
Guidance for Industry and FDA Staff

Dear Health Care Provider Letters: Improving Communication of Important Safety Information

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

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Procedural**

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Dear Health Care Provider Letters: Improving Communication of Important Safety Information

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**U.S. Department of Health and Human Services
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Guidance for Industry and FDA Staff¹

Dear Health Care Provider Letters: Improving Communication of Important Safety Information

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to industry and FDA staff on the content and format of Dear Health Care Provider (DHCP) letters.² DHCP letters are correspondence — often in the form of a mass mailing from the manufacturer or distributor of a human drug or biologic or from FDA — intended to alert physicians and other health care providers about important new or updated information regarding a human drug or biologic (hereafter “drug” and “product” refer to both biologic and small molecule drug products). DHCP letters may also be distributed by email and are often made available on the Internet (e.g., on company Web sites or through patient advocacy groups). This guidance provides recommendations on (1) when to issue a DHCP letter, (2) the types of information to include in a DHCP letter, (3) how to organize that information so that it is communicated effectively to health care providers, and (4) formatting techniques to make the information more accessible.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² The concepts provided in this guidance may be used, in appropriate circumstances, to help develop correspondence to meet certain communication plan requirements for Risk Evaluation and Mitigation Strategies (REMS) under section 505-1(e)(3) of the Federal Food, Drug, and Cosmetic Act.

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II. BACKGROUND

New or updated information about drug products emerges throughout a product's life cycle. For marketed products, there are occasions when it is important to communicate this information promptly to health care providers involved in prescribing or dispensing a drug or in caring for patients who receive a drug. The DHCP letter is one of the mechanisms used to communicate important new information about a marketed product. FDA regulations describe the process for mailing important new information about drug products (21 CFR 200.5), but do not provide instructions on the format and content of the actual letter. Nor do the regulations provide information on electronic or other means of communication.

Formal and informal evaluations of DHCP letters have shown that the communication quality of these letters — the extent to which the information is accessible and can be understood — has varied widely. A 2005 study (the Mazor study) evaluated the quality of a group of DHCP letters sent during 2000 and 2001 that were intended to communicate important new drug safety information.³ The Mazor study found a correlation between the quality or perceived quality of a DHCP letter and the extent to which physicians perceived the new information as important. Letters that were evaluated as clearer, more concise, better organized and formatted and that focused on the most important aspects of the new safety information were considered more effective in communicating the new information.

FDA therefore believes that guidance on the format and content of the DHCP letter would help improve the effectiveness of DHCP letters in communicating drug information. This guidance provides recommendations intended to improve the quality of DHCP letters and enhance the communication of important drug information. These recommendations are based on some of the findings and recommendations from the Mazor study, FDA's own experience in evaluating DHCP letters, and the Agency's general risk communication experience.

III. FDA CONSULTATION ON DEVELOPMENT OF DHCP LETTERS

FDA believes that effective communication of important new information in DHCP letters can best be accomplished if FDA and the manufacturer work together to determine:

- Whether a DHCP letter should be used to convey new information
- How to present the new information in the DHCP letter
- The target audience for the information in the DHCP letter
- The time frame for distributing the DHCP letter

FDA encourages manufacturers to consult with the appropriate review division (e.g., the Offices of Drug Evaluation within the Office of New Drugs, the Office of Generic Drugs) during the development of a DHCP letter to ensure that the letter clearly and accurately reflects both the manufacturer's and FDA's understanding of the issue and the action required. In addition to

³ Mazor KM, Andrade SE, Auger J, Fish L, Gurwitz JH, 2005, "Communicating Safety Information to Physicians: An Examination of Dear Doctor Letters," *Pharmacoepidemiol Drug Saf*, 14 (12):869-875.

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providing a broader range of input into the content of the letter, such consultation could help ensure FDA's concurrence that the content of the letter is not in some way false or misleading.

