DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

June Bray
Director, Regulatory Affairs
Berlex Laboratories, Inc.
340 Changebridge Road
PO Box 1000
Montville, NJ 07045-1000

RE: **NDA 20-570**
Quadramet (Samarium Sm-153 lexidronam) Injection
MACMIS # 10,389

Dear Ms. Bray:

This letter objects to Berlex Laboratories, Inc.'s (Berlex) dissemination of violative promotional materials for Quadramet. Specifically, as part of its routine monitoring program, the Division of Drug Marketing, Advertising, and Communications (DDMAC), has identified a brochure (01-531-1070) and videotape (01-531-1080) submitted under cover of Form FDA 2253 that are false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow:

Unsubstantiated Claims

Promotional materials are misleading if they claim that a drug is better, more effective, or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence. Your brochure entitled, "Metastatic prostate cancer: treatment with Quadramet," describes a patient with metastatic prostate cancer to the bone. Specifically, your brochure describes that this patient presented with extreme pain, rated 10 on a scale of 10, despite opioid therapy, and became pain free (0 on a scale of 10) after 5 days of treatment with Quadramet. Your brochure also claims that the patient has remained pain free for 16 months since Quadramet therapy. However, the approved product labeling (PI) for Quadramet presents the results of clinical trials that have much different results. Specifically, treatment with Quadramet frequently resulted in increased short-term pain followed by moderate pain relief in some patients. For example, 4 weeks after administration of Quadramet, 41% of patients had some relief from pain, and 14% had marked relief of pain.

You also claim in the brochure that all of the patient's pain medication was stopped 3 days after treatment with Quadramet and that "this patient has not required additional prescription pain medication since receiving Quadramet in December 1999." This claim is not consistent with the PI that states in trial A, morphine equivalent analgesic use increased from baseline with

both Quadramet and placebo. In study B, the placebo treated patients increased their use of opioid analgesics, while the Quadramet treated patients decreased (but did not discontinue) their use of opioid analgesics.

Therefore, your brochure that implies that 5 days after treatment with Quadramet, patients will have 100% pain relief for an extended time as defined as a score of 0 on a scale of 10, without prescription pain medications is misleading. Only a small percent of treated patients would be expected to have the very successful outcome you describe. Your presentation of the information on the back page of the brochure that "patients notice improvement for up to 4 weeks" and that "pain relief usually lasts an average of 16 weeks" fails to correct the overwhelming impression from the presentation of the case study that Quadramet is more effective than has been shown by substantial evidence.

You make similar, unsubstantiated claims in your videotape entitled, "Every Patient's Right—Understanding and managing bone pain." In the videotape, you claim in patient testimonials that one can expect to be pain free without opioid analgesics after administration of Quadramet. As explained above, these patient experiences are not representative of the results seen in the vast majority of patients studied in clinical trials. Therefore, your videotape is misleading because it claims that Quadramet is more effective than has been shown by substantial evidence.

Requested Actions

In order to address these objections, we request that you immediately cease the dissemination of the violative brochure and videotape and all similar promotional materials that contain the same or similar messages.

You should respond in writing to us regarding this issue by November 26, 2001. Your response should include Berlex's intent to comply with the above request, the date that it ceased disseminating these and any other violative promotional materials with the same or similar messages, and a list of the discontinued materials.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. DDMAC reminds Berlex that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 10,389 and NDA 20-570.

Sincerely,

{See appended electronic signature page}

Warren Rumble
Regulatory Review Officer
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/

Warren Rumble
11/9/01 01:28:58 PM

Metastatic prostate cancer:
treatment with Quadramet®

Case provided by Dr. James Welsh, MS, MD, Johns Hopkins University

64-YEAR-OLD AFRICAN-AMERICAN MAN

Primary diagnosis: Prostate cancer, diagnosed 1995.

— Patient's PSA 12.3 at diagnosis

Secondary diagnosis: Metastatic prostate cancer to the bone, diagnosed 1999.

