Regulation of the Promotion of Prescription Drugs

Thomas Abrams, R.Ph., M.B.A.
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
August 23, 2006

Goal and Objectives

- Goal
  - To protect and promote public health
- Objectives
  - Ensure that RX drug promotion is not false or misleading
  - Ensure that balanced picture of drug is conveyed
  - Get more useful information about drugs and diseases to the American public

Mechanisms for Meeting Objectives

- Comprehensive surveillance and enforcement program
- Voluntary compliance
  - Comments on draft promotion, when requested
  - Educational efforts
  - Guidance documents

Voluntarily Compliance - Advice to Industry

- Provide comments on draft promotional materials (voluntary submissions)
  - Launches
  - Direct-to-consumer (DTC) broadcast ads
  - Other materials
- Educational efforts
  - Outreach
  - Website
- Guidance Documents

Guidances

- Describes FDA's current thinking on a topic
  - Helps to clarify issues that industry/public has questions
- Are not regulations
- Does not create or confer any rights for or on any person and does not operate or bind FDA or the public

Policy Updates

- Direct-to-Consumer Promotion (DTC)
- Risk Information
- Guidance Development

Direct-to-Consumer Promotion

- Increasing interest
- Statements about DTC from various groups
- PhRMA and Industry Actions
- FDA Actions

FDA Actions and DTC

- Research on DTC conducted
- Sept 2003 – Public Meeting held on DTC research
- Feb 2004 – 3 draft guidances issued
- Nov 2004 – DTC Research Final Report
- Nov 2005 – DTC Part 15 Meeting held

Risk Information

- Most common violation cited in DDMAC's letters
- Important to public health
- American public entitled to balanced picture

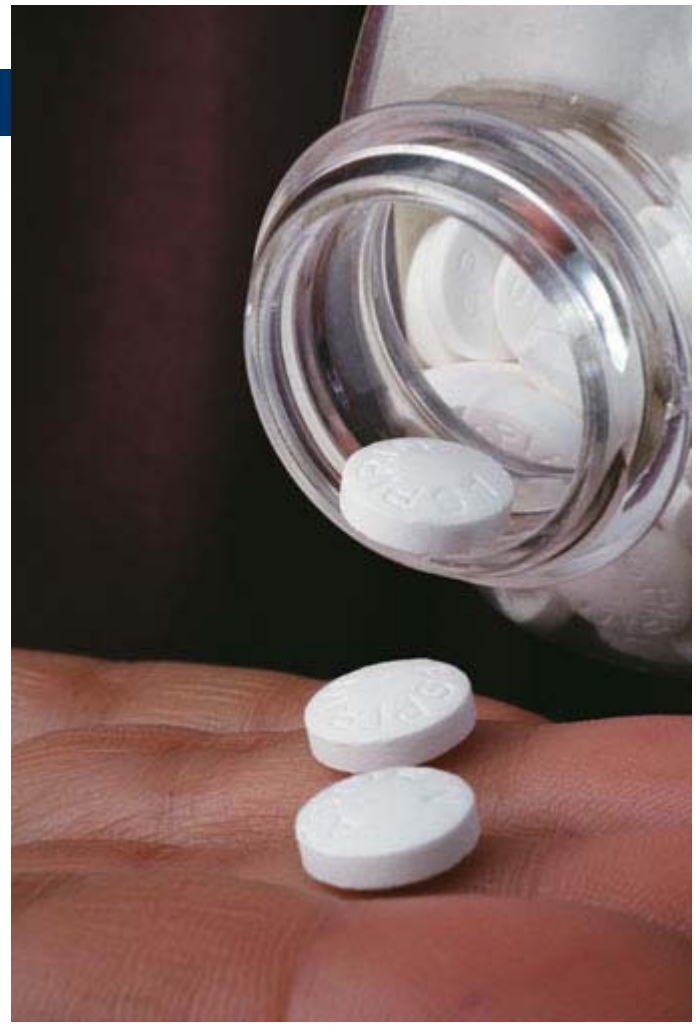
Risk Information

- Industry
  - include serious and common risks
    - cannot omit risk from promotion
  - make efforts to better present risk info
- FDA
  - taking necessary and appropriate enforcement actions
  - working on draft guidance for risk info presentation