Discussion with the appropriate FDA review division should also address the intended target audience(s) for the DHCP letter so the letter can be directed more selectively to those health care providers (and their professional societies) who need the information. For example, a DHCP letter describing a product used to treat Alzheimer's disease should be sent to neurologists, psychiatrists, geriatricians, and internists. A DHCP letter describing a recommended action for pharmacists should be directed to pharmacists; a letter describing revised safety information and use instructions for dialysis patients should be distributed to dialysis centers and nephrologists. Further, the means by which the letter will be distributed (e.g., mass mailing, electronic distribution) should be discussed.

The planned time frame for distributing the letter to the target audience should be determined through discussion between the manufacturer and the FDA review division so that the intended audience receives the information promptly, as appropriate to the issue being communicated.

IV. WHEN TO USE A DHCP LETTER AND WHICH TYPE OF DHCP LETTER TO USE

When is a DHCP Letter Needed?

In general, a DHCP letter is used to notify health care providers about important new or updated information about a drug. In most cases, the information relates to an important safety concern that could affect the decision to use a drug or require some change in behavior by health care providers, patients, or caregivers to reduce the potential for harm from a drug. Some DHCP letters are written as part of Risk Evaluation and Mitigation Strategies (REMS) communication programs to inform intended target audiences about the implementation of a new or modified REMS or to present additional required safety information about the product. In some cases, a DHCP letter provides information on how to improve the effectiveness of a drug or information about drug shortage issues. A DHCP letter also may be needed to correct misleading information in advertising or other types of prescription drug promotion.

Three types of DHCP letters are specifically described in FDA regulations (21 CFR 200.5): Important Drug Warning Letters, Important Prescribing Information Letters, and Important Correction of Drug Information Letters. As described in the previous paragraph, DHCP letters relating to other topics (e.g., REMS, drug shortages) may use the concepts and recommendations from this guidance.

A. Important Drug Warning Letters

Important Drug Warning letters are used to convey important new safety information that "concerns a significant hazard to health" (21 CFR 200.5(c)(1)) and therefore could affect the decision to use a drug or require a change in behavior concerning use of the drug (e.g., a specific type of monitoring). This type of DHCP letter is used to convey information that is being incorporated into one or more of the following sections of the prescribing information: **BOXED**

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WARNINGS, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS. Examples of the types of safety concerns that are communicated in Important Drug Warning letters include, but are not limited to, the following:

- Previously unknown serious or life-threatening adverse reactions
- Clinically important new information about a known adverse reaction
- Identification of a subpopulation at greater risk in whom the drug should be used with added caution (e.g., patients with renal or hepatic failure, HIV+ patients)
- Identification of a subpopulation in which the drug is contraindicated
- A drug interaction or medication error that may result in a serious or life-threatening adverse reaction
- Implementation of a new or modified REMS

See Appendix A: Important Drug Warning - Model Letter.

B. Important Prescribing Information Letters

Important Prescribing Information letters (21 CFR 200.5(c)(2)) are used to convey important changes to the prescribing information other than those changes that are described in an Important Drug Warning letter (section IV.A). An Important Prescribing Information letter ordinarily is used to convey important changes to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the prescribing information. The types of information that are communicated in Important Prescribing Information letters include, but are not limited to, the following:

- Change in the INDICATIONS AND USAGE section intended to minimize risk, improve effectiveness, or convey a limitation of the indications
- Change to the dose or dosage regimen intended to minimize risk or improve effectiveness
- Change in the supply of the drug to address a drug shortage issue

A DHCP letter should not be used to merely announce a new indication, even an important one.

If the new information results in the addition of serious risk information to the BOXED WARNINGS, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections of the prescribing information, in addition to changes to the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections, the letter should be elevated to an Important Drug Warning letter.

See Appendix B: Important Prescribing Information - Model Letter.

C. Important Correction of Drug Information Letters

Important Correction of Drug Information letters (21 CFR 200.5(c)(3)) are intended to correct false or misleading information or other misinformation in prescription drug promotional labeling and advertising that is the subject of a Warning Letter or other Agency action. This

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guidance provides recommendations for the format and content of such letters (see, in particular, section V.A.6). However, the circumstances in which FDA would seek to have a manufacturer disseminate corrective information using a DHCP letter are outside the scope of this guidance.

See Appendix C: Important Correction of Drug Information - Model Letter.

