DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Maria Anne Rocha
Senior Manager, Regulatory Affairs
Sunovion Pharmaceuticals Inc.
84 Waterford Dr.
Marlborough, MA 01752-7010

RE: NDA # 021912
BROVANA® (arformoterol tartrate) Inhalation Solution
MA # 382

Dear Ms. Rocha:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed patient brochures titled Neb SABA Patient Type [BROV138-12], DPI Patient Type [BROV136-12], MDI Patient Type [BROV137-12], and Add-On Patient Type [BROV139-12], for BROVANA® (arformoterol tartrate) Inhalation Solution (Brovana) submitted by Sunovion Pharmaceuticals Inc. (Sunovion) under cover of Form FDA 2253. The patient brochures are misleading because they overstate the efficacy of Brovana, make unsubstantiated claims, including unsubstantiated superiority claims, and minimize the risks associated with the drug. Thus, the patient brochures misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1 (e)(6)(i), (ii); (e)(7)(viii).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Brovana.[1] According to its FDA-approved product labeling (PI) (emphasis in original):

> BROVANA (arformoterol tartrate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA Inhalation Solution is for use by nebulization only.
>
> **Important Limitations of Use**
> BROVANA Inhalation Solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease[.]

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

> BROVANA Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of BROVANA Inhalation Solution in asthma have not been established.

Brovana is associated with a number of serious risks. The PI contains a Boxed Warning regarding asthma-related death as well as Contraindications in patients with a history of hypersensitivity to arformoterol, racemic formoterol, or to any other components of Brovana and in patients with asthma without the use of a long-term asthma control medication. The PI also contains Warnings and Precautions including deterioration of disease and acute episodes, excessive use of Brovana and use with other Long-Acting $Beta_2$-Agonists (LABA), paradoxical bronchospasm, cardiovascular effects, coexisting conditions, hypokalemia and hyperglycemia, and immediate hypersensitivity reactions.

The most common adverse reactions associated with Brovana during clinical trials were pain, chest pain, back pain, diarrhea, sinusitis, leg cramps, dyspnea, rash, flu syndrome, peripheral edema, and lung disorder.

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.

Pages 1, 3, and 4 of each of the patient brochures contain the tagline (bolded emphasis in original), "**Get back into daily living**," in conjunction with the Brovana trade dress. These claims, along with the headline claim (bolded emphasis in original), "**With the right COPD medicine, you may get back to daily living**[,]" on page 3 of each of the patient brochures, misleadingly overstate the efficacy of Brovana by suggesting that an outcome of treatment with Brovana is the ability for patients to resume their baseline activities of daily living. According to the CLINICAL STUDIES section of the PI, treatment with Brovana demonstrated an approximately 11% change in mean forced expiratory volume in one second (FEV_1) from study baseline FEV_1 at the end of the dosing interval over 12 weeks of treatment compared to placebo. Although Brovana may improve patients' mean FEV_1, we are not aware of substantial evidence or substantial clinical experience demonstrating that the magnitude of the effect the drug has on FEV_1 taken together with any drug-related side effects (e.g., paradoxical bronchospasm, cardiovascular effects, pain, chest pain, back pain, diarrhea, sinusitis, leg cramps, dyspnea, rash, flu syndrome, peripheral edema, and lung disorder), results in an overall positive impact on patients' ability to resume their baseline activities of daily living. If you have data to support these claims, please submit them to FDA for review.

Unsubstantiated Superiority Claims/Unsubstantiated Claims

Promotional materials are misleading if they contain a drug comparison that represents or suggests 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 1 of the patient brochures includes the following headline claims, respectively (bolded emphasis in original):

- "If you have COPD**, Are you using your nebulizer sometimes 4 or more times a day?**" (NEB SABA [nebulizer Short-Acting Beta$_2$-Agonists] Patient Type brochure)

- "If you have COPD**, Do you feel you're just not able to breathe in all your medicine?**" (DPI [dry-powder inhaler] Patient Type brochure)

- "If you have COPD**, Is it hard for you to depress your inhaler and time your breaths to get your medicine out?**" (MDI [metered dose inhaler] Patient Type brochure)