Guidance Development

- Presentation of Risk Information
- Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements (Brief Summary)
- Help-seeking and Other Disease Awareness Communications by or on Behalf of Drug and Device Firm (Help-seeking)

Enforcement



Surveillance

- Disseminated materials submitted to FDA
  - Post-marketing reporting requirements (Form 2253)
- Conference attendance
- Complaints
- Surveillance including websites, tv ads, and journal ads

Enforcement Options

- Untitled letters (notice of violation or NOV)
- Warning Letters
- Injunctions/consent decrees
- Seizures
- Criminal actions

Enforcement Analysis

- 13 Warning Letters issued in past 12 months (July 1, 2005 to June 30, 2006)
- Compares to 5 WLs average of previous years
- Stopped and corrected misleading promotion
- Actions needed to achieve compliance

Types of Violations - Most Common

- Inadequate Risk Information
- Misleading Effectiveness Claims
- Misleading Comparative Claims

Risperdal Warning Letter

- “Dear Healthcare Provider” Letter
- Suggested that Risperdal is not associated with increased risk of diabetes
- Failed to communicate consequences of hyperglycemia and need for monitoring
- Failed to communicate potential seriousness of risk – e.g. ketoacidosis, coma, death

Risperdal WL (cont.)

- Suggested Risperdal is safer than other atypical antipsychotics re: risk of diabetes
- Public health concerns re: format, content, and timing of communication

JANSSEN PHARMACEUTICA INC.

November 10, 2003

Dear Healthcare Provider,

The Food and Drug Administration (FDA) has requested all manufacturers of atypical antipsychotics to include a warning regarding hyperglycemia and diabetes mellitus in their product labeling. In addition to Janssen, the FDA made this request to the following manufacturers:

AstraZeneca – Seroquel® (quetiapine)
Bristol-Myers Squibb – Abilify™ (aripiprazole)
Eli Lilly and Company – Zyprexa® (olanzapine)
Novartis – Clozaril® (clozapine)
Pfizer – Geodon® (ziprasidone)

In an effort to keep you updated with the most current product information available for the management of your patients, enclosed please find updated prescribing information for RISPERDAL® (risperidone).

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-4] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

For additional information about RISPERDAL or any other Janssen product, please call 1-800-JANSSEN (526-7736) from 9AM to 5PM EST, Monday through Friday.

Sincerely,

Ramy Mahmoud, MD
Vice President CNS Medical Affairs
Janssen Pharmaceutica, Inc.

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000
US.JANSSEN.COM

Hyperglycemia-related adverse events have infrequently been reported in patients receiving RISPERDAL. Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research[1-8] suggests that RISPERDAL is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. Evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics.

JANSSEN PHARMACEUTICA INC.

IMPORTANT CORRECTION OF DRUG INFORMATION

July 21, 2004

Dear Health Care Provider:

The Food and Drug Administration's (FDA) Division of Drug, Marketing, Advertising, and Communications (DDMAC) has asked us to contact you because Janssen Pharmaceutica Products, L.P. recently received a Warning Letter concerning the promotion of Risperdal® (risperidone). This letter provides important corrective information about Risperdal relating to hyperglycemia and Diabetes Mellitus.

The Warning Letter concludes that Janssen disseminated a Risperdal Dear Health Care Provider (DHCP) dated November 10, 2003 that omitted material information about Risperdal, minimized potentially fatal risks, and made misleading claims suggesting superior safety to other atypical antipsychotics without adequate substantiation, in violation of the Federal Food, Drug and Cosmetic Act.