V. CONTENT AND FORMAT OF DHCP LETTERS

A. Content Recommendations

In general, FDA believes that a DHCP letter should clearly state the following at or near the beginning of the letter to most effectively communicate new information:

- Purpose of the letter (e.g., to inform prescribers about a specific new drug safety issue)
- Description of the new information
- Existing information that has changed, if any (e.g., information that is no longer valid in light of the new information)
- Action for a health care provider to take in response to the new information, if any

The letter should be clear and concise and contain sufficient detail to meaningfully inform the target audience. We recommend the letter not exceed two pages (or comparable length of electronic content). The letter should avoid discussion of noncritical information that could obscure the more important information and should include the appropriate contact information. (See Appendix A for an example of a letter that reflects these recommendations.) For example, if the letter concerns an adverse reaction, it should provide manufacturer and FDA contact information for reporting new cases of the reaction. Ordinarily, it is not sufficient merely to state that the labeling has changed and to provide the new labeling language. New information should be summarized, highlighted, and presented using language from the new labeling, as appropriate. The recommended content and format for DHCP letters is described below in items 1–8.

These content recommendations apply to DHCP letters distributed electronically to the extent practicable for the type of communication used. For additional recommendations specific to electronic distribution, consult the guidance for industry *Using Electronic Means to Distribute Certain Product Information*.⁴

1. Envelope and Letter Heading

Depending on the nature of the information contained in the DHCP letter, one of the following statements is required to appear on the envelope (corresponding to the three types of DHCP letters described in section IV of this document) (21 CFR 200.5).

- **IMPORTANT DRUG WARNING**

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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- IMPORTANT PRESCRIBING INFORMATION
- IMPORTANT CORRECTION OF DRUG INFORMATION

FDA recommends repeating the heading from the envelope on the letter in a similar format because mail may be opened and separated from its envelope before reaching the intended recipient. The letter heading may use a smaller font than the envelope heading, if necessary. For a DHCP letter distributed electronically, the letter heading should be the statement that would have appeared on the envelope if paper distribution had been used. The electronic distribution guidance referenced in footnote 4 contains recommendations on how to make an electronically distributed DHCP letter distinctive in appearance so that it will be promptly recognized and read. Additionally, if the letter is distributed by email, FDA recommends using the letter heading as the subject line of the email. FDA also recommends including the letter as the body of the email, not as a separate attachment.

2. Addressees (Target Audience)

A DHCP letter should be directed to all health care providers who are likely to prescribe, dispense, or administer the drug, as well as others who need to know the information. The letter should be directed to the full range of health care providers who could prescribe the drug, including nurse practitioners and physician assistants who have prescribing authority. The DHCP letter should also be sent to other health care providers who may need to know the information even if they do not prescribe the drug. For example, the emergency departments or primary care physicians might not routinely prescribe the drug that is the subject of a DHCP letter, but might be providing care for patients with a drug-induced adverse reaction described in the letter. Similarly, a DHCP letter that announces the introduction of a new medication guide should be sent to pharmacists who would be required to distribute the medication guide to their patients.

3. Subject Line

A subject line that includes the drug name (proprietary, followed by established or proper) and a concise description of the issue that is addressed in the body of the letter (e.g., drug safety concern) should immediately follow the letter heading. The subject line also may include characterization of the seriousness of the problem (e.g., serious, life-threatening, or fatal adverse reactions) and the population at risk. Vague terms intended to characterize the incidence of a reaction (e.g., rare, infrequent) should generally be avoided. However, statements regarding a well-defined increase in the magnitude of risk or rate of a reaction (e.g., rate of reaction X is doubled) and the rate observed in controlled trials or epidemiological studies can be appropriate. Consider placing the subject line within a border, text box, or in bold type to further draw attention to the information. See the following examples:

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Subject: Severe, Life-Threatening, and Fatal Cases of Hepatotoxicity Reported with DRUG NAME

Subject: Limitations on Use of DRUG NAME in Patients with Decreased Renal Function Because of Risk of Worsening Renal Function and Increased Mortality

Subject: Threefold Increase in Risk of Macular Edema in Elderly Taking DRUG NAME

4. *Initial Paragraphs:* Important Drug Warning or Important Prescribing Information Letters

In the initial paragraphs of the letter, briefly summarize information essential to a health care provider's understanding of the nature and management of the problem and actions taken to address the issue. This guidance describes a two-paragraph format, but in some cases a single paragraph is adequate to convey the most important information.

