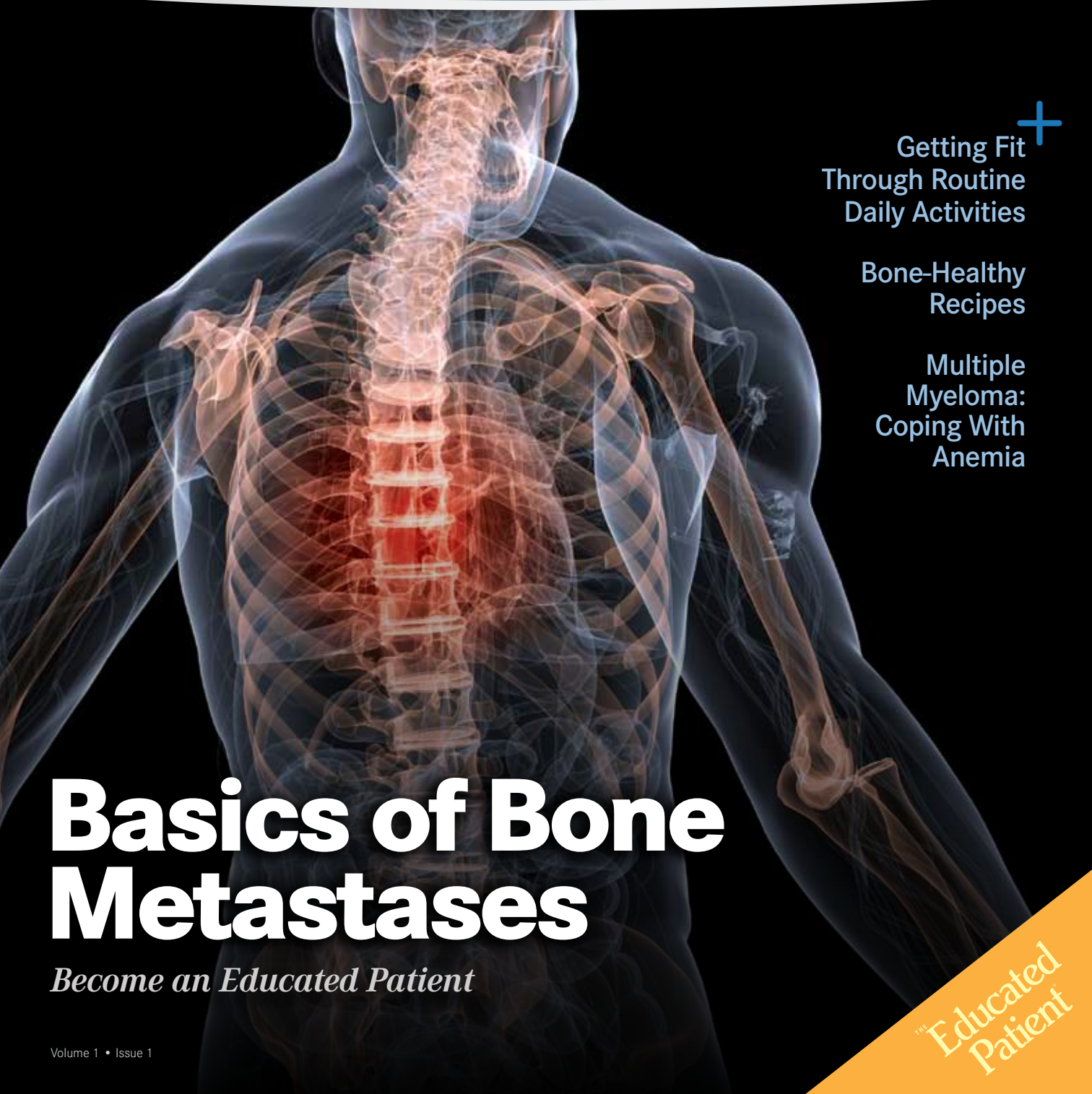
Compass

navigating bone metastases



Getting Fit Through Routine Daily Activities

Bone-Healthy Recipes

Multiple Myeloma: Coping With Anemia

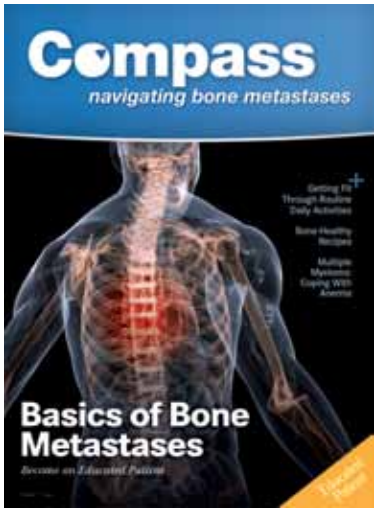
Basics of Bone Metastases

Become an Educated Patient

Volume 1 • Issue 1

The Educated Patient®

From the Publisher



Welcome to this inaugural issue of *Compass*, brought to you by Novartis Oncology. Compass is a magazine for patients with cancer who have, or are at risk for, bone metastases, and for patients with bone lesions resulting from multiple myeloma. We hope you use *Compass* to navigate your journey with bone metastases.

Each issue will include a number of regular features intended to help patients better understand their disease and give them information to enhance their recuperative powers.

Compass will include fact-based articles to bolster patients' knowledge. In this issue, for example, is an article on the basics of bone metastases to help you understand the normal process of bone building.

Compass will include useful information for all cancer patients with solid tumors from bone metastases or with bone lesions resulting from multiple myeloma. Each issue will also have a tumor focus; some features in this issue, for example, focus solely on multiple myeloma, with information about the Multiple Myeloma Research Foundation and a story about how to cope with anemia. The next issue may feature breast, prostate, or lung cancer.

This issue's Fitness Connection contains information about how to stay fit while taking part in your routine daily activities. The column's author, Lisa Marie Bernardo, PhD, RN, HFS, is a certified cancer exercise trainer and health fitness specialist through the American College of Sports Medicine. Our Cooking Connection section, written by chef Katie Huggard, includes easy and delicious recipes that are rich in vitamin D and calcium.

We hope that this issue of *Compass* will not only inspire and entertain you, but also help you find the resources you need to ensure the best possible care.

Sincerely,

Your *Compass* Team

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Oncology Specialty Group

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Basics of Bone Metastases

Become an Educated Patient

Learn how bone forms and about the basics of bone metastases. Understand symptoms and complications. Understanding bone metastases is the first step toward the best possible care.