— Intense uptake in sacro-iliac joints, sacrum, and coccyx

— Severe bone pain (10 on a scale of 10 on VAS)

Initial treatment course

— In 1995, radical prostatectomy

— PSA remained elevated (never returned to zero)

— Postoperatively treated with 61.2 Gray external beam radiation

Secondary treatment course

— In 1999, patient's PSA rose to 63.8

— Bone scan revealed multiple metastases to sacrum and 6th and 7th ribs

— Lupron® therapy initiated

DECEMBER 1999 TO PRESENT

On December 15, 1999, patient presented at Johns Hopkins with extreme pain (10 on a scale of 10). Pain was not controlled with MS Contin® 30 mg BID.

Lupron was discontinued and palliative external beam radiation recommended; however, prior radiation posed technical difficulties and more radiation to this area could cause rectal damage.

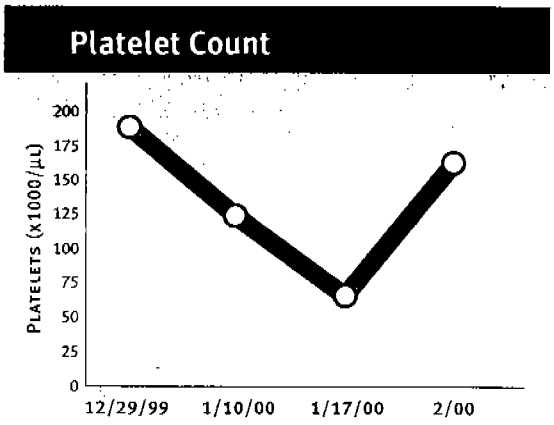
Administration of Quadramet®

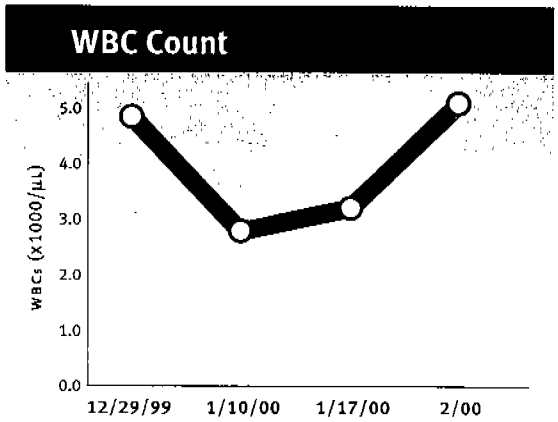
- On December 22, 1999, patient received 92 mCi Quadramet® (based on recommended weight-based dosage of 1.0 mCi/kg)
- On December 23, patient received a single fraction of external beam radiation (600 rads) delivered to sacrum with opposed lateral fields

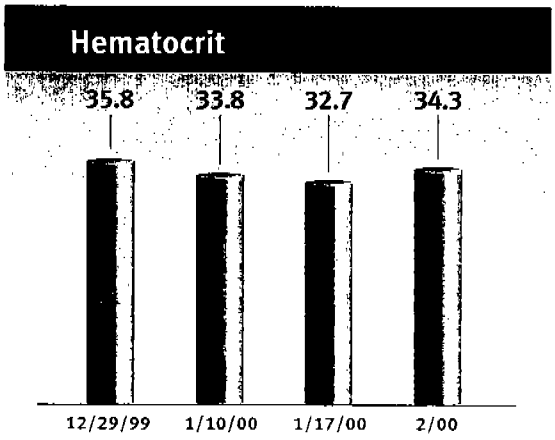
Outcome

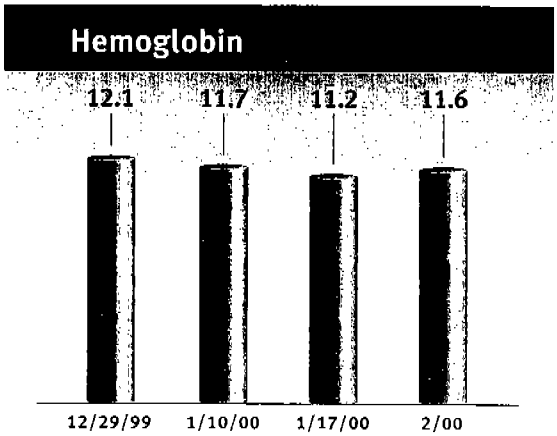
Patient's pain was reevaluated on December 27, 1999 (5 days after treatment).