Limit the initial paragraphs to the following types of information (to the extent known and relevant to the issue that is the subject of the letter):

(a) First Paragraph: Concise Description of the Issue

- Product name(s) and brief description of the indications and usage (more detail about indications and usage can be included in subsequent paragraphs, if warranted)
- Concise description of the issue that gave rise to the new warning or other change in the prescribing information, including the nature and severity of the issue (e.g., adverse reaction or other potential harm)
- For communicating labeling changes, verbatim language from prescribing information may be included if brief (a few sentences). If the new language is lengthy or the change involves more than one section of labeling, summarize the new information in the letter and direct the reader to the full prescribing information, as appropriate.
- Population(s) at risk (may be a subpopulation of the population for whom the drug is indicated)
- Degree of risk, if known. If there are reliable incidence and/or prevalence data from a controlled trial, observational study, or other source, include that information. If the new information is based on spontaneous reports, the

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number of reports may be included if that number is an important factor in explaining why FDA is taking regulatory action to revise the prescribing information and alert the health care community.

- Whether the risk occurred with indicated or unapproved use of the drug
- Rationale for change in indication, usage or dose
- Availability of a new or modified Medication Guide addressing the issue

(b) Second Paragraph: Actions Required to Address the Issue, If Any

- Recommended action, including but not limited to:
 - Discontinue use
 - Limitations to use (e.g., specific populations, second line therapy)
 - Dose reduction
 - Patient monitoring for specific clinical findings or laboratory results
 - Additional testing required before prescribing
- Patient counseling, including but not limited to, advising patients to:
 - Contact their health care provider if they experience a specific clinical sign or symptom
 - Stop the drug immediately if they experience a specific clinical sign or symptom
 - Consult their health care provider before discontinuing the drug

5. *Interior Paragraphs: Important Drug Warning or Important Prescribing Information Letters*

Use subsequent interior paragraphs, if needed, to provide additional detail that would be helpful in understanding the issue, such as:

- Attributes of affected patient populations or subsets
- Summary of the data or other information that is the basis for a new safety warning (e.g., summary information about a controlled clinical trial, epidemiologic study, or spontaneous adverse event reporting)
- Limitations of the data and other information (e.g., what is known and what is not known)
- Mechanism of the adverse reaction
- Whether the event is common to the drug class
- Additional research undertaken to better understand an adverse reaction
- Further discussion of a drug's indication(s)

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6. Correction of Drug Information Letters

For letters intended to correct information in prescription drug advertising or promotional labeling, the letter should include:

- Purpose of the letter (to correct false or misleading claims or other misinformation)
- Statement that the information was the subject of a Warning Letter or other regulatory action by FDA, if applicable
- Where and how the incorrect information was conveyed to health care providers
- The information that was deemed false or misleading and why it was false or misleading
- Corrected information
- Indication, including limitations to use
- Risk information
- Reference to the full prescribing information (which must be enclosed in the letter) and to the medication guide or other approved patient information, if any.
- Statement that the letter is not intended to be a complete description of the benefits and risks

In addition, the letter should be free of promotional claims and presentations.

7. Final Paragraph

The final paragraph should include the following information, to the extent relevant:

- How to report new cases of the adverse reaction or other safety issue described in the letter
- Company contact information for direct inquiries regarding the safety issue
- FDA contact information

Example:

Health care providers and patients are encouraged to report adverse events in patients taking TRADENAME to SPONSOR at 1-800-xxx-xxxx. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You also may contact our medical information department at 1-800--xxx-xxxx if you have any questions about the information contained in this letter or the safe and effective use of TRADENAME.

Also include reference to the full prescribing information (which must be enclosed in the letter) and to the medication guide or other approved patient information, if any.