Specifically, the Warning Letter stated that the DHCP letter omitted important information regarding hyperglycemia and diabetes, including the potential consequences and the recommendation of regular glucose control monitoring that was added to the approved product labeling for Risperdal; minimized the potentially fatal risks of hyperglycemia-related adverse events such as ketoacidosis, hyperosmolar coma and death; minimized the importance of blood glucose monitoring; suggested that Risperdal did not increase the risk of diabetes, contradicting the Warning in the revised product labeling; and made misleading claims suggesting that Risperdal has a lower risk of hyperglycemia and diabetes than other atypical antipsychotics without adequate substantiation which is inconsistent with the Prescribing Information for Risperdal.

(Continued on reversed side)

1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200
(609) 730-2000

US.JANSSEN.COM

In order to provide you with complete and accurate information regarding hyperglycemia and Diabetes Mellitus relative to Risperdal, please be advised that the Risperdal Prescribing Information was updated with the addition of the Warning in November 2003.

WARNINGS

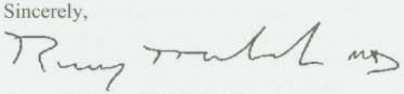
Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

If you have any questions regarding this important safety information, please contact Janssen Medical Affairs at 1-800-JANSSEN. Please refer to the full prescribing information for Risperdal included with this letter. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN or the FDA MedWatch program by phone (1-800-FDA-0178), or by e-mail (www.fda.gov).

Sincerely,



Ramy Mahmoud, MD, MPH
Vice President, CNS
Janssen Medical Affairs, LLC
Enclosure: Risperdal Package Insert

