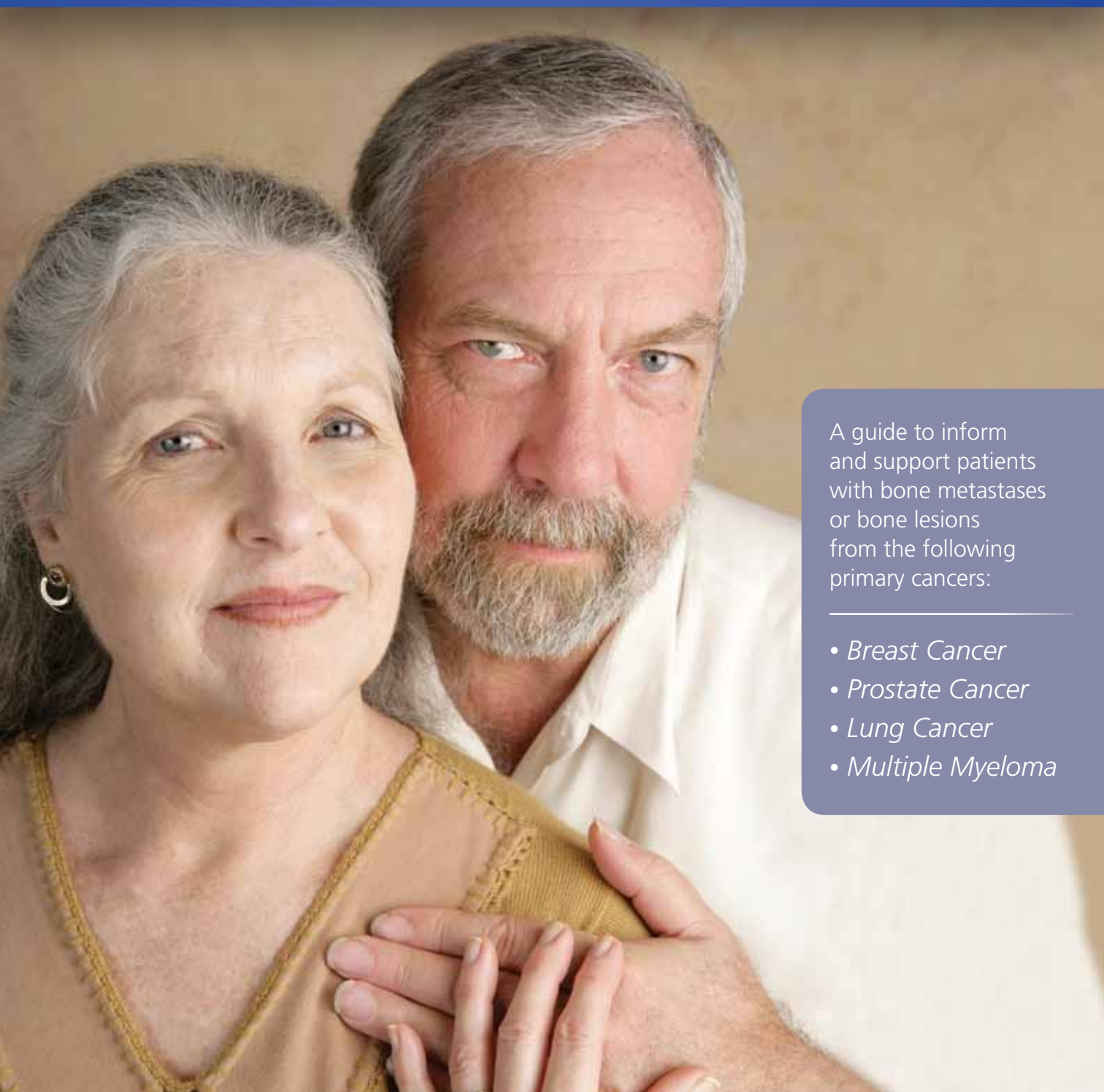
THE Educated Patient®

BONE METASTASES

WHEN CANCER SPREADS TO THE BONES

Resource Guide



A guide to inform and support patients with bone metastases or bone lesions from the following primary cancers:

- *Breast Cancer*
- *Prostate Cancer*
- *Lung Cancer*
- *Multiple Myeloma*

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 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 2-5.

†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 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 (mid-range of measured albumin in mg/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 of 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)

(continued)

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 (%)	
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 postmarketing 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; ***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. However, no *in-vivo* drug interaction studies have been performed.