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8. *Types of Information That Should Not Be in a DHCP Letter*

Additional detail that could obscure more important information or divert attention from more important information should be omitted. Examples of such information include, but are not limited to:

- Market information about the drug, including numbers of prescriptions, patient exposures, approvals, and pending approvals
- Extensive details about the design of a clinical study
- Information about a safety review panel
- Plans to further investigate the problem, if not specifically related to safety
- Promotional language or claims

B. Format Recommendations

Format the letter in a way that will help make the information in the letter easily accessible to the reader. We recommend using typographic and formatting techniques to maximize readability, including:

- Two-page limit
- Informative paragraph headings
- Vertical lists with bullets or numbering, where appropriate
- Text emphasis techniques to draw attention to major points (e.g., bold font, larger font, italics)
- Minimum 12-point font
- Easily readable font based on the type of media used (e.g., serif or sans serif)
- Use of upper and lowercase letters (i.e., avoid all caps)
- Adequate spacing and leading (i.e., letters should not touch within lines; lines of text should not touch one another)
- Use of white space to delineate paragraphs and organize text⁵

These format recommendations also apply to DHCP letters distributed electronically to the extent practicable for the type of communication used (see footnote 4).

VI. ASSESSMENT OF THE DHCP LETTER IMPACT

Manufacturers should conduct an evaluation, for their own use, of the extent to which the target audience received the DHCP letter and is aware of the information that was communicated in the letter.

If the DHCP letter is part of a REMS, there must be an evaluation plan in place, as specified in the REMS. Additional information on REMS evaluations may be found in the draft guidance for

⁵ See, for example, Chapparro B, Baker JR, Shaikh AD, Hull S, and Brady L, 2004, "Reading Online Text: A Comparison of Four White Space Layouts," *Usability News*, 6(2). Available at <http://psychology.wichita.edu/surl/usabilitynews/62/whitespace.htm>.

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industry *Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications.*⁶

VII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The time required to complete this information collection is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Office of Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, WO Bldg. 51, Silver Spring, MD 20993-0002

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⁶ When final, this guidance will represent the FDA's current thinking on this topic.

Month Year

IMPORTANT DRUG WARNING - MODEL LETTER

Subject: Serious Risks with Use of Tradename (established name) Tablets:

- **Central Nervous System Posttransplant Lymphoproliferative Disorder (PTLD), and**
- **Progressive Multifocal Leukoencephalopathy (PML)**

Dear Health Care Provider:

The purpose of this letter is to inform you of important safety information for Tradename, a selective co-stimulation blocker approved for prophylaxis of organ rejection in adult patients receiving liver transplants.

Serious Risks With Use of Tradename

Risk of Central Nervous System Posttransplant Lymphoproliferative Disorder (PTLD) and Progressive Multifocal Leukoencephalopathy (PML)

- Patients treated with Tradename are at an increased risk for developing PTLD, specifically involving the central nervous system (CNS), which can be fatal.
- Risk factors for PTLD include cytomegalovirus (CMV) infection and T cell depleting therapy.
- In clinical trials with Tradename, three cases of PML were reported in patients receiving Tradename at doses higher than the recommended regimen.

Contraindications (use only if relates to new drug warning)

Tradename is contraindicated in transplant recipients with CMV infection.

Prescriber Action

Counsel patients about the risks and benefits of Tradename, including:

- The potential risks for PTLD and PML
- The need for CMV prophylaxis for at least 6 months after transplantation

Tell your patients to contact their doctor immediately to report any changes in memory, speech, behavior, or vision.

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Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking TRADENAME to SPONSOR at 1-800-xxx-xxxx. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You may also contact our medical information department at 1-800-xxx-xxxx if you have any questions about the information contained in this letter or the safe and effective use of Tradename.

This letter is not intended as a complete description of the benefits and risks related to the use of Tradename. Please refer to the enclosed full prescribing information (and medication guide, *if there is a medication guide for this product*, or any other approved patient information).