Departments

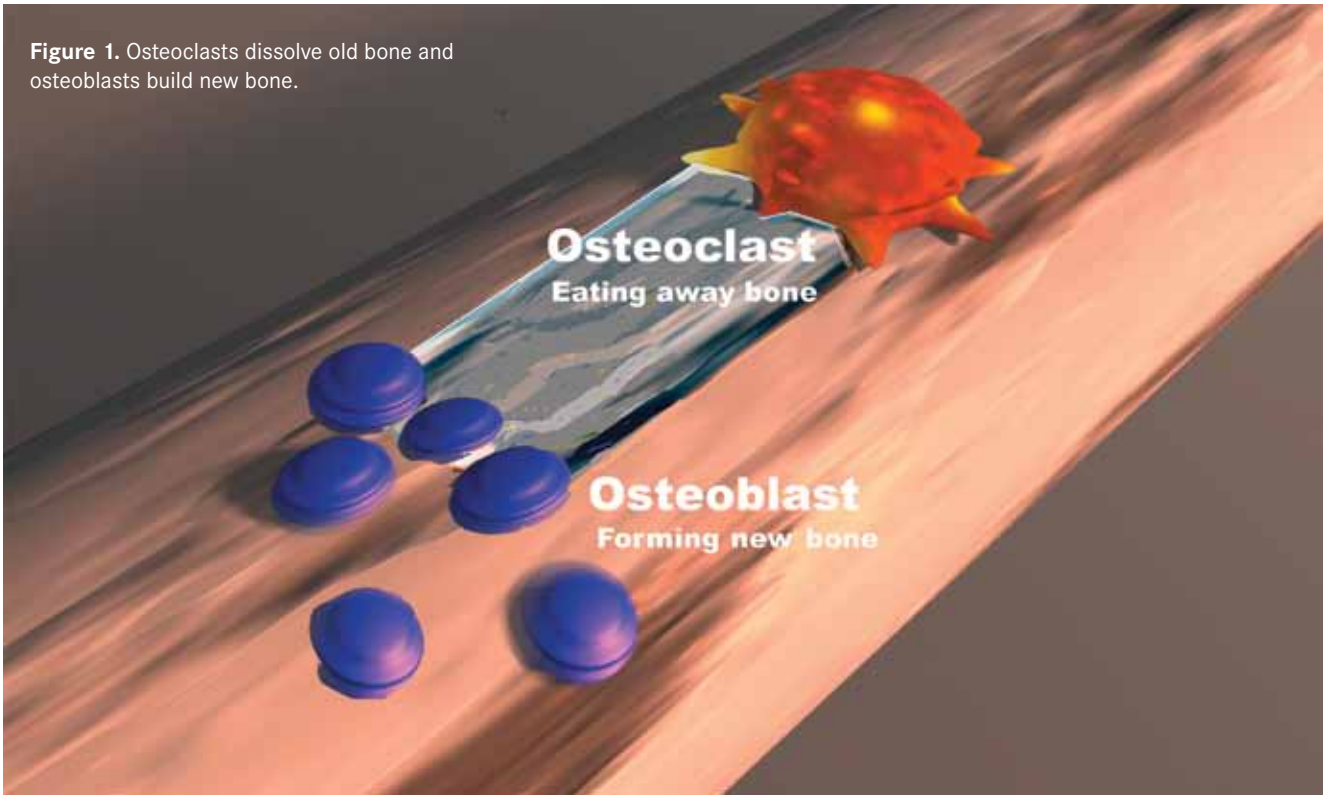

Figure 1. Osteoclasts dissolve old bone and osteoblasts build new bone.

Basics of Bone Metastases

How Bone Forms

Once you're an adult and your skeleton is fully developed, you probably won't grow any taller, but the bone formation process continues throughout your entire life

Bones respond to the stresses of everyday use and abuse by constantly remodeling themselves.[1,2] In fact, it is estimated that 10% of adult bone is renewed each year.[3] During this cycle, old bone decomposes (resorption), then is rebuilt in a more effective manner.

This process is done at the cellular level. Cells called osteoclasts dissolve the old bone and clear it away, then signal their helpers, the osteoblasts, to build new bone to replace the old (Figure 1).[1,2] Some of the the osteoblasts remain behind within the bone cavity. These cells assume a new role as "osteocytes," which detect changes within the bone and, when necessary, signal for another wave of osteoclasts and osteoblasts to restart the process.[3] Often, this process works flawlessly, unless invaders, such as cancer cells, arrive to give the bone cells some trouble.

What Are Bone Metastases?

Cancer cells can spread from where they originally began to other parts of the body through the bloodstream, despite treatment.[4] This process is called metastasis (meh-TASS-tuh-sis). When cancer spreads to the bones, the condition is called bone metastases. Cancer cells that have metastasized to the bone can damage the bone and make it weaker and more likely to break. Bone metastases are a common cause of pain in people with cancer. Although cancer can spread to any bone in the body, metastases are most often found in the bones near the center of the body. The most common sites of bone metastases are the:

- Upper legs and arms
- Pelvis
- Rib cage
- Skull
- Spine

When cancer spreads to the bones, the tumors that develop at the new location are not new cancers, but an extension of the original cancer. For example, if the original tumor was in the breast, and it spread to two or more bones, it would be called "breast cancer with bone metastases." Certain types of cancer are more likely to spread to the bone. These include breast cancer, prostate cancer, lung cancer, and multiple myeloma. Bone metastases should not be confused with primary bone cancer, a rare disease, which starts at the bone.

How Do Bone Metastases Damage the Bone?

Bone metastases can wear away portions of the bone, leaving small holes. These holes cause the bone to be weaker and more fragile. Sometimes bone metastases can cause the buildup of abnormal bone. This new, abnormal bone is weak and unstable.[5] In both cases, bone metastases have made the bone more prone to break or collapse. Consequently, one of the most common complications of bone metastases is a bone fracture (broken bone). Surgery may be needed to treat a fracture or to stabilize a weak area to prevent a fracture.

Symptoms and Complications

Bone metastases can produce fractures of the hips, long bones, or vertebrae that may make it difficult for a patient to function. This can sometimes require orthopedic surgery.[6] Bone metastases can also lead to spinal cord compression, as a result of vertebral collapse, which may lead to paralysis.[6] Pain associated with bone metastases may require radiation therapy.[6] Receiving treatment for bone metastases as early as possible may help reduce and delay some of the following complications:

Fractures. When bones are weakened by cancer, they can break more easily. Broken bones from metastases take longer to heal than normal fractures. In some cases, a fracture is the first sign of bone metastases. The long bones of the arms and legs and the bones of the spine are the most common sites of fracture.[6]

Spinal cord compression. When cancer spreads to the spine, it can squeeze (compress) the spinal cord.[6] This can show up in different ways:

- Back pain (may travel down one or both legs)
- Numbness of the legs or stomach
- Leg weakness or trouble moving the legs
- Unexpectedly passing urine or stool (incontinence) or problems passing urine[1]

When patients notice symptoms like these, they should call the doctor immediately or go to the emergency department. If not treated right away, serious injury to the spinal cord can occur. In severe cases, spinal cord compression can lead to collapse of the spinal cord and paralysis (the inability to move).[4]

High blood calcium levels. As cancer cells damage the bones, calcium is released into the blood. High levels of calcium in the blood (known as "hypercalcemia") can cause the following symptoms[6]:

- Reduced appetite
- Nausea
- Thirst
- Constipation
- Tiredness
- Confusion

Patients with any of these symptoms should discuss them with a doctor to be sure these symptoms are not due to hypercalcemia. Without treatment, hypercalcemia can become serious and cause abnormal heart rhythm or coma.[4]

Know Your Options

A patient's personal role in his or her own care can't be overstated. By being informed about your disease you may be better able to make decisions that are right for you. There are many treatments that help treat bone metastases. Ask your doctor for more information. Learning the basics about how the bone forms and how bone metastases interrupt this process is not only fascinating, it is also one of the first steps toward better bone health. ■

