DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Mr. Michael D. Becker
President and Chief Executive Officer
Cytogen Corporation
650 College Road East
Suite 3100
Princeton, NJ 08540

Re: NDA# 20-570
Quadramet® (Samarium SM 153 Lexidronam) Injection
MACMIS# 13449

WARNING LETTER

Dear Mr. Becker:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a direct-to-consumer (DTC) broadcast radio advertisement (ad) (Q-0119-05), patient testimonial video (Q-0095-05), and website (www.quadrametus.com) for Quadramet (Samarium SM 153 Lexidronam) Injection submitted by Cytogen Corporation (Cytogen) under cover of Form FDA 2253. These promotional pieces overstate the effectiveness of Quadramet and fail to reveal and minimize important risk information associated with the use of Quadramet. Therefore, the promotional pieces misbrand Quadramet within the meaning of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) & (n); 321(n), and FDA implementing regulations. See 21 CFR 202.1(e). These violations are extremely concerning from a public health perspective because they overpromise the benefits and minimize the risks of Quadramet to a very sick and vulnerable population.

DDMAC has previously objected, in an untitled letter dated November 9, 2001, to your dissemination of Quadramet promotional material that made unsubstantiated efficacy claims. We are very concerned that you are continuing to promote Quadramet in a violative manner.

Background

The Indications section of the approved product labeling (PI) for Quadramet states:

> **"Quadramet is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan."**

Quadramet is associated with several important warnings and precautions. For example, the PI for Quadramet contains the following important risk information:

> **WARNINGS:** QUADRAMET causes bone marrow suppression. In clinical trials, white blood cell counts and platelet counts decreased to a nadir of approximately 40% to 50% of baseline in 123 (95%) of patients within 3 to 5 weeks after QUADRAMET, and tended to return to pretreatment levels by 8 weeks…Because of the unknown potential for additive effects on bone marrow, QUADRAMET should not be given concurrently with chemotherapy or external beam radiation therapy unless the clinical benefits outweigh the risks…Blood counts should be monitored weekly for at least 8 weeks, or until recovery of adequate bone marrow function.

Furthermore, the Information for Patients section of the PI contains special instructions for patients receiving Quadramet therapy:

> **Information for Patients** Patients who receive QUADRAMET® should be advised that for several hours following administration, radioactivity will be present in excreted urine. To help protect themselves and others in their environment, precautions need to be taken for 12 hours following administration. Whenever possible, a toilet should be used, rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely and patients should wash their hands thoroughly. If blood or urine gets onto clothing, the clothing should be washed separately, or stored for 1-2 weeks to allow for decay of the Sm-153.
>
> Patients who respond to QUADRAMET® might begin to notice the onset of pain relief one week after QUADRAMET®. Maximal pain relief generally occurs at 3-4 weeks after injection of QUADRAMET®. Patients who experience a reduction in pain may be encouraged to decrease their use of opioid analgesics.

Additionally, the clinical trials section indicates that Quadramet was evaluated in two randomized, blinded, placebo controlled clinical trials. Patients in Study A had a significant decrease in pain from baseline at weeks 3 and 4 while patients in study B had a significant decrease at weeks 2, 3, and 4. Pain did not approach zero in either study. Additionally, in study A the weekly opioid analgesic use generally increased from baseline in both the Quadramet and placebo treatment groups; the difference between the groups was not statistically significant. In study B, in which patients were encouraged to adjust their pain medication as needed, there was a statistically significant difference between the Quadramet and placebo groups at weeks 3 and 4 in weekly opioid analgesic use; the placebo treated patients increased their use of opioid analgesics, while the Quadramet treated patients decreased their use.

Overstatement of Efficacy

Your promotional pieces imply that Quadramet is more effective in treating cancer pain and more beneficial to patients receiving the drug than has been demonstrated by substantial evidence or substantial clinical experience.

For example, the patient video makes statements that suggest that Quadramet is a cancer therapy that can provide a therapeutic benefit other than pain relief. Specifically, the video includes the following statement: "Quadramet doesn't make you lose your hair, it targets the cancer and that is what is so great about it. It knows where to go. I think it's amazing." These statements, both explicitly and

through implied comparison to cancer therapy (i.e. "it doesn't make you lose your hair"), misleadingly suggest that Quadramet is a cancer therapy that can provide a therapeutic benefit other than pain relief. This misimpression is reinforced by such statements on the website as "Now I have time to enjoy life" which can be construed to mean that patients on Quadramet can be expected to live longer.

