Understanding **Quadramet®**

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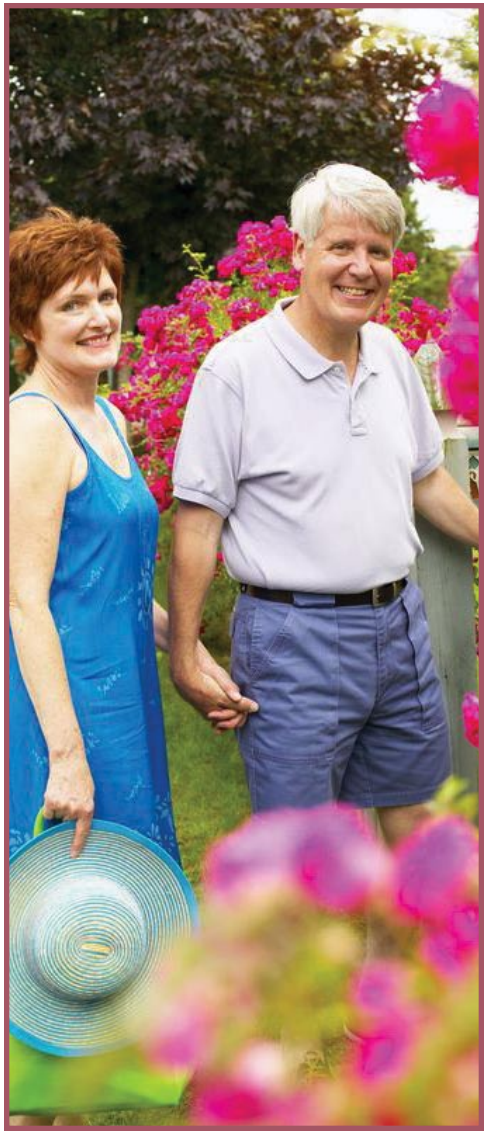

Introduction

Quadramet® belongs to a class of drugs called radiopharmaceuticals and is used to treat bone pain that often results when cancer has spread to the bone. Quadramet® is currently approved by the United States Food and Drug Administration (FDA) to relieve pain in patients who have confirmed **osteoblastic*** metastatic bone lesions that are evident on a **bone scan**. To explain, when cancer spreads (**metastasizes**) to the bone, it is often characterized as **osteolytic** (the breakdown of bone), osteoblastic (the formation of bone), or mixed (a mixture of osteolytic and osteoblastic components).

In general, **myeloma** results in osteolytic lesions that are associated with excessive bone destruction. Other cancers, such as prostate cancer, are often associated with excessive bone formation when they metastasize. Recent observations, however, indicate that osteolytic and osteoblastic lesions simply represent two extremes of a broad spectrum – and most bone metastases exhibit characteristics of both.

Radiopharmaceuticals, like Quadramet®, are a type of **systemic** therapy – meaning one dose can target multiple sites of bone metastasis.

If patients have confirmed osteoblastic lesions, they may benefit from treatment with Quadramet®. Ongoing studies in the

** Words and phrases in* ***bold*** *are defined in the Glossary section in this booklet*

United States are currently evaluating the specific benefits that Quadramet® can offer to patients with myeloma.

This booklet is intended to provide a basic understanding of what you can expect from Quadramet® therapy, including:

- What Quadramet® is and how it works to treat pain from cancer that has metastasized to the bone,
- How to handle Quadramet® therapy safely,
- What **side effects** might be expected from Quadramet® therapy, and
- How Quadramet® may be used in combination with other therapies.

This information may be useful not only to patients, but also to friends, family, loved ones, and other caregivers. Information about Quadramet® is also available at www.cytogen.com. A copy of the full prescribing information for Quadramet® may be obtained in the United States from Cytogen Corporation by calling toll free at 800-833-3533 or by visiting www.cytogen.com.

Please remember that myeloma, like all cancers, is a complicated disease. A doctor or nurse should address any specific questions about treatment.

What is Quadramet®?

Quadramet® (Samarium Sm-153 Lexidronam Injection) belongs to the **radiopharmaceutical** drug class. Radiopharmaceuticals were first used in the 1950s to provide pain relief for cancer that metastasizes to the bone. Phosphorous-32 and strontium-89 were the first radiopharmaceuticals. Quadramet® is indicated for the relief of pain in patients with confirmed osteoblastic metastatic bone lesions that are enhanced on a **radionuclide** bone scan.