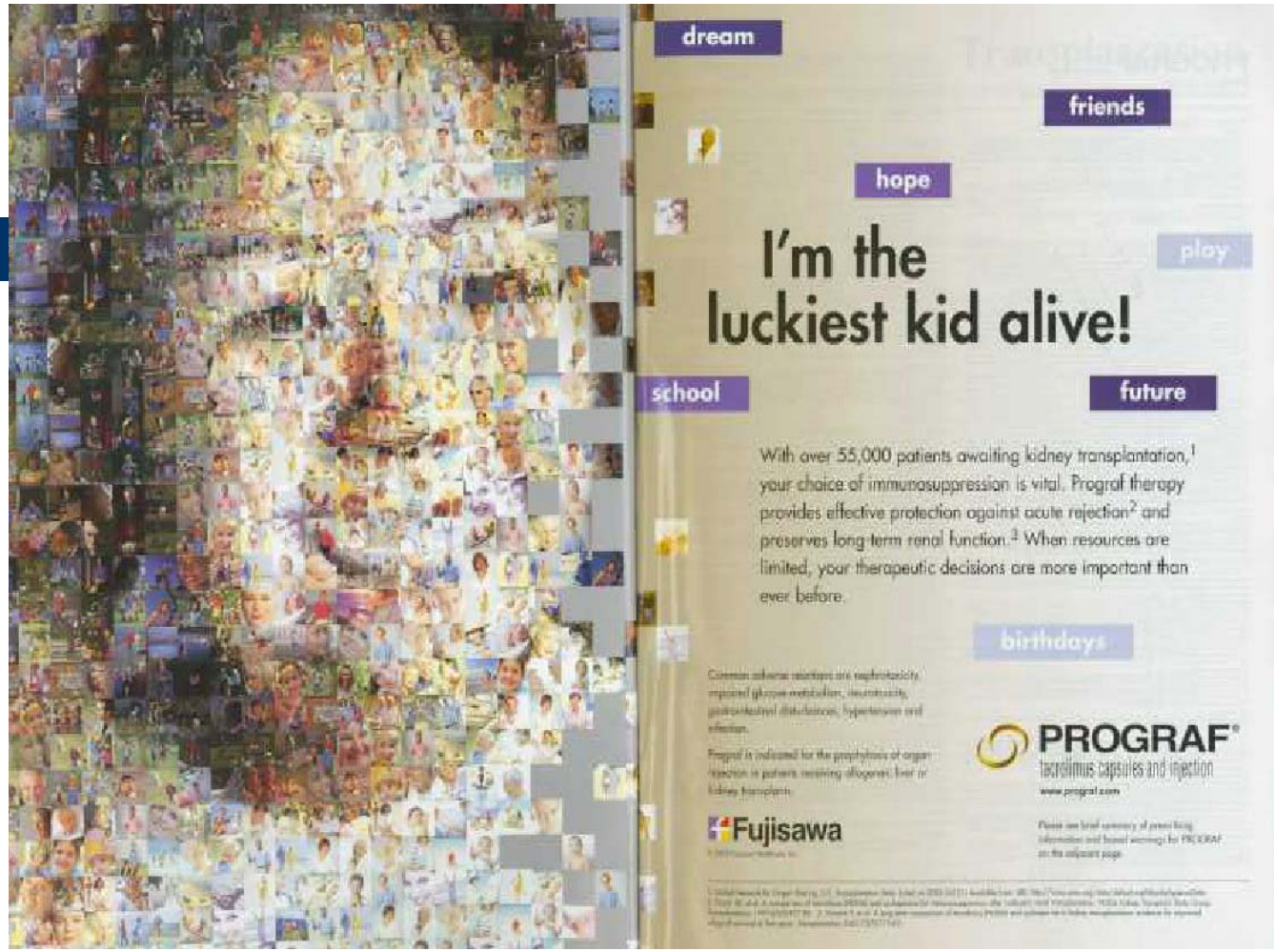
01-RS1516

Prograf Warning Letter

- Journal advertisement
- Presented safety and efficacy claims, but failed to provide adequate risk information.

Prograf WL (cont.)

- Common adverse reactions are nephrotoxicity, impaired glucose metabolism, neurotoxicity, gastrointestinal disturbances, hypertension, and infection.
- This is not sufficient to described the serious risks associated with the use of the product.


dream
friends
hope
play
I'm the luckiest kid alive!
school
future
birthdays
With over 55,000 patients awaiting kidney transplantation,[1] your choice of immunosuppression is vital. Prograf therapy provides effective protection against acute rejection[2] and preserves long-term renal function.[3] When resources are limited, your therapeutic decisions are more important than ever before.
PROGRAF®
tacrolimus capsules and injection
www.prograf.com
Fujisawa

Important Correction of Information about Prograf® (tacrolimus capsules and injection)

Fujisawa Healthcare Inc., maker of Prograf, ran ads for Prograf that the FDA determined violated provisions of the drug advertising and promotion regulations on the risk of increased susceptibility to infection and the risk of insulin-dependent post-transplant diabetes mellitus and failed to include necessary qualifying information concerning the risk of development of lymphoma.

Fujisawa takes this opportunity to properly highlight the risks associated with Prograf, a drug for the prophylaxis of organ rejection in patients receiving allogenic liver or kidney transplants.[1]

WARNING: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and qualified facilities should manage patients prescribed Prograf. The physician responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf injection is contraindicated in patients with a hypersensitivity to castor oil. Monitoring of patients for signs and symptoms of anaphylaxis during the initial infusion with Prograf is recommended.

In the original Phase III kidney transplant clinical study, where Prograf was used in combination with azathioprine and prednisone and dosed to initial target trough blood levels, insulin dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney patients. Insulin dependence was reversible in 15% of these patients at one year and 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk. In the original Phase III liver transplant clinical study, insulin dependent PTDM was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post transplant.

Prograf has been associated with nephrotoxicity, particularly when used in high doses. To avoid nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Discontinue Prograf or cyclosporine at least 24 hours prior to initiating the other. Further delay dosing if Prograf or cyclosporine concentrations are elevated.

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials, respectively, and may require treatment (see **ADVERSE REACTIONS**). Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Prograf therapy (see **PRECAUTIONS**).