In addition, the patient video and website misleadingly imply that patients receive immediate pain relief from Quadramet, overstate the extent of the pain relief from Quadramet, and misleadingly imply that patients will not need to use other analgesics (such as narcotics) after treatment with Quadramet. For example, the patient testimonial video, which presents the experiences of one patient, a woman with breast cancer who used Quadramet, and her son, contains statements such as the following:

> "When cancer spreads to the bones, it's not unusual for patients to experience pain so severe that they can barely function. That's why there's Quadramet. It's a different kind of medication specially made for bone pain from cancer. Quadramet travels to sites of bone reformation due to metastatic bone cancer to provide relief with a single injection."
>
> "[My mother] took morphine for the pain…. And it would make her drowsy and she was out of it, and it was so sad to see her in that state of mind because that is not like her at all – that's not her personality...After the Quadramet shot started to take effect, she was back to her old self, she wasn't drowsy."
>
> "Our friend that recommended it was so passionate about it. He said there is this terrific stuff out – it's called Quadramet…And the more the word gets out about something that is beneficial to people's lives, it is going to help the community and help everyone."
>
> "It helped me so tremendously."

Similarly, the Quadramet website homepage and FAQs page make numerous efficacy claims for Quadramet, including such claims as: "Quadramet targets the sites of bone pain and can provide long-lasting relief" and that "a single Quadramet treatment takes just one minute and can provide pain relief for an average of 16 weeks in responding patients."

These claims, both in the patient video and in the website, imply that patients receive more pain relief from Quadramet than is demonstrated by substantial evidence or substantial clinical experience. According to the PI, the results in the Clinical Trials section show that pain scores from patients using Quadramet did not approach zero (no or low pain). Rather, Table 3 indicates that patients started with a pre-treatment pain score of around 4 on a 10 point scale, and for patients treated with Quadramet the score decreased to around 2.7 or 2.8 by week 4. Furthermore, both the video and website also imply that after treatment with Quadramet, patients will not need to use narcotics or other analgesics. In fact, the data from the Clinical Trials section of the PI indicate that in one of the two studies of the drug (Study A), the weekly analgesic use generally **increased** from baseline in both the Quadramet and placebo treatment groups. Only in Study B was there a statistically significant difference in change from baseline analgesic use in comparison to placebo, and while use decreased, this study did not demonstrate that patients stop using narcotics after treatment with Quadramet.

Both the patient video and website also fail to reveal that patients who respond to treatment with Quadramet will not begin to notice the onset of pain relief until at least a week after injection. Rather, these promotional pieces imply that Quadramet gives immediate relief through claims like "relief with

a single injection" and "treatment takes just one minute and can provide pain relief for an average of 16 weeks in responding patients."

In addition to suggesting that Quadramet is more effective at treating pain than has been shown, the patient video and website are also misleading because they make claims regarding the ability to resume normal daily activities without data to support such claims.

The patient video contains numerous claims regarding resumption of normal daily activities with Quadramet, such as the following (emphasis added):

> After the Quadramet shot started to take effect, **she was back to her old self**, she wasn't drowsy. **She was ambitious and walking around. She was able to live her regular – do her daily things**. And I am surprised she didn't sit here and cook a big meal for you guys.

Similarly, the website homepage contains claims that suggest Quadramet allows patients to return to daily activity, such as: "Now I have time to enjoy life" and "When pain is predominant, quality of life is often diminished…Quadramet can give you around-the-clock pain relief for up to 16 weeks without the known side effects of opioids."

These claims misleadingly imply that patients will be able to resume their normal daily activities as a result of using Quadramet. FDA is not aware of substantial evidence or substantial clinical experience to support these claims. As discussed above, Quadramet has been shown to aid in the reduction of pain, but does not eliminate pain nor does it eliminate the need for concomitant narcotic therapy. Moreover, the patients for whom Quadramet is indicated are suffering from a serious (and eventually fatal) underlying disease that Quadramet does not treat (metastatic bone lesions), which may in ways other than through bone pain prevent them from engaging in normal daily activities. Furthermore, the implication from the FAQs section of the website that Quadramet will help a patient perform "all normal life activities--driving, going to work, dining out--just as before," without the "side effects of opioids" is misleading because patients on Quadramet, as is shown in the PI, still use other analgesics for pain relief, including narcotics, which have side effects such as drowsiness and nausea, and can have additional serious side effects, such as radioactive urine, not seen with opioids.

Thus, the patient video and website misleadingly suggest that Quadramet is more effective than has been demonstrated at treating bone pain from cancer, more beneficial to patients receiving the drug than has been demonstrated, and also misleadingly suggest that Quadramet will allow patients to resume normal daily activities in the absence of substantial evidence or substantial clinical experience.

Omission and Minimization of Risk

The radio ad, patient video, and Quadramet website misleadingly omit and minimize the risks associated with Quadramet treatment.

