DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Bruce C. Cozadd
Chairman and Chief Executive Officer
Jazz Pharmaceuticals
3180 Porter Drive
Palo Alto, CA 94304

RE: NDA #021590
FazaClo® (clozapine, USP) Orally Disintegrating Tablets
MA #66

WARNING LETTER

Dear Mr. Cozadd:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer (DTC) patient brochure (FZCL-10/008) for FazaClo® (clozapine, USP) Orally Disintegrating Tablets (FazaClo) submitted by Azur Pharma, Inc. (Azur),[1] now Jazz Pharmaceuticals (Jazz), under cover of Form FDA 2253. The patient brochure is false or misleading because it omits and minimizes important risk information associated with FazaClo, broadens the approved indication of the drug, presents unsubstantiated superiority claims, and overstates the drug's efficacy. Thus, the patient brochure misbrands FazaClo in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & 321(n). *Cf.* 21CFR 202.1 (e)(5)(i), (iii); (e)(6)(i), (ii); (e)(7)(viii). These violations are concerning from a public health perspective because they suggest that FazaClo is safer and more effective than has been demonstrated.

Background

Below is the indication and summary of the most serious and most common risks associated with the use of FazaClo.[2,3]

Treatment-Resistant Schizophrenia

FazaClo® (clozapine, USP) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure

[1] Azur Pharma, Inc. was acquired by Jazz Pharmaceuticals on January 18, 2012.
[2] 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.
[3] The approved product labeling (PI) for FazaClo referenced in this letter is the most recent version, dated January 9, 2012

associated with its use, FazaClo® (clozapine, USP) should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.

. . .

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

FazaClo® (clozapine, USP) is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death.

. . .

FazaClo is associated with a number of serious risks, many of which are potentially fatal, including Boxed Warnings for agranulocytosis, seizures, myocarditis, other adverse cardiovascular and respiratory effects and increased mortality in elderly patients with dementia-related psychosis. FazaClo is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug; in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of clozapine-induced agranulocytosis or severe granulocytopenia; and in severe central nervous system (CNS) depression or comatose states from any cause. Furthermore, FazaClo should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The PI also contains Warnings regarding eosinophilia; QT interval prolongation; neuroleptic malignant syndrome (NMS); tardive dyskinesia (TD); and hyperglycemia and diabetes mellitus. In addition, the PI includes Precautions regarding, among other things, avoiding extended treatment in patients failing to show an acceptable level of clinical response and periodically re-evaluating the need for continuing treatment in patients exhibiting beneficial clinical responses; cardiomyopathy; fever; pulmonary embolism; phenylketonurics; hepatitis; anticholinergic toxicity associated with the eye, gastrointestinal (GI) system, and prostate; and interference with cognitive and motor performance.

As stated in the PI, FazaClo is associated with the following common adverse reactions (incidence of greater than 5%): CNS complaints, including drowsiness/sedation, dizziness/vertigo, headache, and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth, and visual disturbances; cardiovascular findings, including tachycardia, hypotension, and syncope; GI complaints, including constipation and nausea; and fever.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials.

The patient brochure is misleading because it presents numerous efficacy claims regarding FazaClo, but omits and minimizes important material risks associated with the drug. For example, while the patient brochure discloses some information regarding the Boxed Warning for agranulocytosis on page 8, it fails to include the important material fact that agranulocytosis is a **potentially life-threatening** adverse reaction. The patient brochure also fails to state that patients must have a baseline white blood cell (WBC) count and absolute neutrophil count (ANC) before initiation of treatment, as well as weekly for 4 weeks following discontinuation of FazaClo. In addition, while the patient brochure states that "during the first 6 months . . . your blood will be tested for its white blood cell count every week. The next 6 months you'll be tested just every other week," it fails to include the material fact that, only after acceptable WBC counts and ANCs have been maintained during the first 6 months of treatment, can a patient then be monitored every 2 weeks for the next 6 months.