Quadramet® received FDA approval in 1997. Quadramet® combines a radionuclide (an atom characterized by the composition of its nucleus and, consequently, the quantity of protons, neutrons, and energy) with more desirable nuclear properties (eg, shorter half-life and lower energy-particle emissions) and greater selectivity than earlier radiopharmaceuticals.

Next-generation radiopharmaceuticals such as Quadramet® offer certain advantages in treating pain associated with bone metastasis:

- A Quadramet® dose is administered in a single injection over a few minutes, usually as an outpatient procedure.
- Patients who respond might begin to notice the onset of pain relief one week after injection with maximal pain relief generally at 3 to 4 weeks. Not all patients

respond to Quadramet®. Some patients have reported a transient increase in bone pain within 72 hours of injection (**flare** reaction) which is usually mild and self-limiting.

- In a clinical trial, 62%–72% of patients receiving the approved dose of Quadramet experienced pain relief in the first four weeks. Two thirds of these responding patients were still experiencing pain relief at 16 weeks.
- If appropriate, radiopharmaceuticals can be used in combination with other treatments. However, because of the unknown potential for additive effects on **bone marrow,** Quadramet® should not be given concurrently with **chemotherapy** or **external beam radiation** unless the clinical benefits outweigh the risks.

How does Quadramet® differ from analgesics?

Analgesics are used to relieve pain. These drugs include over-the-counter medications such as aspirin and acetaminophen, as well as prescription-only drugs such as morphine and other **opiates**. Although these drugs can effectively provide general pain relief, some of them, especially morphine and the other opiates, may cause unpleasant side effects, including constipation, nausea or vomiting, and drowsiness.

Quadramet® delivers treatment directly to the site and source of bone pain and has a different side effect profile. Please see the side effects section for a full listing of Quadramet®'s potential side effects. Patients who experience a reduction in pain from Quadramet® treatment may be encouraged by their doctors to reduce their use of opioid analgesics. 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).

How does Quadramet® differ from bisphosphonates?

Quadramet® targets new bone formation and bisphosphonates target bone destruction. Together, Quadramet® and **bisphosphonates** target the two activities present in bone metastasis.

Who can benefit from Quadramet® therapy?

Quadramet® has demonstrated significant reductions in pain scores in randomized clinical trials. These trials included patients with prostate, breast, and other cancers. Quadramet has been found to be effective in patients suffering bone pain associated with different stages of cancer, including:

- Patients who have been newly diagnosed with myeloma or bone metastasis,
- Patients who have not responded to other treatments, and
- Patients in whom cancer has returned after initial successful treatment.

Before Quadramet® is administered, consideration should be given to the patient's current clinical and hematologic status and to bone marrow response history to treatment with myelotoxic agents.

How does Quadramet® work?

The exact mechanism of action of Quadramet in relieving the pain of bone metastases is not known.

Quadramet® contains a radioactive ingredient that is designed to target areas where cancer is attacking bone. In clinical studies, more Quadramet® accumulates in osteoblastic lesions than in normal bone, with a lesion-to-bone ratio of approximately 5:1. This targeting means that healthy bone and other normal tissues receive lower exposure to radioactivity than do lesions. In addition, because Quadramet® is a systemic therapy, one dose can target multiple sites of bone metastases.

What are the possible side effects of Quadramet®?

The most common side effect with Quadramet® is bone marrow toxicity, which causes a decrease in the number of blood cells in your body. Bone marrow toxicity occurred in 47% of patients in clinical trials.

Bone marrow toxicity may increase your risk of infections by reducing the number of white cells, which guard against infection; or bleeding by reducing the number of platelets, which control blood clotting, so it is important for your doctor to consider your hematologic status prior to treatment with Quadramet®, especially if you are undergoing other therapies that may also affect your blood counts.

Non blood-related adverse events that occurred in 5% or more patients and that occurred more commonly in the Quadramet® group than in those patients who were given a placebo were pain flare (7%), infection (7%), spinal cord compression (6.5%), diarrhea (6%), arrhythmias (5%) and hematuria, which is blood in the urine (5%). Because of the unknown potential for additive effects on bone marrow, Quadramet® should not be given concurrently with chemotherapy or external beam radiation unless the clinical benefits outweigh the risks. Patients taking Quadramet® should have their blood counts monitored for at least 8 weeks, or until recovery of adequate bone marrow function. Quadramet® should not be used in patients

who have known hypersensitivity to EDTMP (Ethylene Diamine Tetramethylene Phosphate) or similar phosphonate compounds; women of childbearing age should have a negative pregnancy test before administration of Quadramet®. If Quadramet® is administered to a nursing mother, formula feeding should be substituted for breast feeding. 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 the environment, precautions need to be taken for 12 hours following administration.