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

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zometa is used in combination with thalidomide.

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*].

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

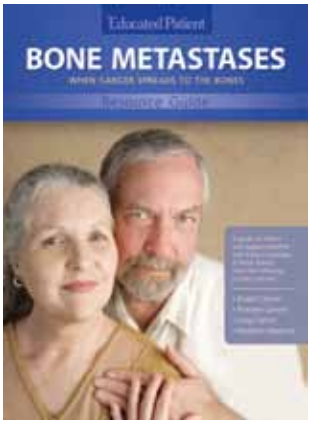
REV: OCTOBER 2009 T2009-101

Manufactured by:
Novartis Pharma Stein AG, Stein, Switzerland for
Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936

From the Publisher

Bone Metastases

A guide toward better care



Bone health poses an important consideration for many people. Many conditions, such as osteoporosis, poor blood supply, and infection, can affect the bones and cause pain. Patients with cancer need to pay extra close attention to how their bones feel, because, amongst other conditions, this type of pain can also be a symptom of bone metastases.

Bone metastases occurs when cancer that originated in one area of the body, such as the breast, prostate, or lung, spreads to the bones. Multiple myeloma, a cancer that starts in the bone marrow, can also cause bone lesions similar to bone metastases. Bone metastases should not be confused with primary bone cancer, which refers to cancer that *starts* in the bone.

Bone metastases can adversely affect a person's quality of life, not only leading to pain, but also to fractures or nervous system disorders. This resource guide discusses how bone metastases cause these problems as they develop and affect normal bone. The guide lists risk factors and treatments for this condition and provides questions for patients to ask their healthcare providers, to help them contend with uncomfortable symptoms.

This guide not only provides the basics on bone metastases, but it also provides online sources that will further patients' understanding, help them cope, and offer them the support they may need. The Web site resources in this guide narrow down the sometimes overwhelming flood of information found on the Internet, so patients can take a more active role in their care. These resources also provide opportunities for patients to communicate with other patients who may be experiencing similar health issues.

Many people live with bone metastases for years. The right resources and information can help patients make important decisions regarding their well-being. If you are a patient, you have already taken the first steps by opening this resource guide. We sincerely hope it will assist you in your discussions with your healthcare providers, and help you to pursue the highest possible level of care.

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Understanding Bone Metastases:

When Cancer Spreads to the Bones

BONES—most of us take them for granted. Although we go through most of our life not thinking much about them, bones have many jobs. They store minerals. They protect our organs. They allow us to stand and move. When cancer spreads to the bone, known as bone metastasis (meh-TASS-tuh-sis), any of these functions can be affected.

If you have bone metastases, it's important to learn as much as possible about your condition and treatment options. Understanding bone metastases can give you the information you need to team up with your doctor as you make decisions about your treatment. By taking an active role in your own care, you'll be taking an important step toward feeling more in control of your bone health.

What Are Bone Metastases?

Cancer can spread from where it originally began to other parts of the body through the bloodstream, despite treatment. This process is called **metastasis**. When cancer spreads to the bones, the condition is called **bone metastases**.[1]

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.[1]

Although cancer can spread to any bone in the body, metastases are most often found in the bones near the center of the body.[1] 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.[2] For example, if the original tumor was in the lung, and it spread to two or more bones, it would be called "lung cancer with bone metastases."

Bone metastases should not be confused with primary bone cancer, a rare disease, which starts at the bone.[2]

How Do Bone Metastases Damage the Bone?

Bone metastases can wear away portions of the bone, leaving small holes.[1] These holes cause the bone to be weaker and more fragile. Sometimes bone metastases can cause the build up of abnormal bone. This new, abnormal bone is weak and unstable.[1] In both cases, the bone metastases have made the bone more prone to break or collapse.[3] Because of this, 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.[2]

Who Gets Bone Metastases?

Some people with cancer develop bone metastases, and some do not.[1] Although it is impossible for doctors to predict which patients will develop bone metastases, certain risk factors can increase the likelihood of developing the condition.[1]

Certain types of cancer are more likely to spread to the bone. These include:

- Breast cancer
- Prostate cancer
- Lung cancer
- Multiple myeloma[1]

Multiple myeloma, also known as myeloma, is a cancer of the blood.[3] Metastases occur in almost all patients with multiple myeloma, in up to 75% of patients with advanced breast or prostate cancer, and in 30% to 40% of patients with lung cancer (see Table, "Cancer with

Cancers with High Incidence of Bone Metastases

Type of Cancer	Incidence
Myeloma	70% to 95%
Breast	65% to 75%
Prostate	65% to 75%
Lung	30% to 40%
Melanoma	14% to 45%

Roodman GD. Chapter 2: Pathophysiology of Bone Metastases. In: Kardamakis D, Vassiliou V, Chow E, (eds). Bone Metastases: A Translational and Clinical Approach. Springer Science + Business Media; 2009:31.