References

1. Clarke, B. Normal bone anatomy and physiology. *CJASN*. 2008.3;3:S131-S139. Available at: http://cjasn.asnjournals.org/content/3/Supplement_3/S131.long. Accessed January 17, 2011.
2. Lemaire V, Tobin FL, Greller LD, et al. Modeling the interactions between osteoblast and osteoclast activities in bone remodeling. *J Theor Biol*. 2004;229(3):293-309. Available at: http://www.ebi.ac.uk/biomodels/papers/Lemaire2004.pdf. Accessed January 17, 2011.
3. Lerner UH: Bone remodeling in post-menopausal osteoporosis. *J Dent Res*. 2006;85:584-595. Available at: http://jdr.sagepub.com/content/85/7/584.long. Accessed December 30, 2010.
4. American Cancer Society: What is bone metastasis? Available at: http://www.cancer.org/Cancer/BoneMetastasis/DetailedGuide/bone-metastasis-what-is-bone-metastisis. Accessed January 17, 2011.
5. American Cancer Society. Bone Metastases: Do we know what causes bone metastases? Available at: http://www.cancer.org/Cancer/BoneMetastasis/DetailedGuide/bone-metastasis-what-causes. Accessed January 17, 2011.
6. Kinnane N. Burden of bone disease. *Eur J Oncol Nurs*. 2007;11:S28-S31.
7. American Cancer Society. Bone metastasis: how are bone metastases diagnosed? Available at: http://www.cancer.org/Cancer/BoneMetastasis/DetailedGuide/bonemetastasis-diagnosis. Accessed January 10, 2011.

Focus: Multiple Myeloma

Multiple Myeloma Research Foundation

www.themmrf.org

The Multiple Myeloma Research Foundation sponsors research programs to discover new therapies for myeloma. Patient information is housed under Living With Multiple Myeloma. Bone disease is discussed under Newly Diagnosed Patients: What is Multiple Myeloma. In the section titled "Bone," you will find a link to Learn more about how the disease affects bone processes. Choose the VIEW X-RAY link to see what myeloma-associated bone damage looks like.

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Multiple Myeloma:
Coping With Anemia

Many people with cancer acquire anemia. It can occur as a direct result of cancer treatments or simply from the cancer itself. Other causes of anemia include blood loss, mineral deficiency, sickle cell disease, or organ problems.

Diagnosed by a low red blood cell count, anemia is caused by low hemoglobin levels in the blood. Hemoglobin is a protein in red blood cells that carries oxygen throughout the body. When there is too little oxygen delivered throughout the body, symptoms arise, such as faintness, shortness of breath, dizziness, fatigue, chest pain, swelling of the hands and feet, and pale skin.

Anemia occurs when hemoglobin levels are 12 g/dL (grams per deciliter) or less. Many people, however, do not experience symptoms until their hemoglobin levels have reached 11 g/dL. Tests your doctors may conduct to determine if you have anemia include a blood chemistry test, to determine if your organs are functioning properly and to see if your vitamin and mineral levels are at a healthy level; a reticulocyte count, a blood test that counts the number of reticulocytes (the young red blood cells just released from the bone marrow) in your blood; a bone marrow exam; and a fecal occult blood test, a test of your stool, used to check for blood.

Once tests determine that you have anemia, your doctor will decide which method of treatment best suits you. Some patients will be advised to simply eat more nutrient-rich foods or to take iron and folic acid supplements. Other patients may be advised to take a prescription to raise hemoglobin levels in the blood, or if hemoglobin levels need to be raised immediately, a red blood cell transfusion may be given. Your doctor will determine what method of treatment is best for you.

During your cancer treatment, it is important to be aware of any anemia symptoms you may experience and talk to your doctor if you have any questions.

Content for this article is from the American Cancer Society; Find Support and Treatment: Anemia in People With Cancer. What is Anemia. Available at: http://www.cancer.org/Treatment/TreatmentsandSideEffects/PhysicalSideEffects/Anemia/anemia-in-people-with-cancer. Accessed January 30, 2011.

Mind/Body Connection

Maintaining a healthy mindset can be important for patients with bone metastases. If you're a patient with bone metastases, you may find it helpful to share your frustrations with family and friends. Look in this section for tips!

Talk About it

Sharing your frustrations and feelings with family, friends, church or synagogue members, and doctors can help release tension, sort through your feelings, gain perspective, and form coping strategies. The love and emotional support from family and friends are like drugs that cannot be measured.

Joining a support group and talking with other people who have bone metastases can help ease your feelings of isolation. In a support group, you can discuss your concerns, gain new insights, and secure some help solving problems from people who know first-hand what you are going through. Studies have shown that breast cancer patients who engaged in group therapy experienced improved quality of life, reduced pain, and improved psychological symptoms.[1]

Your doctor, or practitioners from your cancer center or infusion site may be able to provide information about local support groups. Support groups are all different, so look for one that is specific and interesting to you. If one does not meet your needs, don't hesitate to try another.

Fresh Air

Did you know that just 5 minutes of walking in a park or gardening in the backyard may benefit your health? A study in *Environmental Science & Technology* followed 1,252 people (of different ages, genders, and mental health status) in the United Kingdom and showed that activity in the presence of nature (called green exercise) led to improvements in both mental and physical health.[2] You might not be up for a walk in the country, but trees and plants produce oxygen and absorb toxins. Visit a local park, farm, or preserve, or simply spend some time in the morning with your tea or coffee in your backyard listening to the sounds of nature. Take refuge from the noise of medical centers, televisions, and cell phones. Close your eyes and breathe in the fresh air. Getting fresh air is a form of stress reduction that is always available, and these days with micromanaged schedules and technologies that keep us indoors, it is a technique too often ignored.

Laugh a Little

Norman Cousins wrote a best-sellling book called "Anatomy of an Illnesss as Perceived by the Patient," which became popular in the 1980s. The book was one of the first books written to inspire patients to become educated and take control of their own health. In that book Cousins describes how he believes that he helped himself heal from a rare disease. Cousins checked into a hotel room and watched some of his favorite comedies, such as Candid Camera and the Marx Brothers. Laughter may not heal you the way it may have helped Cousins, but it will help you to forget your troubles for a while and put you in a positive state of mind so you can move forward and take an active role in your own treatment. Here are a few jokes to get you started:

A man walks into a doctor's office. He has a cucumber up his nose, a carrot in his left ear, and a banana in his right ear.
"What's the matter with me?" he asks the doctor.
The doctor replies, "You're not eating properly."[3]

A guy walks into work, and both of his ears are all bandaged up. The boss says, "What happened to your ears?"
He says, "Yesterday I was ironing a shirt when the phone rang and shhh! I accidentally answered the iron."
The boss says, "Well, that explains one ear, but what happened to your other ear?"
He says, "Well, jeez, I had to call the doctor!"[4]

A warthog hits this lady and the husband calls 911.
The operator asks, "Where are you at"?
The husband replies, "I'm on Eucolipstic Road."
The operator asks, "Can you spell that for me?"
"Well... I'll just drag her over to Oak so you can you pick her up there?"[5]

References

1. American Psychological Association: Monitor on Psychology. How do mind-body interventions affect breast cancer? More data emerge on the ways psychological support may affect the lives of breast cancer patients. Available at: http://www.apa.org/monitor/jun02/mindbody.aspx. Accessed December 28, 2010.
2. In the Green of Health: Just 5 Minutes of 'Green Exercise' Optimal for Good Mental Health. *Science Daily*. May 21, 2010. Available at: http://www.sciencedaily.com/releases/2010/05/100502080414.htm. Accessed January 10, 2011.
3. http://www.workjoke.com
4. http://www.juliantrubin.com
5. http://www.cleanjoke.com

This column provides exercise options for people at risk for or living with bone metastases. The information published in this column is not medical advice. Readers should discuss with their oncology team the physical activity and exercise options that are best for them.