- Patient reported pain at 0 on a scale of 10
- All pain medications had been stopped by Christmas (3 days after treatment)
- At followup visits in January, March, and November 2000, patient remained free of pain
- Low platelet count was monitored; platelets had rebounded fully by February
- Patient was alive and feeling well as of last follow-up visit in April 2001



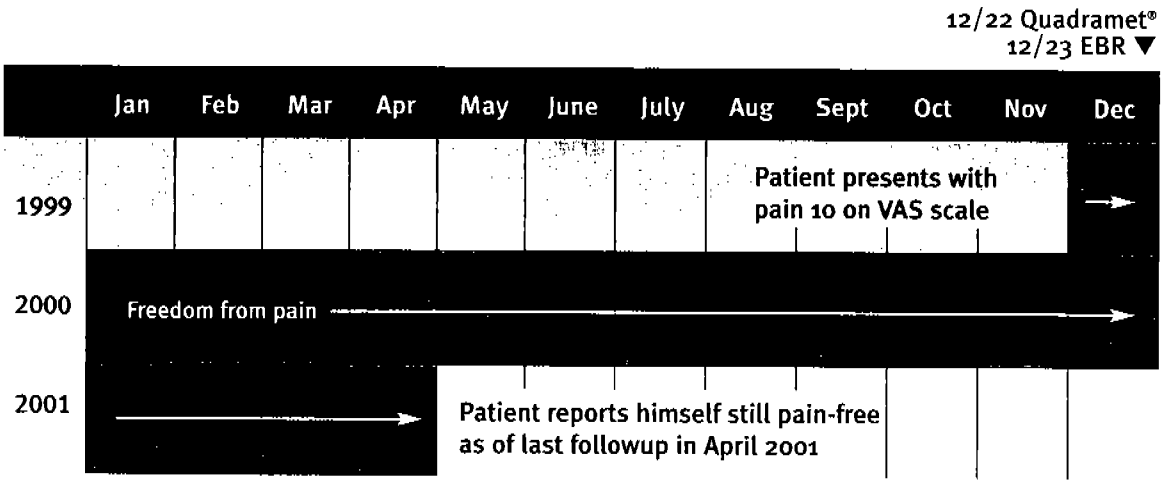






Living pain-free with Quadramet® treatment

This patient has not required additional prescription pain medication since receiving Quadramet® in December 1999. The calendar below clearly illustrates the exceptional positive change in the patient's quality of life.



Treatment options

stay open with Quadramet®

Quadramet® is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan: in other words, in patients with a positive bone scan and pain.

RESPONSE

- Patients who respond may notice onset of pain relief as soon as 1 week after administration[1]
- Quadramet® delivers 75% of the radiation dose in 4 days[2]

RELIEF

- Patients notice improvement for up to 4 weeks, and can reduce and often eliminate use of opioids[1,2]
- Pain relief usually lasts an average of 16 weeks

RECOVERY

- White blood cells and platelets generally reach predictable nadirs at 3–5 weeks[1]
- Blood counts usually return to pretreatment levels within 8 weeks[1]
- Blood counts should be monitored weekly for at least 8 weeks or until recovery of adequate bone marrow function

Quadramet® causes myelosuppression. Prior to administration, clinical benefits should be judged to outweigh the risks in patients having compromised bone marrow reserves or undergoing other therapies that cause myelosuppression.

Please see accompanying full prescribing information.

References
1. Quadramet® prescribing information.
2. Serafini AN, Houston SJ, Resche I, et al. Palliation of pain associated with metastatic bone cancer using samarium-153 lexidronam: a double-blind placebo-controlled clinical trial. *J Clin Oncol.* 1998;16:1574–1581.

AT FIRST SIGHT
QUADRAMET.
(SAMARIUM SM-153 LEXIDRONAM INJECTION)

BERLEX®

01-531-1070 August 2001