Sincerely,

Company Representative

Enclosure(s): Tradename Full Prescribing Information

Month Year

IMPORTANT PRESCRIBING INFORMATION - MODEL LETTER

Subject: Introducing New Strength for Tradename (established name) for Oral Suspension: Changing the Concentration from 12 mg/mL to 6 mg/mL and Dispenser From mgs to mLs

Dear Health Care Provider:

The purpose of this letter is to introduce a new strength of Tradename for Oral Suspension 6 mg/mL. We have changed the concentration from 12 mg/mL to 6 mg/mL and the dispenser from mgs to mLs to help reduce the potential for prescribing and dosing confusion. The 12 mg/mL concentration is no longer being manufactured. Tradename is indicated in patients 1 year and older for treatment of uncomplicated influenza.

Dosing and Administration

The dosing for Tradename for mL (Oral Suspension) is based on the patient's weight. A 10 mL oral dosing dispenser is provided with the oral suspension. Patients with a weight of 15 kg (33 lbs) or less should receive 5 mL of the oral suspension for each dose. Patients weighing 16 kg thru 23 kg (34 lbs thru 51 lbs) should receive 7.5 mL per dose. Patients weighing 24 kg thru 40 kg (52 lbs thru 88 lbs) should receive 10 mL per dose; and patients weighing 41 kg (89 lbs) or more should receive 12.5 mL for each dose. (This requires administering a 10 mL dose, followed by another 2.5 mL dose.) Frequency for treatment is twice daily for 5 days.

Prescriber Action *(use only if relates to new prescribing information)*

Counsel patients about the risks and benefits of Tradename, including:

- The new dosing requirements to ensure appropriate dosing.
- The potential risks for X
- Patients should stop using the drug immediately if they experience zzz side effect.
- Patients should contact their doctor immediately if they experience abcd side effect.

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking TRADENAME to SPONSOR at 1-800-xxx-xxxx. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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You may also contact our medical information department at 1-800-xxx-xxxx if you have any questions about the information contained in this letter or the safe and effective use of Tradename.

This letter is not intended as a complete description of the benefits and risks related to the use of Tradename. Please refer to the enclosed full prescribing information (and medication guide, *if there is a medication guide for the product*, or any other approved patient information).

For additional information, please call Sponsor at 1-800-xxx-xxxx or visit www.tradename.com.

Sincerely,

Company Representative

Enclosure(s): Tradename Full Prescribing Information

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CORRECTION OF DRUG INFORMATION - MODEL LETTER

Subject: Correction of Information for Tradename (established name) Tablets in response to FDA Warning Letter

Dear Health Care Provider:

You may have seen a Sales Aid for Tradename (established name) Tablets distributed by SPONSOR sales representatives. The U.S. Food and Drug Administration (FDA) issued a Warning Letter to SPONSOR because it determined that the Sales Aid failed to include important risk information regarding Tradename. This letter is being sent to you at the request of the U.S. Food and Drug Administration's (FDA) Office of Prescription Drug Promotion (OPDP).

Important Risk Information Omitted from the Tradename Sales Aid Outlined in the FDA Warning Letter

Risk of Central Nervous System Posttransplant Lymphoproliferative Disorder (PTLD) and Progressive Multifocal Leukoencephalopathy (PML)

- Patients treated with Tradename are at an increased risk for developing PTLT, specifically involving the central nervous system (CNS), which can be fatal.
- Risk factors for PTLT include cytomegalovirus (CMV) infection and T cell depleting therapy.
- In clinical trials with Tradename, three cases of PML were reported in patients receiving Tradename at doses higher than the recommended regimen.

Indication for Tradename

Tradename is indicated for the prophylaxis of organ rejection in adult patients receiving liver transplants.

This letter is not intended as a complete description of the benefits and risks related to the use of Tradename. Please refer to the enclosed full prescribing information (and medication guide, *if there is a Medication Guide for the product*, or any other approved patient information).

Reporting Adverse Events

Health care providers and patients are encouraged to report adverse events in patients taking TRADENAME to SPONSOR at 1-800- xxx-xxxx. You are encouraged to report negative side

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effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

You may also contact our medical information department at 1-800-xxx-xxxx if you have any questions about the information contained in this letter or the safe and effective use of Tradename.

For additional information, please call Sponsor at 1-800-xxx-xxxx or visit www.tradename.com.

Sincerely,

Company Representative

Enclosure(s): Tradename Full Prescribing Information