Accepting a ride when you aren't up to driving is a way to enjoy a change of scenery.

Getting Fit Through Routine Daily Activities

Being physically active strengthens our bodies, keeps our minds engaged, and boosts our spirits. People living with or at risk for bone metastases can enjoy the benefits of physical activity, provided the activities are safe and appropriate for your condition. Patients should talk with their doctors before beginning any physical activity.

Activities of daily living include those routines performed as part of your day-to-day life patterns. There are three categories: occupational, household, and transportation.

Occupational: Getting ready for work is a part of your daily routine. Bathing, dressing, and engaging in the mental activities of planning your daily routine are included in this category. While at your job, notice the physical, mental, and spiritual activities that you perform. Activities of daily living at your occupation include work (ie, using a computer, operating equipment); preparing and eating a meal at break time or on your lunch hour; and walking to and from meetings, rooms, and other places, gathering supplies, and so forth.

When reflecting on occupational activities of daily living, you may find that you have a wide range of physical and mental activities, which may explain your fatigue, or conversely, your buoyancy, at the end of the day!

Household: These activities encompass everything you perform in a day and may include personal hygiene, cooking, cleaning, walking to the mailbox, washing clothes, and any other physical activity that keeps your household running. Such activities can be a full-time job! For people living with bone metastases, lifting, pushing, pulling, and similar activities may not be permitted, so they may need to limit activities such as lifting small children, pushing a large vacuum cleaner, or rearranging furniture. Speak to your doctor to see what activities may be right for you.

Transportation: This includes movement performed to get to and from a destination. Walking, riding a bike, driving, or riding in a car are all transportation-related activities. Upon reaching your destination, the transportation activities continue, typically in the form of walking. If you are permitted to ride a bicycle or motorized vehicle, such as an ATV, remember to wear a helmet. Such transportation modes may not be recommended for you, due to the risk of falling and bone fracture.

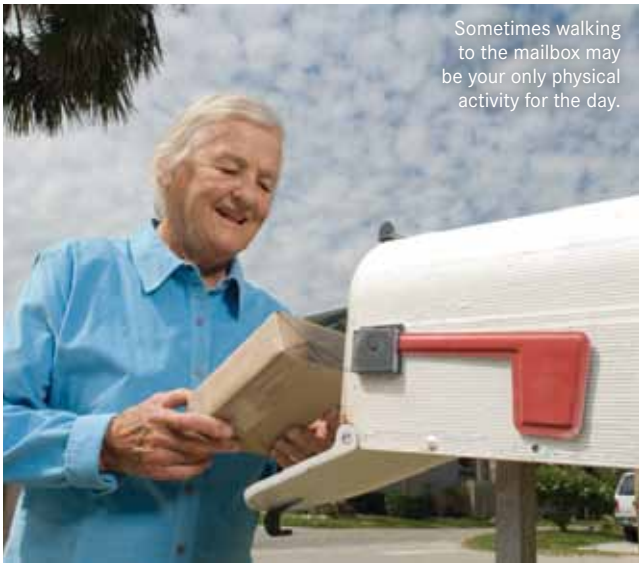
Your Activities of Daily Living

Now that you know about activities of daily living, think about your own life and your own physical, mental, and spiritual activities. There is no rule about how much physical activity a person living with bone metastases or bone lesions needs each day. This means that some days, you may feel like walking to the mailbox, while other days you won't. Patients should talk to their doctors about the level of activity that may be appropriate for them, depending on their condition.

Here are a few points to consider with your activities of daily living:

- **Measure your activities.** How active are you at home, at work, and outside of the home? If you want to measure your physical steps, obtain a pedometer and wear it for a day. Note not only the number of steps you took that day, but also your overall energy level, and your mental and spiritual strength. Be compassionate with yourself, and always congratulate yourself at the end of the day for your level of physical activity.

Staying hydrated while at work and home helps to reduce fatigue when physically active.



Sometimes walking to the mailbox may be your only physical activity for the day.

- **Be aware of how you feel physically, mentally, and spiritually.** Your "dose"of activities of daily living may be too much or too little. You are the best judge. If you are permitted to vacuum the rug, but find it too taxing, ask for help, use a broom to sweep the rug, or avoid vacuuming until you feel up to it. While at your job, taking the steps between floors may be too tiring. Use the elevator, walk with a friend, or avoid the steps on the days you don't feel up to it.

- **Ask a buddy to join you in your activities of daily living.** Invite a buddy or two at work to join you in preparing lunch or obtaining supplies. At home, enlist family members to help with meal preparation, household chores, and shopping, while you focus on your own needs. It's OK to ask for help when you need it! When traveling, go with a friend or family member to the store or market; the extra help comes in handy to push the cart and load the car.

Spring is a great time to take stock of your current activities of daily living, find new ways to be active, and learn which activities are right for you. Keep track of your activity level, and be aware of those activities that are uplifting or fatiguing. Inform your oncology team of any changes in your activity level that are unusual for you. Most of all, enjoy yourself!

Column author: Lisa Marie Bernardo, PhD, RN, HFS, is a certified cancer exercise trainer and health fitness specialist through the American College of Sports Medicine. She has more than 30 years of nursing experience and has published on a wide variety of health-related topics. She is certified as an instructor through Stott-Pilates, Yoga Alliance, and the GYROTONIC Expansion System. Contact Lisa at lisa@lisabernardo.com.

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Take advantage of all that's available to you.
Enroll in ZometaCares today.

Compass

*navigating bone metastases**

Compass—a program from Novartis Oncology designed to empower, inspire, and support patients

- Compass is a Web site that serves as the entry point to www.bonemets.com
- By signing up, enrollees will gain access to a series of informational e-mails about ZOMETA and bone metastases
- Upon enrollment into the program, users will be included into 1 of 3 possible segments
  - On ZOMETA
    Objective Adherence
  - Diagnosed with bone metastases but not on ZOMETA
    Objective Appropriate treatment
  - Diagnosed with cancer but not bone metastases
    Objective Awareness
- E-mails will include information on the complications of bone metastases and how ZOMETA may work to treat them, as well as additional lifestyle tips
- Healthcare providers and oncology nurses can offer Compass as a supportive and information-rich resource to their patients

* For prostate cancer patients, ZOMETA is only for those who have failed at least one hormonal therapy.

Highlights from Important Safety Information

Indication

ZOMETA (zoledronic acid) injection is indicated for the treatment of hypercalcemia of malignancy (HCM) and patients with multiple myeloma and documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy. Safe and efficacious use of ZOMETA has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.

Important Safety Information

- Hypersensitivity reactions, including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported
- Patients being treated with ZOMETA should not be treated with Reclast® (zoledronic acid)
- Patients treated for hypercalcemia of malignancy should be adequately rehydrated prior to administration of ZOMETA and have their electrolytes monitored during treatment
- Please see Important Safety Information

Please see accompanying full Prescribing Information.