High Incidence of Bone Metastases.").[4] People with large tumors or tumors that have spread to the lymph nodes are more likely to have their cancer spread to bones.[1] Lymph nodes are small, pea-sized organs that act as filters or traps for foreign particles. They are important for the proper functioning of the immune system, which protects people against disease.[1]

When a cancer is first discovered after it has spread to other organs, a patient's risk of bone metastases increases.[2] If the cancer is detected early, before it spreads, a person may have a better chance of successful treatment and a lower risk of bone metastases.[2]

Symptoms & Complications

Bone metastases can damage the bone and produce many different problems that can affect overall health.Receiving treatment for bone metastases as early as possible may help prevent complications later.[1]

Common symptoms and side effects of bone metastases may include:

Bone pain. Pain is the most common symptom of bone metastases and is usually the first symptom that patients notice. Bone pain often results from fractured bone or spinal cord damage. At first, the pain may come and go. It may tend to be worse at night or with bed rest. Eventually, the pain may increase and become severe.[5]

Because bone pain is usually the earliest symptom of bone metastases, it's important for patients to pay attention to how their bones feel.[1] They should tell their doctor about any pain, even if they think it might be due to some other problem, such as arthritis or stiffness from lack of activity. Not all pain indicates metastases.[5] A doctor can help patients distinguish between pain from metastases and other aches and pains.

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.[5]

Spinal cord compression. When cancer spreads to the spine, it can squeeze (compress) the spinal cord.[5] 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 room. 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).[1]

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[5]:

- 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.[1]

Patients need to tell their doctor right away if they have any new bone symptoms or changes in old symptoms. Treating the symptoms of bone metastases early may help reduce the chances of developing more problems later on.[1]

Treatment

When a patient hears that he or she has bone metastases, it is difficult, but knowing that there are many treatment options available to help manage any symptoms or complications should be reassuring.

When a doctor determines the need for treatment, understanding all of the options is important for the patient. Below are brief descriptions of the different kinds of treatment available for bone metastases. Selecting the right treatment approach will depend on what type of cancer the patient has, the extent of the metastases, and other individual characteristics.

Radiation therapy. Radiation can help ease bone pain caused by cancer. Radiation is a beam of energy aimed at the cancer that has spread to the bones. Doctors do this to help shrink or slow down cancer growth. Radiation is usually given several times to the place that needs treatment. If the bone is too weak, doctors may first have to reinforce the bone through surgery.[1]

Surgery. A doctor may recommend surgery on the patient's bone to ease pain and to keep it from breaking. To do this, doctors may place metal or glue in the bone to support it. After surgery, the patient may need to stay in the hospital for several weeks. It may take several months before they can put weight on the affected bone.[1]

RANKL Inhibitor. Bone metastases cause increased levels of a substance called RANKL, which is important in how bone is formed and reformed.[6] Higher RANKL levels cause osteoclasts to destroy bone.[6] A drug that acts against the RANK-L substance, called denosumab was recently approved for the prevention of skeletal-related events in patients with bone metastases; however, it is not indicated for multiple myeloma patients.[6,7] When patients with breast cancer that has spread to the bone, took denosumab in clinical trials, it helped prevent problems like fractures.[6] The medicine is administered every 4 weeks via needle inserted just under the skin (subcutaneously).[7]

Questions for the Doctor

Knowing what questions to ask the healthcare provider can help patients secure the answers they need to make cancer treatment decisions that are right for them. Below are some sample questions for patients to ask at their doctor visits:

Are there possible complications from bone metastases? If so, what preventive measures can I take?

What are my treatment options?

What are the risks and benefits of each kind of treatment?

What are the side effects of each treatment, and what can I do to help reduce or manage these side effects?

How will we know if treatment is working?

How will I know if any pain I experience is from bone metastases or something else (such as arthritis)?

How will each treatment affect my daily life or that of my loved one?

Are there new treatments or clinical trials that I should consider?

Should I have routine bone tests to monitor the health of my bones?