Furthermore, while the patient brochure includes the statement: "**Please see the enclosed Full Prescribing Information, Including BOXED WARNINGS regarding . . . seizures, dementia-related psychosis in elderly patients, myocarditis and other adverse cardiovascular and respiratory effects**" (emphasis original) on page 8, it fails to include important material facts about each of these significant risks associated with FazaClo. Specifically, the patient brochure fails to include the important information that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk for death, and that FazaClo is not approved for use in these patients. It also fails to include the information that FazaClo should be used with caution in patients with a history of seizures or other predisposing factors and that patients should be advised not to engage in activity where sudden loss of consciousness could cause serious risk to themselves or others. Furthermore, the brochure does not disclose that there is an increased risk of potentially fatal myocarditis in patients treated with clozapine, especially in the first month of treatment, or that orthostatic hypotension, with or without syncope, can occur with clozapine treatment and be accompanied by respiratory and/or cardiac arrest.

The patient brochure also completely omits other important risks associated with FazaClo, including all contraindications; warnings such as QT interval prolongation, neuroleptic malignant syndrome (NMS), tardive dyskinesia (TD), hyperglycemia and diabetes mellitus; and precautions, such as interference with cognitive and motor performance. It also fails to disclose any information regarding common adverse reactions associated with the use of FazaClo.

In addition, the brochure minimizes the risks of FazaClo by failing to present risk information in a manner reasonably comparable with the presentation of claims relating to the

effectiveness of the drug. Specifically, while there are numerous efficacy claims throughout the patient brochure, there is no discussion of risk information until page 8 of the 12-page patient brochure, and it is relegated to a brief, incomplete disclosure under the heading "**Side effects**" (emphasis original).

We acknowledge that page 3 of the patient brochure contains the statement, "**Please see page 8 for important safety information**" (emphasis original), and that page 8 of the patient brochure includes the statement "**Please see the enclosed Full Prescribing Information** . . ." (emphasis in original). However, this does not mitigate the misleading omission and minimization of risk information in this brochure.

By omitting and minimizing information regarding the serious risks associated with FazaClo, the brochure misleadingly suggests that FazaClo is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Page 4 of the patient brochure states:

> FazaClo is a medication prescribed to treat the symptoms of schizophrenia and schizoaffective disorders in patients who have not had good results with other medications. FazaClo also reduces the risk of recurrent suicidal behavior in patients with these disorders.

This claim is misleading because it suggests that FazaClo is indicated for the overall treatment of schizoaffective disorder. However, according to the INDICATIONS AND USAGE section of the PI, FazaClo is only indicated for reducing the risk of recurrent suicidal behavior in patients with schizoaffective disorder, not for overall treatment of the disorder itself. In addition, page 6 of the patient brochure contains a presentation titled, "**What is schizoaffective disorder?**" (emphasis original), that states, "Patients may have crying spells, feelings of hopelessness, fatigue or insomnia, and also may suffer from periods of lack of concentration, unrealistically grand thoughts, or emotional highs." This presentation further contributes to the misleading impression that FazaClo is indicated to treat the symptoms of schizoaffective disorder in general.

The claim on page 4 mentioned above also fails to adequately define the patient population for which FazaClo is approved in the management of treatment-resistant schizophrenia. Specifically, the INDICATIONS AND USAGE section of the PI states that, "FazaClo® (clozapine, USP) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia." (emphasis added)

By suggesting that FazaClo is indicated for the overall treatment of schizoaffective disorder and failing to adequately define the patient population for which FazaClo is approved in the management of treatment-resistant schizophrenia, the patient brochure misleadingly implies that FazaClo is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Page 4 of the patient brochure makes the following claim:

> Researchers say that clozapine, the active ingredient in FazaClo, is the most effective medication for reducing or eliminating symptoms in patients who have not had success with other products.

This claim misleadingly suggests that clozapine is more effective than all other schizophrenia treatments when this has not been demonstrated by substantial evidence or substantial clinical experience. While we acknowledge that clozapine has been demonstrated to be more effective than chlorpromazine and is the only product currently approved to treat severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia, FDA is not aware of adequate, well-controlled studies demonstrating that clozapine is more effective than all other products for treatment-resistant schizophrenia.

In addition, page 7 of the patient brochure makes the claim (emphasis original):

- **"How FazaClo (clozapine, USP) Orally Disintegrating Tablets may help**
  . . .
  - FazaClo generally produces little or none of the restlessness, stiffness, shakiness, or tremor you may have experienced with other medications."