ZOMETA®
(zoledronic acid) 4 mg/5 mL Injection

Bone-Healthy Recipes

Cooking With Katie: easy and delicious recipes rich in vitamin D and calcium.

Please consult your doctor regarding any potential food allergies you may have before trying these recipes.

Cooking With Katie author **Katie Huggard** is a chef at Schnucks in St. Louis, MO. Huggard is a graduate of Forest Park Culinary School and a member of the American Culinary Federation.

Easy Onion Cheese Bread

What you need...

4 slices of sourdough bread
½ cup cheddar cheese (shredded)
2 cloves of garlic (minced)
½ cup white onion (finely chopped)
2 tbsp margarine
1 tbsp olive oil

What you do...

Preheat oven to 350 degrees. Heat oil in small skillet over medium-high heat and sauté onion and garlic until thoroughly cooked and the garlic is lightly browned. Remove onion and garlic from heat. In a small bowl combine the cheese, onion, and garlic and mix. Spread margarine evenly on one side of each bread slice and top with the cheese mixture. Place the bread on a baking sheet and bake for 5-8 minutes or until cheese is completely melted. To serve, slice each piece of bread diagonally. Serves 4.

Scrambled Egg Stuffed Tomatoes

What you need...

6 large eggs
2 tbsp fresh basil (chopped)
2 tbsp fresh Italian flat leaf parsley (chopped)
3 garlic cloves (minced)
½ cup shredded cheddar cheese
6 tbsp milk
4 large, firm, ripe tomatoes
1 tbsp olive oil

What you do...

Preheat oven to 350 degrees. Cut a half-inch slice off the top of each tomato and reserve the tops. With a spoon, scoop out the seeds, pulp, and juice into a small bowl and place the tomatoes on a baking sheet. Heat the olive oil in a 12-inch skillet over medium heat. In a large bowl combine eggs, basil, parsley, garlic, cheese, milk, and 3 tablespoons reserved tomato juice and pulp, then whisk until the eggs yolks are broken and the ingredients are thoroughly mixed. Pour the egg mixture into the skillet and allow to cook, stirring occasionally to scramble the eggs. When the eggs are still runny but mostly cooked, remove the skillet from the heat. Divide the scrambled eggs into 4 portions and spoon 1 portion into each hollowed out tomato and replace the tomato caps. Place pan in the oven and cook for 8-10 minutes. Serves 4.

Grilled Banana and Strawberry Smoothie

What you need...

3 bananas
16 oz frozen strawberries
2 cups plain Greek yogurt
⅓ cup granulated sugar (more or less to taste)
4 graham crackers

What you do...

Peel the bananas, then grill them on a grill or stovetop until they are soft. Place the bananas in the refrigerator until cool, then slice into half-inch pieces. In your blender combine the yogurt, frozen strawberries, bananas, and sugar then blend until smooth. Serve in a chilled glass garnished with a graham cracker. Serves about 4.

Salmon BLT

What you need...

1 lb of salmon fillets (4 fillets)
½ lb cooked bacon (crumbled)
4 hamburger buns
1 head of romaine lettuce
2 roma tomatoes
½ cup plain Greek yogurt
1 lemon
3 gloves of garlic (minced)
1 tbsp salt (divided)
1 tbsp fresh ground pepper (divided)
1 tbsp extra virgin olive oil

What you do...

In a 12-inch skillet heat the oil over medium high heat. Using half the salt and half the pepper, salt and pepper the salmon fillets. Place salmon fillets face down in the skillet to sear the tops and cook for about 4 minutes on each side or until the salmon turns opaque and is thoroughly cooked. Using a spatula, remove the skin of each salmon, reserving only the meat and cover to keep warm. Meanwhile, in a small bowl, combine yogurt, garlic, the other half of the salt and pepper, and the zest of the lemon and mix until combined. Spread the yogurt mixture on both halves of each hamburger bun. Place one leaf of romaine lettuce on the bottom half of each bun and top with the salmon fillets. Slice the roma tomatoes and place 3 slices of tomato on top of each fillet, top with bacon, and top with the other half of the hamburger bun. Serves 4.

When Cancer spreads to the bone, choose to help protect against bone complications with ZOMETA*†

ZOMETA has helped reduce and delay bone complications[1,2]

- Since its FDA approval in 2002
- In more than 4 million people around the world

ZOMETA has helped people with bone metastases and bone lesions from the following types of cancer[1]:

- Multiple myeloma
- Breast cancer
- Prostate cancer*
- Lung cancer
- Other solid tumor types

*ZOMETA should not be given to people with prostate cancer unless hormone therapy did not work.

Highlights from Important Safety Information

- Hypersensitivity reactions, including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported
- Patients being treated with ZOMETA should not be treated with Reclast® (zoledronic acid)
- There have been reports of renal toxicity with ZOMETA. Renal toxicity may be greater in patients with renal impairment. Treatment in patients with severe renal impairment is not recommended. Do not use doses greater than 4 mg and monitor serum creatinine before each dose
- Osteonecrosis of the jaw has been reported. Preventive dental exams should be performed before starting ZOMETA and invasive dental procedures should be avoided
- Because ZOMETA can cause fetal harm, women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant
- Severe and occasionally incapacitating bone, joint, and/or muscle pain may occur. Discontinue ZOMETA if severe symptoms occur

Your doctor will monitor your kidney function before each dose. Tell your doctor if you are on other drugs, including aminoglycosides, loop diuretics, and drugs which may be harmful to the kidney.

Indication

ZOMETA (zoledronic acid) 4 mg/5 mL Injection is a treatment to reduce and delay bone complications due to multiple myeloma and bone metastases from solid tumors; used with anti-cancer medicines. ZOMETA is not an anti-cancer therapy. If you have prostate cancer, you should have failed treatment with at least one hormonal therapy prior to taking ZOMETA.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see full brief summary on pages 14-17.

†ZOMETA is given to reduce and delay bone complications from multiple myeloma and solid tumors that spread to the bone. ZOMETA is not an anticancer therapy. ZOMETA is given along with anticancer medicines.

References: 1. ZOMETA Prescribing Information. Novartis Pharmaceuticals Corporation. **2.** Data on file. Novartis Pharmaceuticals Corporation.

NOVARTIS ONCOLOGY

May 2010

ZOM-1007218

ZOMETA® (zoledronic acid) 4 mg/5 mL Injection

Indication

ZOMETA (zoledronic acid) injection is a treatment for hypercalcemia of malignancy (HCM; a condition resulting in high calcium blood levels due to cancer). ZOMETA is also used to reduce and delay bone complications due to multiple myeloma and bone metastases from solid tumors; used with anti-cancer medicines. ZOMETA is not an anti-cancer therapy. If you have prostate cancer, you should have failed treatment with at least one hormonal therapy prior to taking ZOMETA.

Important Safety Information

Do not use ZOMETA if you have had a severe allergic reaction to zoledronic acid or any components of ZOMETA. These reactions, including rare cases of hives and angioedema (swelling often near your eyes and lips), and very rare cases of life-threatening allergic reactions, have been reported. ZOMETA is in a class of drugs called bisphosphonates, and contains the same active ingredient as that found in Reclast® (zoledronic acid). If you are treated with ZOMETA, you should not be treated with Reclast.