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. ...Seizures have occurred in adult and pediatric patients receiving Prograf (see **ADVERSE REACTIONS**). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

The principal adverse reactions of Prograf are tremor, headache, hypertension, gastrointestinal disturbance, and renal dysfunction.

Please see accompanying brief summary of product information.

[1] It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally.

PROGRAF®
tacrolimus capsules and injection
Fujisawa

Cubicin Warning Letter

- Journal advertisement and website
- Broadens the indication
  - treatment of all infections caused by Staph aureus
- PI states it is not indicated for pneumonia
  - In Phase 3 studies of community-acquired pneumonia, death rate was higher

IMPORTANT CORRECTION OF DRUG INFORMATION
CUBICIN® (daptomycin for injection)

October 2004

Dear Healthcare Practitioner:

Earlier professional journal publications contained advertisements for Cubicin® (daptomycin for injection) that were the subject of a Warning Letter ("the Letter") from the U.S. Food and Drug Administration in August 2004. The Letter stated that the advertisements violated provisions of the drug advertising and promotion regulations by failing to reveal material facts regarding important risk information and potential consequences that may result from the use of the drug, as well as broadening the approved indication for CUBICIN, by implying that CUBICIN is safe and effective for all infections caused by MRSA and MSSA.

Specifically, the ad failed to include information on the monitoring of creatine phosphokinase (CPK) levels, which is described in the Precautions section of the package insert for CUBICIN:

> In clinical trials, elevations in serum creatine phosphokinase (CPK) were reported as adverse events in 2.8% of daptomycin patients compared to 1.8% of comparator patients. Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. CPK levels should be monitored weekly and any unexplained elevations should be monitored more frequently. CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1000 U/L, or in patients without reported symptoms who have marked elevation in CPK (≥10X ULN).

In addition, CUBICIN's approved indication is the following:

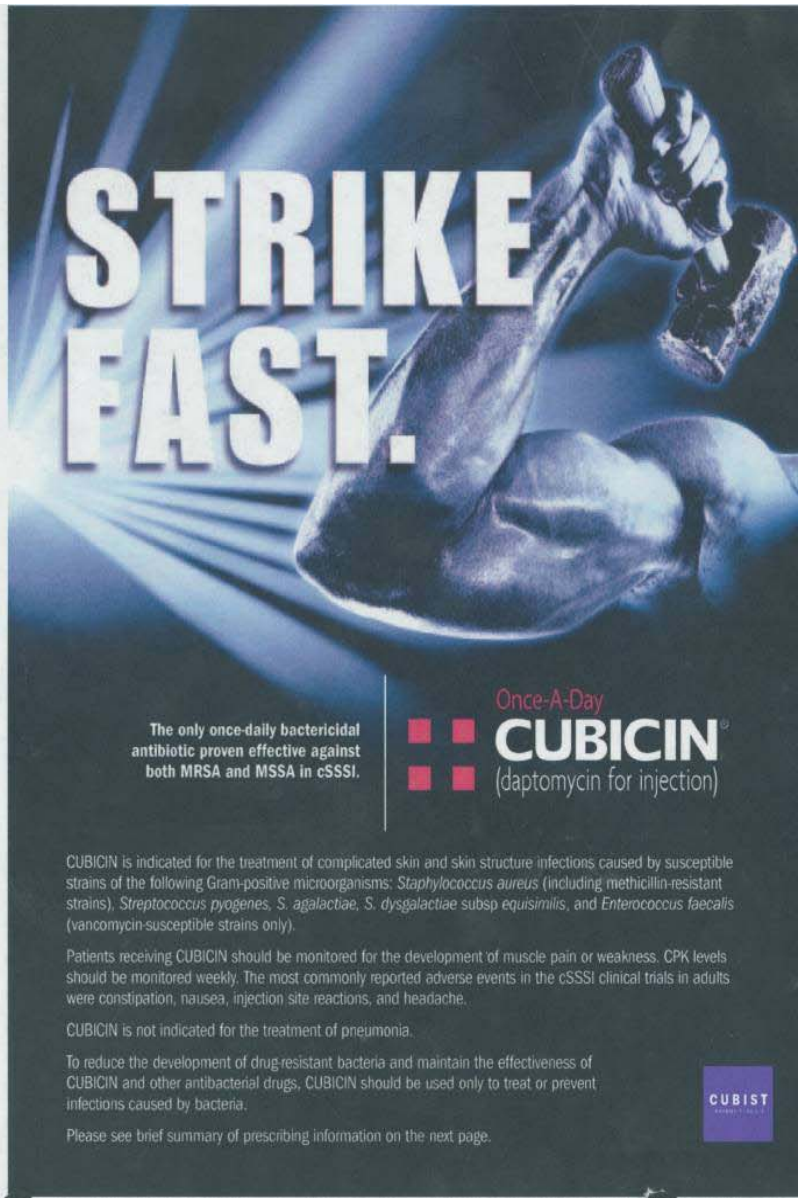
> CUBICIN is indicated for the treatment of complicated skin and skin structure infections caused by susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant strains), *Streptococcus pyogenes, S. agalactiae, S. dysgalactiae* subsp *equisimilis,* and *Enterococcus faecalis* (vancomycin-susceptible strains only). CUBICIN is not indicated for the treatment of pneumonia.

