DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Julie Van Heerden
Director, Global Regulatory Affairs and Safety
Amgen
One Amgen Center Drive
Thousand Oak, CA 91320-1799

RE: NDA 21-688
SENSIPAR® (cinacalcet HCl) Tablets
MACMIS #: 16884

Dear Ms. Van Heerden:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer patient brochure for SENSIPAR® (cinacalcet HCl) tablets (Sensipar) submitted by Amgen Inc. (Amgen) under cover of Form FDA 2253. This piece is false or misleading because it omits and minimizes the risks associated with the use of Sensipar and broadens the indication for Sensipar. Thus, the promotional material misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(e)(3)(i), (e)(5)(iii), & 202.1(e)(6)(i).

Background

According to its FDA-approved product labeling (PI), Sensipar is indicated, among other things, for the treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease (CKD) on dialysis.

Sensipar is associated with a number of serious risks. It is contraindicated in patients with hypersensitivity to any of the components of Sensipar. The PI includes warnings regarding the risk of seizures as well as hypotension and/or worsening heart failure in patients with impaired cardiac function. Specifically, the PI states that serum calcium levels should be closely monitored in patients receiving Sensipar, particularly in patients with a history of a seizure disorder.

The PI includes precautions concerning the risks of hypocalcemia, adynamic bone disease and hepatic insufficiency. Regarding hypocalcemia, Sensipar treatment should not be initiated if serum calcium is less than the lower limit of the normal range (8.4 mg/dL). The PI also states that adynamic bone disease may develop if intact parathyroid hormone (iPTH) levels are suppressed below 100 pg/mL. According to the PI, the recommended target range

for iPTH levels is 150-300 pg/mL in patients treated with Sensipar (citation omitted). If iPTH levels decrease below the recommended target range, the dose of Sensipar and/or vitamin D sterols should be reduced or therapy discontinued. Additionally, patients with moderate and severe hepatic impairment should be monitored throughout treatment with Sensipar. The most frequently reported adverse events in three double-blind placebo-controlled clinical trials in patients taking Sensipar for secondary hyperparathyroidism with CKD on dialysis (Sensipar vs. placebo) were nausea (31% vs. 19%), vomiting (27% vs. 15%), and diarrhea (21% vs. 20%).

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 or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The patient brochure is misleading because it omits and minimizes risks associated with Sensipar treatment, thus implying that Sensipar is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Specifically, the patient brochure entirely omits some of the serious risks associated with Sensipar, including the risk of adynamic bone disease. According to the PI, adynamic bone disease may develop with Sensipar use if iPTH levels are suppressed below 100 pg/mL. The patient brochure also fails to disclose the risk of Sensipar therapy to those patients who have hepatic impairment. According to the PI, "Patients with moderate to severe hepatic impairment should be monitored throughout treatment with Sensipar®."

Additionally, the risk presentations that are included in the brochure on page 9 and the back cover minimize the risks associated with Sensipar. For example, the following presentation appears on page 9 (emphasis in original):

- "**Are there side effects?**
  - **Sensipar®** is well tolerated. The most common side effects are nausea, vomiting, and diarrhea. **Sensipar®** side effects typically last a short time."

The headline "Are there side effects?" in this presentation implies that the text below contains a comprehensive list of the drug's side effects. *Cf*. 21 C.F.R. 202.1(e)(6)(xviii). However, the only "side effects" this section provides are the most common adverse events associated with Sensipar therapy. This presentation minimizes the risks associated with the drug by failing to disclose any of the serious risks associated with the drug or to include any reference to the presence or location of this information elsewhere in the brochure. This presentation also minimizes the severity, frequency, and duration of these adverse events by claiming that Sensipar is "well tolerated" and that side effects "typically last a short time." Regarding severity of nausea and vomiting, a higher percentage of patients in the Sensipar group had their drug dose altered or discontinued because of symptoms of nausea and vomiting compared to the placebo group, and a higher percentage of patients in the Sensipar group had moderate or severe experiences. Regarding frequency of nausea and vomiting, a higher