BEFORE YOU RECEIVE QUADRAMET®

- Tell your doctor if you are pregnant, trying to become pregnant, or nursing. Quadramet® can be harmful to fetuses and infants and should not be used by pregnant women. Women of childbearing age should have a negative pregnancy test before administration of Quadramet®. Men and women should be advised to use an effective method of contraception after administration. If Quadramet® is administered to a nursing mother, formula feeding should be substituted for breast feeding.
- Tell your doctor if you have had an allergic reaction to any drugs.
- Drink at least 2 cups (1 pint) of fluid just before you receive Quadramet®.

AFTER YOU RECEIVE QUADRAMET®

You should take some basic steps after receiving Quadramet® to protect yourself and others:

- Remember that for about 12 hours, radioactivity will be present in your urine.
- During the first few hours after your injection, drink extra fluids and urinate as often as possible.
- If you are a man, use a toilet if possible, rather than a urinal.
- Flush the toilet several times when you are finished urinating, clean up any spilled urine immediately, and wash your hands thoroughly.
- If any urine or blood gets on your clothing, wash those clothes separately or store them for 1 to 2 weeks before washing.

If you have been receiving chemotherapy or radiation therapy for your cancer, your doctor will decide if and when you should continue after you receive Quadramet®. Quadramet® therapy may affect your **blood cell counts**, which may in turn affect other treatment decisions. Therefore, for about 8 weeks after treatment, you should tell other health care professionals you see, including your dentist and pharmacist, that you have received Quadramet®.

Who should not receive Quadramet®?

Before you receive Quadramet®, your doctor should consider your current medical and blood count status, along with your history of response to treatment with other drugs that suppress bone marrow. Because of the potential for additive effects on bone marrow, Quadramet® should not be given at the same time as chemotherapy or external-beam **radiation therapy** unless your doctor feels the possible benefits outweigh the risks. Similarly, Quadramet® should not be given to patients whose bone marrow supply has been affected, either from disease or other therapy, unless your doctor feels the possible benefits outweigh the risks. Quadramet® should not be used in patients who have known hypersensitivity to EDTMP or similar phosphonate compounds. Quadramet® can be harmful to fetuses and infants and should not be used by pregnant or nursing women. If Quadramet® is administered to a nursing mother, formula feeding should be substituted for breast feeding.

How is Quadramet® given?

Quadramet® is given **intravenously** over a 1-minute period through an **indwelling catheter**. In most cases, Quadramet® can be given on an outpatient basis.

Can Quadramet® be taken with other cancer treatments?

As mentioned, Quadramet® can be given with analgesics, including opiates. Moreover, patients who experience a reduction in pain from Quadramet® treatment may be encouraged by their doctors to reduce their use of opioid analgesics.

It is not typically recommended that Quadramet® be taken at the same time that patients are receiving chemotherapy or external-beam radiation therapy, but your doctor can best assess the possible benefits and risks.

Will insurance cover the cost of Quadramet®?

Insurance coverage varies. Individual insurance companies can provide information regarding their Quadramet® coverage. For more information, you can also call the Cytogen Benefit Verification line at 1-888-837-4397 (1-888-VERIFYQ).

A final note

Quadramet® is a treatment for relief of bone pain from metastatic bone disease for a number of diseases. As with any drug, however, it can cause harm if misused. It is important that you follow all advice from your health care professionals while you are taking Quadramet®, and you should promptly contact your doctor or nurse with any questions.

You may have questions or concerns regarding your Quadramet® treatment once your therapy begins. Some of these concerns may be about Quadramet® itself. Others may be about the outcome of treatment and its side effects. Still other concerns may be more emotional or financial in nature. Many resources are available. You should share your concerns with the members of your treatment team, so that they can help you. Communication will help lead to the active management of side effects, minimize symptoms, and help alleviate fears and concerns during treatment. Involvement in your personal care will ultimately lead to confidence and a sense of control regarding treatment choices.

About the IMF

"One person can make a difference,
Two can make a miracle."