We direct you to the brief summary of prescribing information on the following page. You may also contact Cubist's Medical Affairs department at 1-866-793-2786 for additional information.

Sincerely,

Michael W. Bonney
President and CEO, Cubist Pharmaceuticals, Inc.

CUBIST



Quadramet Warning Letter

- DTC radio ad, patient testimonial video, and website
- Overstatement of effectiveness
- Omission and minimization of risk information
  - Bone marrow suppression
  - Radioactivity in excreted urine

Quadramet Warning Letter

- Quadramet doesn’t make you lose your hair, it targets the cancer and that is what so great about it. It knows where to go. I think it is amazing.
- Quadramet travels to the site of bone reformation due to metastatic bone cancer to provide relief with a single injection.
- After the Quadramet shot started to take effect, she was back to her old self, she wasn’t drowsy.
- And I am surprised that she didn’t sit here and cook a big meal for you guys.

CYTOGEN

IMPORTANT CORRECTION OF DRUG INFORMATION

Dear Healthcare Consumer:

Cytogen Corporation received a Warning Letter on July 18, 2005 from the Food and Drug Administration's (FDA) Division of Drug Marketing, Advertising, and Communications (DDMAC) relating to the drug QUADRAMET® (Samarium Sm 153 Lexidronam) concerning a Patient Testimonial Video (the "Patient Testimonial"), a radio ad broadcast in the Atlanta, Georgia area (the "Atlanta Radio Ad"), and the www.quadrametus.com Web-Site (the "Web-Site").

The Warning Letter concluded that the Patient Testimonial and the Web-Site overstated how well QUADRAMET works and that the Patient Testimonial, Web-Site, and Atlanta Radio Ad failed to talk about and minimized important risk information related to the use of QUADRAMET, in violation of the Federal Food, Drug and Cosmetic Act.

Specifically, the Warning Letter objected to the Patient Testimonial and the Web-Site because they suggested that patients get instant pain relief from a QUADRAMET injection, suggested that no other painkillers would be needed after injection with QUADRAMET, suggested more pain relief than is shown by scientific data, and suggested the ability to get back to normal daily activities after QUADRAMET injection without data to support such claims. The Web-Site suggested that patients on QUADRAMET can be expected to live longer and did not mention the safety measures that are needed when using Quadramet because it is a radioactive therapy. Furthermore, the Patient Testimonial suggested that Quadramet is a therapy to treat cancer in addition to pain, which it is not.

Therefore, we direct you to the following Important Information on QUADRAMET.