percentage of patients in the Sensipar group had multiple episodes compared to the placebo group during every four week period between 0 and 52 weeks of treatment. Regarding the duration of side effects, there were a significant number of patients whose nausea and vomiting did not last a "short time," contrary to the suggestion made in the brochure. During clinical trials, the median duration for nausea and vomiting in the Sensipar group were 4 and 3 days, respectively, and the mean duration for nausea and vomiting in the Sensipar group were 22 and 16 days, respectively. The brochure provides no mention of this information.

Furthermore, the patient brochure presents the following claim within the "Important Safety Information" section on the back cover: "While on Sensipar®, your doctor may have to do blood tests." This presentation minimizes the need for **continual** laboratory monitoring of serum calcium, serum phosphorous, and iPTH levels associated with Sensipar therapy. According to the PI, in the PRECAUTIONS section concerning hypocalcemia, "Serum calcium **should** be measured within 1 week after initiation or dose adjustment of Sensipar®**"** (emphasis added). Further, the "Laboratory Tests" section of the PI concerning patients with CKD on dialysis with secondary hyperparathyroidism states, "Serum calcium and serum phosphorus **should** be measured within 1 week and iPTH **should** be measured 1 to 4 weeks after initiation or dose adjustment of Sensipar®. Once the maintenance dose has been established, serum calcium and serum phosphorus **should** be measured approximately monthly, and PTH every 1 to 3 months" (emphasis added). This statement on the back cover ("your doctor **may** have to do blood tests") misleadingly suggests that monitoring may not be necessary for some patients, thereby minimizing the risk of hypocalcemia associated with the drug.

Furthermore, the patient brochure fails to present the serious risk information it does include with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug. Specifically, the patient brochure prominently presents efficacy claims throughout several pages of the brochure with colorful graphics, ample white space, and descriptive headers. In contrast, the warnings and precautions that are disclosed in the brochure are presented in a single paragraph on the back cover of the brochure.

DDMAC notes the statement, "*Please see accompanying Sensipar® package insert for full product information*" (emphasis in original) appears on the back cover of the brochure and that a removable PI is located in its interior pocket. However, this does not mitigate the misleading omission and minimization of risk information in the brochure itself.

Broadening of Indication/Misleading Communication of the Limits of the Indication

The front cover of the patient brochure states: "**For patients on dialysis** Help your lab values **move in the right direction with Sensipar®."** (emphasis in original). This presentation is false or misleading because it fails to communicate the drug's full approved indication, including material limitations, and thereby broadens the indication of Sensipar. Specifically, Sensipar is not indicated for all patients on dialysis, but only for patients on dialysis who require treatment for secondary hyperparathyroidism with CKD. We note the

inclusion of the full indication on the back cover of the patient brochure. However, this presentation on the last page of the twelve-page patient brochure is not sufficient to mitigate the misleading impression created by this initial presentation that Sensipar is useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the patient brochure misbrands Sensipar in violation of the Act, 21 U.S.C. 352(a) and 321(n). *Cf*. 21 CFR 202.1(e)(3)(i), (e)(5)(iii), & 202.1(e)(6)(i).

DDMAC requests that Amgen immediately cease the dissemination of the violative promotional material for Sensipar. Please submit a written response to this letter on or before November 10, 2008, stating whether you intend to comply with this request, listing all violative promotional materials the same as or similar to those described above, and explaining your plan for discontinuing use of such materials.

Please direct your response to the undersigned at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD, facsimile at (301) 847-8444. In all future correspondence regarding this matter, please refer to MACMIS #16884 in addition to the NDA number. We remind you that only written communications are considered official. If you choose to revise your promotional materials, DDMAC is willing to assist you with your revised materials by commenting on your revisions before you use them in promotion. The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Sensipar comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Michael Sauers
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Michael A Sauers

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