This claim misleadingly suggests that FazaClo is superior to other available treatments for schizophrenia based on its risk profile. FDA is not aware of substantial evidence or substantial clinical evidence to support this claim. As stated in the ADVERSE REACTIONS section of the PI, FazaClo is associated with adverse reactions, such as tremor (6%), restlessness (4%), akathisia (*e.g.*, motor restlessness) (3%), rigidity (3%), hyperkinesia (*e.g.,* involuntary/uncontrolled muscle movement) (1%), and epileptiform movements/myoclonic jerks (*e.g*., involuntary contraction of muscle groups) (1%).

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The patient brochure makes the following claims (emphasis original):

- "FazaClo can be highly effective in relieving distressing symptoms such as agitation, unusual thoughts, hearing voices, . . .lack of motivation, and lack of interest in social activities." (Page 3)

- **"How FazaClo (clozapine, USP) Orally Disintegrating Tablets may help**
  - Over a period of time, symptoms like voices or unusual thoughts usually diminish or disappear." (Page 7)

These claims misleadingly imply that treatment with FazaClo will improve the specific individual symptoms of agitation, unusual thoughts, hearing voices, lack of motivation, and lack of interest in social activities. However, FDA is not aware of substantial evidence or substantial clinical experience to support these claims. The effectiveness of clozapine for treatment-resistant schizophrenia was demonstrated in a clinical trial studying its effect on the Brief Psychiatric Rating Scale (BPRS) total score, the cluster of four key BPRS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought criteria), and the Clinical Global Impression (CGI) scale. Demonstrating an effect on the composite total scores of these scales does not demonstrate an effect on an individual component of these scales. Therefore, the clinical study used to demonstrate efficacy of clozapine is not considered substantial evidence to support claims of efficacy in treating the individual symptoms of schizophrenia listed above.

Page 7 of the patient brochure claims, "You may experience renewed interest in attending school, or holding a job; and you may want to join in more social activities with your family and friends." This claim misleadingly implies that FazaClo will improve a patient's academic, work, or social functioning. The FDA is not aware of substantial evidence or substantial clinical experience to support this claim. As noted above, the effectiveness of clozapine was demonstrated in a clinical trial studying its effect on the BPRS total score, a cluster of four key BPRS items, and the CGI scale. These rating scales do not measure a patient's academic, work, or social functioning, and thus the clinical study used to demonstrate efficacy of clozapine is not considered substantial evidence to support a claim that clozapine improves a patient's academic, work, or social functioning. If you have data to support this claim, please submit them to FDA for review.

In addition, the patient brochure claims:

- "[C]lozapine, the active ingredient in FazaClo, is the most effective medication for reducing <u>or eliminating symptoms</u>. . ." (Page 4, underlined emphasis added)

This claim and the aforementioned claim on page 7 that treatment with FazaClo will cause symptoms to "disappear" are misleading because they suggest that the outcome of treatment with FazaClo is the complete resolution of symptoms in patients with treatment-resistant schizophrenia. In addition, page 3 of the brochure states, "**A new road to recovery**...Your health care professional has just started you or someone you love on a new road to recovery by prescribing FazaClo (clozapine, USP) Orally Disintegrating Tablets" (bolded emphasis original, underlined emphasis added). This statement, in the context of claims that FazaClo will "eliminate" symptoms, or cause them to "disappear," further contributes to the misleading impression that the outcome of treatment with FazaClo is the complete resolution of symptoms in patients with treatment-resistant schizophrenia. However, the improvements in the BPRS total score, cluster of four key BPRS items, and CGI scale seen in patients at the end of the 6-week clinical trial used to demonstrate efficacy of clozapine do not support claims implying elimination of treatment-resistant schizophrenia symptoms or recovery. Furthermore, the clinical trial did not evaluate the long-term effect of clozapine in patients with treatment-resistant schizophrenia to determine if patients experienced improvement with no relapses or tolerability issues that would cause discontinuation of the drug, and that treatment with clozapine had a sustained effect or response for the schizophrenic patient. Therefore, the clinical trial does not constitute substantial evidence to support claims implying elimination or disappearance of symptoms. If you have data to support these claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the patient brochure misbrands FazaClo in violation of the FD&C Act, 21 U.S.C 352(a) & 321(n). *Cf.* 21 CFR (e)(5)(i), (iii); (e)(6)(i), (ii); (e)(7)(viii).

OPDP requests that Jazz immediately cease the dissemination of violative promotional materials for FazaClo such as those described above. Please submit a written response to this letter on or before October 2, 2012 stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for FazaClo that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). 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. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA #66 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

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

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA
Director
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT T DEAN
09/18/2012