If you have HCM, you should drink plenty of clear fluids before using ZOMETA. If you have kidney problems, tell your doctor. The risk of adverse reactions (especially related to the kidney) may be greater for you. ZOMETA treatment is not for patients with severe kidney problems. Patients with kidney problems on multiple cycles of ZOMETA or other bisphosphonates are at greater risk for further kidney problems. It is important to get your blood tests while you are receiving ZOMETA. Your doctor will monitor your kidney function before each dose. Tell your doctor if you are on other drugs, including aminoglycosides, loop diuretics, and drugs which may be harmful to the kidney.

Osteonecrosis of the jaw (ONJ) has been reported mainly in cancer patients treated with intravenous bisphosphonates, including ZOMETA. Many of these patients were also receiving anti-cancer drugs and corticosteroids, which may make it more likely to get ONJ. If you have advanced breast cancer or a type of cancer called multiple myeloma, or if you have had dental extraction, periodontal disease, local trauma, including poorly fitting dentures, you may be at greater risk of getting ONJ. Many reports of ONJ involved patients with signs of local infection, including bone/bone marrow inflammation. You should maintain good oral hygiene and have a dental examination with preventive dentistry prior to beginning ZOMETA. While on treatment, avoid invasive dental procedures, if possible, as recovery may take longer. If you develop ONJ while on bisphosphonate therapy, dental surgery may worsen the condition. If you require dental procedures, there are no data available to suggest whether stopping ZOMETA treatment reduces the risk of ONJ. A causal relationship between bisphosphonate use and ONJ has not been established. Based on your condition, your doctor will determine the treatment plan you will receive.

Do not use ZOMETA if you are pregnant or plan to become pregnant, or if you are breast-feeding.

Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates, including ZOMETA. Do not continue using ZOMETA if severe symptoms develop, as some patients had the symptoms reappear after taking ZOMETA or another bisphosphonate again. In aspirin sensitive patients, bronchoconstriction (tightening of the airways in the lungs) has been observed while taking bisphosphonates.

If you are an HCM patient with liver problems, talk to your doctor about whether ZOMETA is appropriate for you.

HCM patients may experience flu-like symptoms (fever, chills, flushing, bone pain and/or joint or muscle pain). Common side effects in HCM patients include fever, nausea, constipation, anemia, shortness of breath, diarrhea, abdominal pain, worsening of cancer, insomnia, vomiting, anxiety, urinary tract infection, low phosphate levels, confusion, agitation, a fungal infection called moniliasis, low potassium levels, coughing, skeletal pain, low blood pressure, and low magnesium levels. Redness and swelling may occur at the site that you are injected.

Common side effects for patients with multiple myeloma and bone metastases due to solid tumors include bone pain, nausea, fatigue, anemia, fever, vomiting, constipation, shortness of breath, diarrhea, weakness, muscle pain, anorexia, cough, joint pain, lower-limb swelling, worsening of your cancer, headache, dizziness (excluding vertigo), insomnia, decreased weight, back pain, numbness/tingling, and abdominal pain. These side effects are listed regardless of any potential association with the medications used in registration studies of ZOMETA in bone metastases patients.

Eye-related side effects may occur with bisphosphonates, including ZOMETA. Cases of swelling related to fluid build-up in the eye, as well as inflammation of the uvea, sclera, episclera, conjunctiva, and iris of the eye have been reported.

Patients with multiple myeloma and bone metastases from solid tumors should be taking an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of vitamin D daily.

Please see full Prescribing Information and talk to your doctor for more information.

Zometa® (zoledronic acid) Injection
Concentrate for Intravenous Infusion
Initial U.S. Approval: 2001

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Hypercalcemia of Malignancy

Zometa is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of >12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin (g/dL)).

1.2 Multiple Myeloma and Bone Metastases of Solid Tumors

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

1.3 Important Limitation of Use

The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions has not been established.

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Zoledronic Acid or Any Components of Zometa

Hypersensitivity reactions including rare cases of urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drugs with Same Active Ingredient

Zometa contains the same active ingredient as found in Reclast® (zoledronic acid). Patients being treated with Zometa should not be treated with Reclast.

5.2 Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia. Zometa should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

5.3 Renal Impairment

Zometa is excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased [*see Adverse Reactions (6.1)*]. Preexisting renal insufficiency and multiple cycles of Zometa and other bisphosphonates are risk factors for subsequent renal deterioration with Zometa. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zometa treatment in patients with hypercalcemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine >400 µmol/L or >4.5 mg/dL were excluded.

Zometa treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine >265 µmol/L or >3.0 mg/dL were excluded and there were only 8 of 564 patients treated with Zometa 4 mg by 15-minute infusion with a baseline creatinine >2 mg/dL. Limited pharmacokinetic data exists in patients with creatinine clearance <30 mL/min [*see Clinical Pharmacology (12.3) in the full prescribing information*].

5.4 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. Postmarketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures). Many reports of ONJ involved patients with signs of local infection including osteomyelitis.

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment [*see Adverse Reactions (6.2)*].

5.5 Pregnancy

Zometa should not be used during pregnancy**.** Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an IV dose if 4 mg based on an AUC comparison) resulted in pre- and postimplantation losses, decreases in viable fetuses and fetal skeletal, visceral, and external malformations. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use In Specific Populations (8.1)*].

5.6 Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. This category of drugs includes Zometa. The time to onset of symptoms varied from one day to several months after starting the drug. Discontinue use if severe symptoms develop. Most patients had relief of symptoms after stopping. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate [*see Adverse Reactions (6.2)*].

5.7 Patients with Asthma

While not observed in clinical trials with Zometa, there have been reports of bronchoconstriction in aspirin sensitive patients receiving bisphosphonates.

5.8 Hepatic Impairment

Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Hypercalcemia of Malignancy

The safety of Zometa was studied in 185 patients with hypercalcemia of malignancy (HCM) who received either Zometa 4 mg given as a 5-minute intravenous infusion (n=86) or pamidronate 90 mg given as a 2-hour intravenous infusion (n=103). The population was aged 33-84 years, 60% male and 81% Caucasian, with breast, lung, head and neck, and renal cancer as the most common forms of malignancy. NOTE: pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

Renal Toxicity

Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes [*see Warnings And Precautions (5) and Dosage And Administration (2) in the full prescribing information*].

The most frequently observed adverse events were fever, nausea, constipation, anemia, and dyspnea (see Table 3).

Table 3 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or Pamidronate 90 mg from the two HCM trials. Adverse events are listed regardless of presumed causality to study drug.