- **FDA Concern: the Patient Testimonial and the Web-Site suggested that patients get instant pain relief from a QUADRAMET injection.**

  Quadramet is given by injection into a vein. Although the injection itself only takes a few minutes, it takes time for the effects of the treatment to be felt. In patients who feel less pain, relief will usually begin about one week after the injection. The most pain relief will usually happen 3 to 4 weeks after the injection of Quadramet.

Some patients have felt a temporary increase in bone pain shortly after injection. This temporary increase in bone pain is usually mild and happens within 72 hours of Quadramet injection. Other pain medicines can usually take care of this pain.

- **FDA Concern: the Patient Testimonial and Web-Site suggested that no other painkiller would be needed after injection with QUADRAMET.**

  Most patients who receive Quadramet also take a variety of other medicines to help treat their pain. These normally include both over the counter medications (such as aspirin and ibuprofen) as well as stronger prescription drugs (such as oxycodone and morphine). In clinical trials of Quadramet, patients who experienced relief of pain were generally able to decrease the amount of these stronger prescription drugs they were taking. However, most patients, including those who feel less pain following a Quadramet injection, still need to take other medicines to help control their pain. Patients who feel less pain after a Quadramet injection may be encouraged to lower their use of pain medicine but only after talking to their doctor.

  FDA Concern: the Patient Testimonial and the Web-Site suggested more pain relief than is shown by scientific studies, and suggested the ability to get back to normal daily activities after QUADRAMET injection without data to support such claims.

  In clinical trials, patients who were given the recommended dose of Quadramet had lower pain scores and were better able to carry out the functions of daily living and to sleep through the night. However, there may be reasons other than pain that get in the way of cancer patients' normal daily activities or sleep and Quadramet does not treat these non-pain related factors.

- **FDA Concern: the Patient Testimonial suggested that QUADRAMET treats cancer and the Web-Site suggested that patients on QUADRAMET can be expected to live longer.**

  The patient testimonial stated that treatment with QUADRAMET does not cause the loss of hair, which is a common side effect of cancer treatment. Because it refers to this common side effect, this statement suggests that Quadramet also treats cancer. Quadramet is prescribed for relief of pain in patients with a certain kind of bone cancer that relates to problems called osteoblastic metastatic bone lesions. Quadramet treats the pain from cancer, not the cancer itself. There are no studies showing that Quadramet helps people live longer than those who do not take it.

- **FDA Concern: the Patient Testimonial, Web-Site, and Atlanta Radio Ad did not mention and minimized important risks that may result from the use of QUADRAMET.**

  Quadramet may cause a decrease in the number of certain blood cells (called white blood cells and platelets) that help prevent infections or bleeding. These types of side effects

may be serious and could cause death. Other treatments, such as some cancer treatments, can cause the same problems. Only your doctor can determine if Quadramet will be safe enough for you to take while you are getting your cancer treatment.

QUADRAMET is not for patients who have known allergic reactions to some substances it contains called phosphonates.

Because it is a radioactive treatment, pregnant women should not be treated with Quadramet.

- **FDA Concern: the Patient Testimonial, Web-Site, and Atlanta Radio Ad did not mention the needed safety measures connected with the use of QUADRAMET, a radioactive therapy.**

  Because the treatment involves radiation, there are some steps that you need to take the day of your injection with Quadramet. For several hours following the injection, radioactivity will be present in urine. To help protect yourself and others in your home and around you, you need to take safety measures for 12 hours following injection. 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 you should wash your hands thoroughly. If blood or urine gets onto clothing, the clothing should be washed separately, or stored for 1-2 weeks before washing to allow for the decay of the radioactive part of the drug.

Please also see the full Prescribing Information on this Web-Site.

Sincerely,

Michael D. Becker, President and
Chief Executive Officer

DDMAC Information

Web addresses:

- DDMAC webpage
  - www.fda.gov/cder/ddmac
- Warning and untitled letters
  - www.fda.gov/cder/warn
- Guidances
  - www.fda.gov/cder/guidance

- Phone number:
  - (301) 796-1200
- Fax numbers:
  - (301) 796-9877 and (301) 796-9878