The prescription drug advertising regulations provide that a broadcast ad must "include information relating to the major side effects and contraindications of the advertised drugs in the audio or audio and visual parts of the presentation (the "major statement"), and unless adequate provision is made for dissemination of the approved…labeling in connection with the broadcast presentation shall contain a

brief summary of all necessary information related to side effects and contraindications." 21 CFR 202.1(e)(1).

The radio ad contains **no** disclosure of risk information specific to Quadramet. The only statement related to risk indicates that, "Like all medicines, there are side effects and risks associated with Quadramet," but fails to describe any of these side effects and risks. Thus, the radio ad does not include a "major statement" of risk information, and contain a brief summary or make adequate provision for dissemination of the PI in connection with the ad.

Similarly, the patient video fails to convey any risks specific to Quadramet during the testimonial portion of the video. Like the radio ad, the beginning of the video contains a voice-over indicating that, "Like all medicines, there are side effects and risks associated with Quadramet." The only specific risk information presented is relegated to the end of the video and is presented in a telescript, where it is unlikely to draw the viewer's attention. The scrolled telescript states in a voice-over:

> In clinical studies, Quadramet has provided pain relief for 62-72% of patients with bone pain from cancer. Quadramet causes a decrease in bone marrow production of certain types of blood cells, which tends to return to pretreatment levels within 8 weeks. If you are receiving other treatments that affect your ability to make these cells, your physician will determine if the clinical benefits of receiving Quadramet outweigh the risks.

This disclosure of risk information completely omits several important risks associated with Quadramet – including the important precautions associated with the administration of this radioactive drug, and common adverse effects – and also minimizes the one risk it does present. Specifically, the risk of bone marrow suppression is minimized because it fails to convey the magnitude of this risk, which can be life-threatening. The presentation of this information also lacks comparable prominence to the numerous benefit claims contained in the testimonial portion of the video, as this information is not presented until the end of the video and is framed by a benefit claim that may make it less likely that the viewer will pay attention to the important risk information that follows.

Finally, the website also omits and minimizes the risks associated with Quadramet. The only risk included on most of the pages on the website is the warning regarding bone marrow suppression. Like the disclosure in the patient video, this fails to convey the magnitude of the risk.

The FAQ webpage includes some discussion of risk within the main part of the page, but this discussion misleadingly minimizes the risks associated with Quadramet. For example, the FAQ page contains the following presentation in response to the question "What are the side effects of Quadramet?":

> Compared to opioids, Quadramet has relatively few side effects. Quadramet causes a temporary decrease in the number of white cells, but blood counts tend to recover to pre-treatment levels within 8 weeks on average. Quadramet does not cause the drowsiness, constipation, nausea, addiction, or other known side effects of opioids.

We are not aware of any head-to-head clinical studies that compare the number of side effects of opioids to those of Quadramet. Therefore the statement "Compared to opioids, Quadramet has

relatively few side effects" is not substantiated. Furthermore, this statement minimizes the potentially life-threatening risks of Quadramet by implying it is safer than opioids. The characterization of the serious risk of bone marrow suppression as "a temporary decrease in the number of white cells" both falsely presents and severely minimizes this risk, because the risk of bone marrow suppression includes both white blood cells and platelet counts, which can cause life-threatening infections and bleeding. Additionally, this response to the general question about side effects associated with Quadramet omits the other important risks from the PI. The FAQ page also contains the following presentation in response to the question "Do I need to take any precautions after receiving Quadramet?":

> There are a few simple precautions you will need to take in the first 12 hours after receiving a Quadramet injection. Talk to your doctor or read the full prescribing information to learn more about Quadramet safety precautions.

This presentation fails to convey any of the necessary precautions associated with use of Quadramet, which is a radioactive therapy, and further contributes to the minimization of risk.

Thus, all of these promotional materials misleadingly omit and minimize risks associated with Quadramet therapy.

Conclusion and Requested Action

Your promotional pieces overstate the effectiveness of Quadramet and fail to reveal and minimize important risk information associated with the use of Quadramet in violation of 21 U.S.C. §§ 352(a) & (n), 321(n); 21 CFR 202.1(e).

DDMAC requests that Cytogen immediately cease the dissemination of violative promotional materials for Quadramet that contain claims the same as or similar to those described above. Please submit a written response to this letter on or before August 2, 2005, describing your intent to comply with this request, listing all promotional materials for Quadramet that contain claims the same as or similar to those described above, and explaining your plan for discontinuing use of such 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 audiences that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, HFD-42 Room 8B-45, 5600 Fishers Lane, Rockville MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS# 13449 in addition to the NDA number. We remind 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 Quadramet (Samarium 153 Lexidronam) Injection comply with each applicable requirement of the 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}

Thomas W. Abrams, R.Ph., MBA
Director
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/

Thomas Abrams
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