- "If you have COPD**, Do you take your medicine correctly, but still feel like you may need something more?**" (Add-On Type brochure)

Furthermore, page 2 of each of the patient brochures includes the following presentation (bolded emphasis in original):

> "**Do any of the statements below capture how you feel? Check the ones that do.**
>
> - **I use my nebulizer sometimes 4 or more times a day—so it's often easier for me just to stay at home. Sometimes I even need it in the middle of the night**
> - **When I use my inhaler, it just doesn't feel like I'm able to breathe in all of my medicine, or that all the medicine is coming out**
> - **My hands don't move as well anymore, so it's hard for me to use my inhaler. I have trouble timing my hands with my breathing**
> - **I'm taking my medicine, but it feels like I may need something more**
>
> **Bring this with you into the exam room, and ask your doctor if BROVANA®** (arformoterol tartrate) Inhalation Solution **is right for you**."

The totality of these claims and presentations as set forth in each of these brochures, along with the headline claim on page 3 of each of the brochures referenced above ("**With the right COPD medicine, you may get back to daily living"**), suggests that Brovana (the "right" COPD medicine) is clinically superior to other available COPD therapies. Specifically, these claims and presentations suggest that Brovana will be effective for patients who have not had success with other COPD therapies based on Brovana's ability to overcome the potential challenges associated with these therapies, such as their respective dosing regimens (e.g., therapies dosed four or more times a day) or delivery systems (e.g., DPIs or MDIs). We are not aware of any adequate and well-controlled head-to-head studies supporting the implication that Brovana is clinically superior to other COPD therapies. We acknowledge that according to the CLINICAL STUDIES section of the PI, the trials associated with the approval of Brovana did include an active comparator, salmeterol. However, these studies were not designed to measure clinical superiority, and thus do not constitute substantial evidence to

support these claims. If you have data to support these claims, please submit them to FDA for review.

In addition, the claims above regarding the potential difficulty patients may encounter depressing an inhaler to administer therapy (e.g. “My hands don’t move as well anymore, so it’s hard for me to use my inhaler.”) are misleading because they imply that patients with compromised manual dexterity will more easily be able to administer Brovana as compared to other COPD inhaler therapies. We are not aware of any evidence to support these claims. Proper use of Brovana, as described in the Medication Guide, includes lengthy directions for use, which include opening a foil pouch and removing a ready-to-use vial, opening the ready-to-use vial, squeezing the medication out of the ready-to-use vial into the reservoir of a jet nebulizer, connecting the reservoir to either a mouthpiece or face mask, connecting the nebulizer tubing to the compressor, and cleaning the nebulizer after use. Therefore, in the absence of adequate evidence to demonstrate that patients with compromised manual dexterity are more easily able to administer Brovana as compared to other inhaled COPD therapies, the above claims are misleading.

Minimization of Risk Information

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 related to the effectiveness of the drug. Factors impacting prominence and readability include typography, layout, contrast, headlines, paragraphing, white space, and other techniques apt to achieve emphasis. The patient brochures prominently present efficacy claims in large, bolded font size and colorful text and graphics surrounded by a significant amount of white space. In contrast, risk information is presented in small font, surrounded by little white space, and in single-spaced format. The overall effect of this presentation undermines the communication of important risk information, minimizing the risks associated with Brovana, and misleadingly suggests that Brovana is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons described above, the patient brochures misbrand Brovana in violation of the FD&C Act, 21 U.S.C. 352(a). *Cf.* 21 CFR 202.1 (e)(6)(i), (ii); (e)(7)(viii).

OPDP requests that Sunovion immediately cease the dissemination of violative promotional materials for Brovana such as those described above. Please submit a written response to this letter on or before November 7, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Brovana that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

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** or by facsimile at (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 # 382 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 Brovana comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Matthew J. Falter, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Kathleen Klemm, Pharm.D.
Team Leader
Office of Prescription Drug Promotion

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/s/

MATTHEW J FALTER
10/24/2013

KATHLEEN KLEMM
10/24/2013