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with more than 15,000 new cases diagnosed each year. While there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian's myeloma diagnosis at the age of 33. It was Brian's dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the 3 goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients, their families, friends, and health care providers. Although Brian died 4 years after his initial diagnosis, his dream didn't. Today the IMF reaches out to an international membership of more than 125,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

The IMF provides programs and services to aid in the research, diagnosis, treatment, and management of myeloma. The IMF ensures that no one must brave the myeloma battle alone.

We care for patients today, while working toward tomorrow's cure.

How Can the IMF Help You?

PATIENT EDUCATION

INFORMATION PACKAGE

Our free IMF InfoPack provides comprehensive information about myeloma, treatment options, disease management, and IMF services. It includes our acclaimed *Patient Handbook*.

INTERNET ACCESS

Log on to www.myeloma.org for 24-hour access to information about myeloma, the IMF, education, and support programs.

ONLINE MYELOMA FORUM

Join the IMF Internet Discussion Group at www.myeloma.org/listserve.html to share your thoughts and experiences.

MYELOMA MINUTE

Subscribe to this free weekly email newsletter for up-to-the-minute information about myeloma.

PATIENT & FAMILY SEMINARS

Meet with leading experts in myeloma treatment to learn more about recent advances in therapy and research.

MYELOMA MATRIX

On our website and in print, this document is a comprehensive guide to drugs in development for myeloma.

MYELOMA TODAY NEWSLETTER

Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)

Toll-free throughout the United States and Canada, the IMF Hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

SUPPORT GROUPS

A worldwide network of more than 100 myeloma support groups hold regular meetings for members of the myeloma community. The IMF conducts annual retreats for myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provide genetic data research in new drug development.

THE INTERNATIONAL STAGING SYSTEM (ISS)

This updated staging system for myeloma will enhance physicians' ability to select the most appropriate treatment for each patient.

RESEARCH GRANTS

Leading the world in collaborative research and achieving extraordinary results, the IMF Grant Program supports both junior and senior researchers working on a broad spectrum of projects. The IMF has attracted many young investigators into the field of myeloma, and they have remained in the field and are actively pursuing a cure for this disease.

Glossary

Alkylating agent: An agent that prevents the growth and division of new cancer cells by inhibiting their ability to replicate DNA.

Analgesic: A drug that relieves pain, including over-the-counter medications such as aspirin and acetaminophen and prescription-only medications such as morphine and other opiates.

Bisphosphonate: A drug that restricts the action of bone-destroying cells.

Blood cell count: The amount of red blood cells, white blood cells, and platelets in the body.

Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets.

Bone scan: A technique that creates images of bones on a computer screen to indicate areas of injury, disease, or healing.

Cell: The smallest unit of life. Millions of microscopic cells comprise each bodily organ.

Chemotherapy: Treatment of disease by means of chemical substances or drugs.

External-beam radiation therapy: Radiation therapy that aims highly focused beams of radiation at the edges of a cancerous site to destroy any abnormal cells and prevent the growth or regrowth of the tumor.

Flare: A sudden worsening of disease or pain.

Indwelling catheter: An instrument that is used to inject or withdraw fluids.

Intravenously: Administered directly to the blood through a vein.

Metastasis: The spread of cancer from the primary tumor to other parts of the body.

Myeloma: A cancer arising from the plasma cells in the bone marrow. The plasma cells in patients with myeloma form abnormal antibodies, possibly damaging the bone, bone marrow, and other bodily organs. Also known as multiple myeloma.

Opiate: A pain-relieving drug derived from opium, such as morphine, hydromorphone, codeine, and oxycodone.

Osteoblastic: Characterized by the formation of bone.

Osteolytic: Characterized by the breakdown of bone.

Plasma cell: A type of white blood cell that produces antibodies.

Platelet: A blood cell that helps with clotting, which in turn helps repair damaged blood vessels.

Protein: A group of compounds that are the main components of a cell.

Radiation therapy: The careful use of high-energy radiation to treat cancer.

Radionuclide: An atom characterized by the composition of its nucleus, and consequently, the quantity of protons, neutrons, and energy.

Radiopharmaceutical: A drug that contains a radioactive ingredient.

Red blood cell: A blood cell that carries oxygen from the blood throughout the body.

Side effect: An effect caused by treatment with a drug. The term usually refers to unwanted effects, but some side effects may be beneficial.

Systemic: Affecting the entire body.

Targeted radiopharmaceutical: A drug that contains a radioactive ingredient that is used to target the cells that are affected by cancer, while minimizing impact on normal cells.

White blood cell: A blood cell that helps fight infection and/or disease.