Table 3: Percentage of Patients with Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)	
Patients Studied				
Total No. of Patients Studied	86	(100)	103	(100)
Total No. of Patients with any AE	81	(94)	95	(92)
Body as a Whole				
Fever	38	(44)	34	(33)
Progression of Cancer	14	(16)	21	(20)
Cardiovascular				
Hypotension	9	(11)	2	(2)
Digestive				
Nausea	25	(29)	28	(27)
Constipation	23	(27)	13	(13)
Diarrhea	15	(17)	17	(17)
Abdominal Pain	14	(16)	13	(13)
Vomiting	12	(14)	17	(17)
Anorexia	8	(9)	14	(14)
Hemic and Lymphatic System				
Anemia	19	(22)	18	(18)
Infections				
Moniliasis	10	(12)	4	(4)
Laboratory Abnormalities				
Hypophosphatemia	11	(13)	2	(2)
Hypokalemia	10	(12)	16	(16)
Hypomagnesemia	9	(11)	5	(5)
Musculoskeletal				
Skeletal Pain	10	(12)	10	(10)
Nervous				
Insomnia	13	(15)	10	(10)
Anxiety	12	(14)	8	(8)
Confusion	11	(13)	13	(13)
Agitation	11	(13)	8	(8)
Respiratory				
Dyspnea	19	(22)	20	(19)
Coughing	10	(12)	12	(12)
Urogenital				
Urinary Tract Infection	12	(14)	15	(15)

The following adverse events from the two controlled multicenter HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug: Asthenia, chest pain, leg edema, mucositis, dysphagia, granulocytopenia, thrombocytopenia, pancytopenia, nonspecific infection, hypocalcemia, dehydration, arthralgias, headache and somnolence.

Rare cases of rash, pruritus, and chest pain have been reported following treatment with Zometa.

Acute Phase Reaction-like Events

Symptoms consistent with acute phase reaction (APR) can occur with intravenous bisphosphonate use. Fever has been the most commonly associated symptom, occurring in 44% of patients treated with Zometa 4 mg and 33% of patients treated with Pamidronate 90 mg. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, flushing, bone pain and/or arthralgias, and myalgias.

Mineral and Electrolyte Abnormalities

Electrolyte abnormalities, most commonly hypocalcemia, hypophosphatemia and hypomagnesemia, can occur with bisphosphonate use.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 4 and 5.

Table 4: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

	Grade 3			
Laboratory Parameter	**Zometa 4 mg**		**Pamidronate 90 mg**	
	n/N	**(%)**	**n/N**	**(%)**
Serum Creatinine[1]	2/86	(2%)	3/100	(3%)
Hypocalcemia[2]	1/86	(1%)	2/100	(2%)
Hypophosphatemia[3]	36/70	(51%)	27/81	(33%)
Hypomagnesemia[4]	0/71	—	0/84	—

Table 5: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials in Patients with HCM

	Grade 4			
Laboratory Parameter	**Zometa 4 mg**		**Pamidronate 90 mg**	
	n/N	**(%)**	**n/N**	**(%)**
Serum Creatinine[1]	0/86	—	1/100	(1%)
Hypocalcemia[2]	0/86	—	0/100	—
Hypophosphatemia[3]	1/70	(1%)	4/81	(5%)
Hypomagnesemia[4]	0/71	—	1/84	(1%)

[1]Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
[2]Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3]Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4]Grade 3 (<0.8 mEq/L); Grade 4 (<0.5 mEq/L)

Injection Site Reactions

Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Ocular Adverse Events

Ocular inflammation such as uveitis and scleritis can occur with bisphosphonate use, including Zometa. No cases of iritis, scleritis or uveitis were reported during these clinical trials. However, cases have been seen in post-marketing use [*see Adverse Reactions (6.2)*].

Multiple Myeloma and Bone Metastases of Solid Tumors

The safety analysis includes patients treated in the core and extension phases of the trials. The analysis includes the 2,042 patients treated with Zometa 4 mg, pamidronate 90 mg, or placebo in the three controlled multicenter bone metastases trials, including 969 patients completing the efficacy phase of the trial, and 619 patients that continued in the safety extension phase. Only 347 patients completed the extension phases and were followed for 2 years (or 21 months for the other solid tumor patients). The median duration of exposure for safety analysis for Zometa 4 mg (core plus extension phases) was 12.8 months for breast cancer and multiple myeloma, 10.8 months for prostate cancer, and 4.0 months for other solid tumors.

Table 6 describes adverse events that were reported by ≥10% of patients. Adverse events are listed regardless of presumed causality to study drug.

Table 6: Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)		Placebo n (%)	
Patients Studied						
Total No. of Patients	1031	(100)	556	(100)	455	(100)
Total No. of Patients with any AE	1015	(98)	548	(99)	445	(98)
Blood and Lymphatic						
Anemia	344	(33)	175	(32)	128	(28)
Neutropenia	124	(12)	83	(15)	35	(8)
Thrombocytopenia	102	(10)	53	(10)	20	(4)
Gastrointestinal						
Nausea	476	(46)	266	(48)	171	(38)
Vomiting	333	(32)	183	(33)	122	(27)
Constipation	320	(31)	162	(29)	174	(38)
Diarrhea	249	(24)	162	(29)	83	(18)
Abdominal Pain	143	(14)	81	(15)	48	(11)
Dyspepsia	105	(10)	74	(13)	31	(7)
Stomatitis	86	(8)	65	(12)	14	(3)
Sore Throat	82	(8)	61	(11)	17	(4)
General Disorders and Administration Site						
Fatigue	398	(39)	240	(43)	130	(29)
Pyrexia	328	(32)	172	(31)	89	(20)
Weakness	252	(24)	108	(19)	114	(25)
Edema Lower Limb	215	(21)	126	(23)	84	(19)
Rigors	112	(11)	62	(11)	28	(6)
Infections						
Urinary Tract Infection	124	(12)	50	(9)	41	(9)
Upper Respiratory Tract Infection	101	(10)	82	(15)	30	(7)
Metabolism						
Anorexia	231	(22)	81	(15)	105	(23)
Weight Decreased	164	(16)	50	(9)	61	(13)
Dehydration	145	(14)	60	(11)	59	(13)
Appetite Decreased	130	(13)	48	(9)	45	(10)

(continued)

Table 6: Percentage of Patients with Adverse Events ≥10% Reported in Three Bone Metastases Clinical Trials by Body System

	Zometa 4 mg n (%)		Pamidronate 90 mg n (%)		Placebo n (%)	
Musculoskeletal						
Bone Pain	569	(55)	316	(57)	284	(62)
Myalgia	239	(23)	143	(26)	74	(16)
Arthralgia	216	(21)	131	(24)	73	(16)
Back Pain	156	(15)	106	(19)	40	(9)
Pain in Limb	143	(14)	84	(15)	52	(11)
Neoplasms						
Malignant Neoplasm Aggravated	205	(20)	97	(17)	89	(20)
Nervous						
Headache	191	(19)	149	(27)	50	(11)
Dizziness (excluding vertigo)	180	(18)	91	(16)	58	(13)
Insomnia	166	(16)	111	(20)	73	(16)
Paresthesia	149	(15)	85	(15)	35	(8)
Hypoesthesia	127	(12)	65	(12)	43	(10)
Psychiatric						
Depression	146	(14)	95	(17)	49	(11)
Anxiety	112	(11)	73	(13)	37	(8)
Confusion	74	(7)	39	(7)	47	(10)
Respiratory						
Dyspnea	282	(27)	155	(28)	107	(24)
Cough	224	(22)	129	(23)	65	(14)
Skin						
Alopecia	125	(12)	80	(14)	36	(8)
Dermatitis	114	(11)	74	(13)	38	(8)

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in three clinical trials of Zometa in patients with bone metastases are shown in Tables 7 and 8.

