5 or 10 mg single dose; separate repeat doses by at least two hours; maximum dose in a 24-hour period: 30 mg (2.1)
- Pediatric patients 6 to 17 years: 5 mg single dose in patients <40 kg (88 lb); 10 mg single dose in patients ≥40 kg (88 lb) (2.2)
- Adjust dose if co-administered with propranolol (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- MAXALT Tablets: 5 and 10 mg (3)
- MAXALT-MLT Orally Disintegrating Tablets: 5 and 10 mg (3)

----------CONTRAINDICATIONS----------
- History of ischemic heart disease or coronary artery vasospasm (4)
- History of stroke or transient ischemic attack (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT$_1$ agonist (e.g., another triptan), or of an ergotamine-containing medication (4)
- Hemiplegic or basilar migraine (4)
- MAO-A inhibitor used in the past 2 weeks (4)
- Hypersensitivity to MAXALT (4)

----------WARNINGS AND PRECAUTIONS----------
- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors (5.1)
- Arrhythmias: Discontinue dosing if occurs (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness; Generally not associated with myocardial ischemia; Evaluate patients at high risk (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue dosing if occurs (5.4)
- Gastrointestinal ischemic events, peripheral vasospastic reactions: Discontinue dosing if occurs (5.5)
- Medication Overuse Headache: Detoxification may be necessary (5.6)
- Serotonin Syndrome: Discontinue dosing if occurs (5.7)

---------- ADVERSE REACTIONS----------
The most common adverse reactions in adults were (incidence ≥5% and greater than placebo): asthenia/fatigue, somnolence, pain/pressure sensation and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------
- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Phenylketonurics: MAXALT-MLT contains phenylalanine (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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

Reference ID: 3059739

Highlights is a half-page summary of the most important prescribing information.

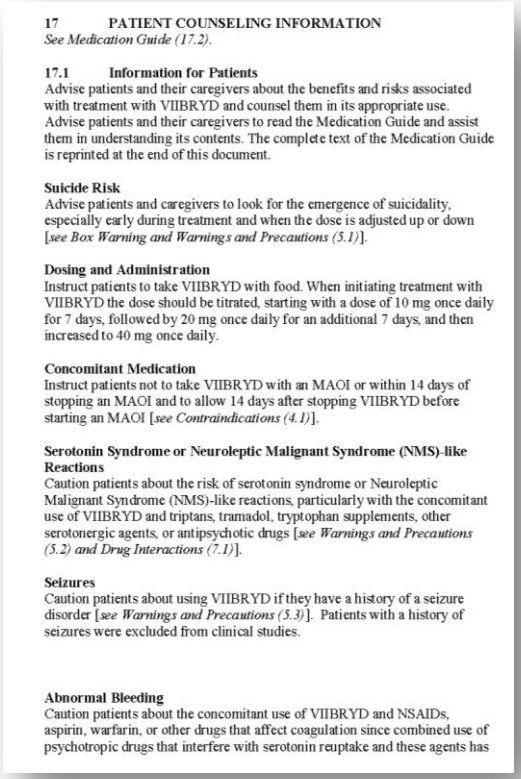
Recent Major Changes within *Highlights* summarizes labeling changes made within the past 12 months to the following sections: *Indications and Usage*, *Dosage and Administration*, *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

Contents creates a standardized order for information in the full prescribing information (FPI) and helps prescribers to quickly locate key subsections. Important changes to the order of FPI include the following:

- *Indications and Usage* and *Dosage and Administration* are relocated to the beginning of FPI.
- *Warnings and Precaution, Drug Interactions,* and *Use in Specific Populations* consolidates and reorganizes information from the previous *Precautions and Warnings* into separate sections.
- *Clinical Studies* and *Nonclincial Toxicology* are now required to be included in FPI.
- *Dosage Forms and Strength* takes selected information from *How Supplied* and presents it earlier in FPI.
- *How Supplied* is moved toward the end of FPI.
- *Patient Counseling Information (PCI)* is introduced to expand information from previous *Precautions* section and to provide key information for prescribers when communicating with patients. PCI references FDA-approved patient labeling.

Appendix 3: PCI Example, Viibryd (vilazodone hydrochloride)

Product example used to demonstrate format only.



17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 Information for Patients

Advise patients and their caregivers about the benefits and risks associated with treatment with VIIBRYD and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk

Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and when the dose is adjusted up or down [*see Box Warning and Warnings and Precautions (5.1)*].

Dosing and Administration

Instruct patients to take VIIBRYD with food. When initiating treatment with VIIBRYD the dose should be titrated, starting with a dose of 10 mg once daily for 7 days, followed by 20 mg once daily for an additional 7 days, and then increased to 40 mg once daily.

Concomitant Medication

Instruct patients not to take VIIBRYD with an MAOI or within 14 days of stopping an MAOI and to allow 14 days after stopping VIIBRYD before starting an MAOI [*see Contraindications (4.1)*].

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

Caution patients about the risk of serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions, particularly with the concomitant use of VIIBRYD and triptans, tramadol, tryptophan supplements, other serotonergic agents, or antipsychotic drugs [*see Warnings and Precautions (5.2) and Drug Interactions (7.1)*].

Seizures

Caution patients about using VIIBRYD if they have a history of a seizure disorder [*see Warnings and Precautions (5.3)*]. Patients with a history of seizures were excluded from clinical studies.

Abnormal Bleeding

Caution patients about the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of abnormal bleeding [*see Warnings and Precautions (5.4)*].

Activation of Mania/Hypomania

Advise patients and their caregivers to observe for signs of activation of mania/hypomania [*see Warnings and Precautions (5.5)*].

Discontinuation of Treatment

Advise patients not to stop taking VIIBRYD without talking first with their healthcare provider. Patients should be aware that discontinuation effects may occur when suddenly stopping VIIBRYD [*see Warnings and Precautions (5.6)*].

Hyponatremia

Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD [*see Warnings and Precautions (5.7)*].

Alcohol

Advise patients to avoid alcohol while taking VIIBRYD [*see Drug Interactions (7.3)*].

Allergic Reactions

Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with VIIBRYD [*see Use in Specific Populations (8.1)*].

Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding an infant and would like to continue or start VIIBRYD [*see Use in Specific Populations (8.3)*].

Interference with Cognitive and Motor Performance

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that VIIBRYD therapy does not adversely affect their ability to engage in such activities.

Appendix 4: PCI Example, Arzerra (ofatumumab)
Product example used to demonstrate format only.

Store ARZERRA refrigerated between 2° to 8°C (36° to 46°F). Do not freeze. Vials should be protected from light.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:

- Signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Bleeding, easy bruising, petechiae, pallor, worsening weakness, or fatigue *[see Warnings and Precautions (5.2)]*
- Signs of infections including fever and cough *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- New neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems *[see Warnings and Precautions (5.3)]*
- Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes *[see Warnings and Precautions (5.4)]*
- New or worsening abdominal pain or nausea *[see Warnings and Precautions (5.5)]*
- Pregnancy or nursing *[see Use in Specific Populations (8.1, 8.3)]*

Advise patients of the need for:

- Periodic monitoring for blood counts *[see Warnings and Precautions (5.2)]*
- Avoiding vaccination with live viral vaccines *[see Warnings and Precautions (5.6)]*

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