DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Korie Osborn
Director, Regulatory Affairs
Azurity Pharmaceuticals Inc.
841 Woburn Street
Wilmington, MA 01887

RE: NDA 208400
XATMEP® (methotrexate) oral solution
MA 50

Dear Ms. Osborn:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the healthcare professional email (XTM-27) for XATMEP® (methotrexate) oral solution (Xatmep) submitted by Azurity Pharmaceuticals Inc. (Azurity) under cover of Form FDA 2253. The email makes false or misleading claims and/or representations about the risks and efficacy associated with Xatmep. Thus, the email misbrands Xatmep within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(7)(viii). These violations are especially concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Xatmep, a drug used in a vulnerable pediatric patient population and that bears a Boxed Warning due to the possibility of serious and life-threatening risks.

Background

Below are the indications and summary of the most serious and most common risks associated with the use of Xatmep.[1] According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) (in pertinent part):

> XATMEP is indicated for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen.

Xatmep is associated with a number of serious risks. According to the PI, Xatmep contains a Boxed Warning that describes severe toxic reactions, including embryo-fetal toxicity.

Xatmep is contraindicated in patients who are pregnant with non-malignant diseases or who

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

have severe hypersensitivity to methotrexate. The PI also contains warnings and precautions regarding bone marrow suppression, serious infections, renal toxicity and increased toxicity with renal impairment, gastrointestinal toxicity, hepatic toxicity, pulmonary toxicity, hypersensitivity and dermatologic reactions, secondary malignancies, ineffective immunization and risks associated with live vaccines, effects on reproduction, increased toxicity due to third-space accumulation, soft tissue and bone toxicity with radiation therapy, laboratory tests, and risk of improper dosing. The most common adverse reactions include ulcerative stomatitis, leukopenia, nausea, abdominal distress, and elevated liver function tests.

Prior Communications

OPDP notes that our advisory comments dated June 19, 2017, to Silvergate Pharmaceuticals, Inc. (b) (4) Azurity appears to be promoting Xatmep without presenting the serious risks of the drug in a truthful and non-misleading manner, despite concerns previously expressed by OPDP.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk or benefits. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The email presents numerous benefit claims regarding Xatmep for the treatment of ALL. Although the presentation includes the Boxed Warning for Xatmep, the email completely omits other important warnings and precautions associated with the drug. For example, the email includes the following claim, "2.5mg/mL provides easy dose titration as body surface area-based dosing is recommended." However, the email omits the warning and precaution regarding the risk of improper dosing. According to the Risk of Improper Dosing subsection of the WARNINGS AND PRECAUTIONS section of the Xatmep PI:

> Both the physician and pharmacist should emphasize to the patient that the recommended dose is taken one time weekly, as directed, and that mistaken daily use of the recommended dose has led to fatal toxicity.

In addition, that section warns that a household teaspoon is not an accurate measuring

[2] On May 20, 2020, FDA acknowledged receipt of Azurity Pharmaceuticals, Inc.'s correspondence notifying the FDA that the corporate name had been changed from Silvergate Pharmaceuticals Inc. to Azurity Pharmaceuticals Inc.

device and could lead to overdosage, which can result in serious adverse reactions.

Furthermore, promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. The email prominently presents benefit claims for Xatmep in the body of the email in a bulleted list. In contrast, the limited risk information (i.e., the Boxed Warning) included in the email is presented after the signature block, which typically signals the close or end of a correspondence. As such, the email fails to also present the limited risk information included in the email with a prominence and readability reasonably comparable to the presentation of information relating to the benefits of the drug.

We note that the email includes the statements, "**For Full Prescribing Information of Xatmep, please click here: Full Prescribing Information**" and "**For more information on Xatmep, please click here: Xatmep Website**" (emphasis original). However, this does not mitigate the email's failure to present the Boxed Warning with sufficient prominence or the omission of other risk information from the email. By minimizing the Boxed Warning and omitting the other material information related to the serious risks associated with Xatmep, the email misleadingly suggests that Xatmep is safer than has been demonstrated.

False or Misleading Benefit Presentation

The body of the email presents the following claim for Xatmep:

- I wanted to let you know that Xatmep® (methotrexate) oral solution is available for your patients with Acute Lymphoblastic Leukemia.

This claim is misleading because it fails to adequately communicate the full approved indication for Xatmep. Specifically, the INDICATIONS AND USAGE section of the PI states the following (underlined emphasis added):

> XATMEP is indicated for the treatment of <u>pediatric patients</u> with acute lymphoblastic leukemia (ALL) <u>as part of a multi-phase, combination chemotherapy maintenance regimen</u>.

This claim is particularly concerning because it suggests the drug is approved for use in patients of all ages without consideration for the necessity of other treatments as part of a combination therapy. We acknowledge that the full indication is presented at the bottom of the email, after the signature block (which, as noted above, typically signifies the end of a correspondence), the heading "**Important Safety Information**," and the Boxed Warning (emphasis original). However, this does not mitigate the misleading impression.

Conclusion and Requested Action

For the reasons discussed above, the email misbrands Xatmep within the meaning of the FD&C Act, and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(7)(viii).

OPDP requests that Azurity immediately cease any violations of the FD&C Act. Please submit a written response to this letter on or before December 8, 2020, addressing the concerns described in this letter, listing all promotional materials (with the 2253 submission date) for Xatmep that contain representations described above, and explaining your plan for discontinuing use of such materials. If you believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 50 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter.

The issues discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure that your promotional materials for Xatmep comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Trung-Hieu Brian Tran, PharmD, MBA
Team Leader
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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