Table 7: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

	Grade 3					
Laboratory Parameter	**Zometa 4 mg**		**Pamidronate 90 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Serum Creatinine[1]*	7/529	(1%)	4/268	(2%)	4/241	(2%)
Hypocalcemia[2]	6/973	(<1%)	4/536	(<1%)	0/415	—
Hypophosphatemia[3]	115/973	(12%)	38/537	(7%)	14/415	(3%)
Hypermagnesemia[4]	19/971	(2%)	2/535	(<1%)	8/415	(2%)
Hypomagnesemia[5]	1/971	(<1%)	0/535	—	1/415	(<1%)

[1]Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
*Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[2]Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3]Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4]Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5]Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Table 8: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Three Clinical Trials in Patients with Bone Metastases

	Grade 4					
Laboratory Parameter	**Zometa 4 mg**		**Pamidronate 90 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**	**n/N**	**(%)**
Serum Creatinine[1]*	2/529	(<1%)	1/268	(<1%)	0/241	—
Hypocalcemia[2]	7/973	(<1%)	3/536	(<1%)	2/415	(<1%)
Hypophosphatemia[3]	5/973	(<1%)	0/537	—	1/415	(<1%)
Hypermagnesemia[4]	0/971	—	0/535	—	2/415	(<1%)
Hypomagnesemia[5]	2/971	(<1%)	1/535	(<1%)	0/415	—

[1]Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)
*Serum creatinine data for all patients randomized after the 15-minute infusion amendment
[2]Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)
[3]Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)
[4]Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)
[5]Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Among the less frequently occurring adverse events (<15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 16% of patients in the Zometa 4 mg group compared with 9% in the pamidronate group. Decreased appetite was reported in slightly more patients in the Zometa 4 mg group (13%) compared with the pamidronate (9%) and placebo (10%) groups, but the clinical significance of these small differences is not clear.

Renal Toxicity
In the bone metastases trials, renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (<1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (≥1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials (see Table 9).

Table 9: Percentage of Patients with Treatment Emergent Renal Function Deterioration by Baseline Serum Creatinine*

Patient Population/Baseline Creatinine				
Multiple Myeloma and Breast Cancer	**Zometa 4 mg**		**Pamidronate 90 mg**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	27/246	(11%)	23/246	(9%)
Abnormal	2/26	(8%)	2/22	(9%)
Total	29/272	(11%)	25/268	(9%)
Solid Tumors	**Zometa 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9%)	1/20	(5%)
Total	18/165	(11%)	11/163	(7%)
Prostate Cancer	**Zometa 4 mg**		**Placebo**	
	n/N	**(%)**	**n/N**	**(%)**
Normal	12/82	(15%)	8/68	(12%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17%)	10/78	(13%)

*Table includes only patients who were randomized to the trial after a protocol amendment that lengthened the infusion duration of Zometa to 15 minutes.

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients with normal and abnormal baseline renal function, including patients treated with 4 mg infused over a 15-minute period. There have been instances of this occurring after the initial Zometa dose.

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of Zometa. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Osteonecrosis of the Jaw
Cases of osteonecrosis (primarily involving the jaws) have been reported predominantly in cancer patients treated with intravenous bisphosphonates including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids which may be a risk factor for ONJ. Data suggests a greater frequency of reports of ONJ in certain cancers, such as advanced breast cancer and multiple myeloma. The majority of the reported cases are in cancer patients following invasive dental procedures, such as tooth extraction. It is therefore prudent to avoid invasive dental procedures as recovery may be prolonged [*see Warnings And Precautions (5)*].

Musculoskeletal Pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported with bisphosphonate use [*see Warnings And Precautions (5)*].

Ocular Adverse Events
Cases of uveitis, scleritis, episcleritis, conjunctivitis, iritis, and orbital inflammation including orbital edema have been reported during postmarketing use. In some cases, symptoms resolved with topical steroids.

Hypersensitivity Reactions
There have been rare reports of allergic reaction with intravenous zoledronic acid including angioedema, and bronchoconstriction. Very rare cases of anaphylactic reaction/shock have also been reported.

Additional adverse reactions reported in postmarketing use include:

CNS: taste disturbance, hyperesthesia, tremor; ***Special Senses:*** blurred vision; ***Gastrointestinal:*** dry mouth; ***Skin:*** increased sweating; ***Musculoskeletal:*** muscle cramps; ***Cardiovascular:*** hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse primarily in patients with underlying risk factors); ***Respiratory:*** bronchoconstriction; ***Renal:*** hematuria, proteinuria; ***General Disorders and Administration Site:*** weight increase, influenza-like illness (pyrexia, asthenia, fatigue or malaise)

persisting for greater than 30 days; ***Laboratory Abnormalities****:* hyperkalemia, hypernatremia.

7 DRUG INTERACTIONS

In-vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. *In-vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In-vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

7.1 Aminoglycosides

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in Zometa clinical trials.

7.2 Loop Diuretics

Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia.

7.3 Nephrotoxic Drugs

Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

7.4 Thalidomide

No dose adjustment for Zometa 4 mg is needed when co-administered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zometa 4 mg given as a 15 minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1-14 and 200 mg once daily on days 15-28). Co-administration of thalidomide with Zometa did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Zometa should not be used during pregnancy. There are no studies in pregnant women using Zometa. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant [*see Warnings And Precautions (5.4)*].

Pregnancy Category D

Bisphosphonates are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. The extent of bisphosphonate incorporation into adult bone, and hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on fetal risk in humans, bisphosphonates do cause fetal harm in animals, and animal data suggest that uptake of bisphosphonates into fetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (intravenous versus oral) on this risk has not been established.

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups (≥0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of ≥0.07 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate-class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and postimplantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation (≤0.5 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses ≥0.05 times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

8.3 Nursing Mothers

It is not known whether Zometa is excreted in human milk. Because many drugs are excreted in human milk, and because Zometa binds to bone long term, Zometa should not be administered to a nursing woman.

8.4 Pediatric Use

Zometa is not indicated for use in children.

The safety and effectiveness of zoledronic acid was studied in a one-year active-controlled trial of 152 pediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine BMD of 0.431 gm/cm^2, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At one year, increases in BMD were observed in the zoledronic acid treatment group. However, changes in BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with Zometa use in children did not raise any new safety findings beyond those previously seen in adults treated for hypercalcemia of malignancy or bone metastases. However, adverse reactions seen more commonly in pediatric patients included pyrexia (61%), arthralgia (26%), hypocalcemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within 3 days after the first infusion and became less common with repeat dosing. Because of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with 0.05 mg/kg dose over 30 min. Mean C_{max} and $AUC_{(0\text{-last})}$ was 167 ng/mL and 220 ng.h/mL, respectively. The plasma concentration time profile of zoledronic acid in pediatric patients represent a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

8.5 Geriatric Use

Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

10 OVERDOSAGE

Clinical experience with acute overdosage of Zometa is limited. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In an open-label study of zoledronic acid 4 mg in breast cancer patients, a female patient received a single 48-mg dose of zoledronic acid in error. Two days after the overdose, the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal, and the patient was discharged seven days after the overdose.

A patient with non-Hodgkin's lymphoma received zoledronic acid 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paresthesia and abnormal liver function tests with increased GGT (nearly 100U/L, each value unknown). The outcome of this case is not known.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy [*see Dosage And Administration (2.4) in the full prescribing information*].

16 STORAGE

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured by
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T2011-01

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