Bisphosphonates (bis-FOSS-fuh-nates): A doctor may prescribe bisphosphonates to help reduce and delay bone problems from cancer that has spread to the bones. Healthy bones are always active. To keep bones strong, one type of cell (called osteoclasts) removes old bone, while another type of cells (called osteoblasts) builds up brand new bone. Bisphosphonates work by stopping osteoclasts from removing too much bone and by stopping osteoblasts from building bone in the wrong place. Bisphosphonates are given as an infusion every 3 or 4 weeks, usually at the patient's doctor's office or wherever he or she receives cancer treatments. These treatments have been widely used since 1995 to prevent serious bone problems in people with cancer that has spread to the bones.[1]

Other Therapies

Build strength: Several measures can be taken to help strengthen the bones. For example, physical therapy can help restore maximum function. In addition, a doctor may recommend that a patient take the following oral supplements every day:

- **Calcium**, to help fortify the bones
- **Vitamin D**, to help the body absorb and use calcium.[8]

Fight pain: Many different drugs or combinations of drugs can be used to treat pain from bone metastases. A patient should speak with his or her physician or treatment team to learn more about available treatment options. Nondrug approaches to managing pain include the use of hot and cold compresses, relaxation techniques, and therapeutic beds or mattresses.[1]

Together, a patient and his or her doctor can discuss the various alternative therapies and decide which one(s)are appropriate for the particular patient.

Taking Control

Regular physical activity can help improve how well patients function physically, as well as their quality of life. Before beginning any type of physical activity, patients need to check with their doctors. The following tips can help them get started. With a doctor's permission:

The Treatment Team

Depending on the type of cancer, the treatment team may include:

MEDICAL ONCOLOGIST
A doctor who specializes in diagnosing and treating cancer.

ONCOLOGY NURSE
A nurse who specializes in helping people with cancer, and who may also be responsible for administering treatment, ordering tests, and prescribing medication under a doctor's supervision.

ONCOLOGY SOCIAL WORKER OR COUNSELOR
A social worker or counselor who specializes in helping patients and loved ones cope with the emotional impact of cancer and who may also help identify other needed resources.

ORTHOPEDIC ONCOLOGIST
A medical doctor and surgeon who specializes in diagnosing and treating bone tumors. You may be referred to an orthopedic oncologist for a bone fracture.

PATHOLOGIST
A doctor who specializes in diagnosing cancer by studying tissue, fluid, or blood.

PATIENT NAVIGATOR
A nurse, social worker, or trained lay person who assists patients and loved ones on their journey through the healthcare system.

RADIATION ONCOLOGIST
A doctor who specializes in treating cancer using various forms of radiation by directing it on the tumor site in the body.

SURGEON
A doctor who performs surgeries to remove cancerous growths in the body.

A patient's personal role in his or her own care can't be overstated. By being informed about the disease patients may be better able to make decisions that are right for them.

- **Start slowly and build up gradually** to avoid injuries. Exercise just a few minutes a day in the beginning, and gradually increase the time and intensity of the workouts to a level the doctor has recommended.
- **Choose aerobic exercises** that are weight-bearing, such as walking, dancing, and climbing stairs.
- **Lift weights** to help strengthen bones and muscles.[9] If the patient has been inactive recently, they should start with *very* light weights and few repetitions.

A patient's personal role in his or her own care can't be overstated. By being informed about their disease patients may be better able to make decisions that are right for them. Following are some suggestions for patients to help them prepare to talk with their doctor.

- **Be prepared for every office visit.** Before each medical appointment, take some time to write down any questions or concerns.
- **Stay active during doctor appointments.** Take notes during appointments, and write down any instructions a doctor gives you so you can remember them once you leave the office.
- **Make sure you understand everything your doctor says.** If anything is unclear, ask your doctor to repeat it.
- **Keep all appointments.** It's important to attend all of your doctor and treatment appointments to ensure the best outcome. If you're not feeling well or you're fatigued, ask someone to drive you to your appointments and stay with you.

Finding Support

Finding support through family, friends, or local support groups can help patients deal with the emotional effects of cancer. Being able to share frustrations and feelings with family and friends is important.

Ask others for help. In many cases friends, family, and members of the community may want to help but they don't know how. The following strategies may help patients to involve these people:

- Make a list of things with which you'd like help. When someone asks if they can help, give them an assignment from your list.
- Get rides to your doctor appointments. Ask people close to you to stay with you during doctor visits and take notes about what your doctor says
- 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. Your doctor or hospital 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 doesn't meet your needs, don't hesitate to try another.

The list of online resources on the following pages offers support and information to help patients take control of their disease. ■

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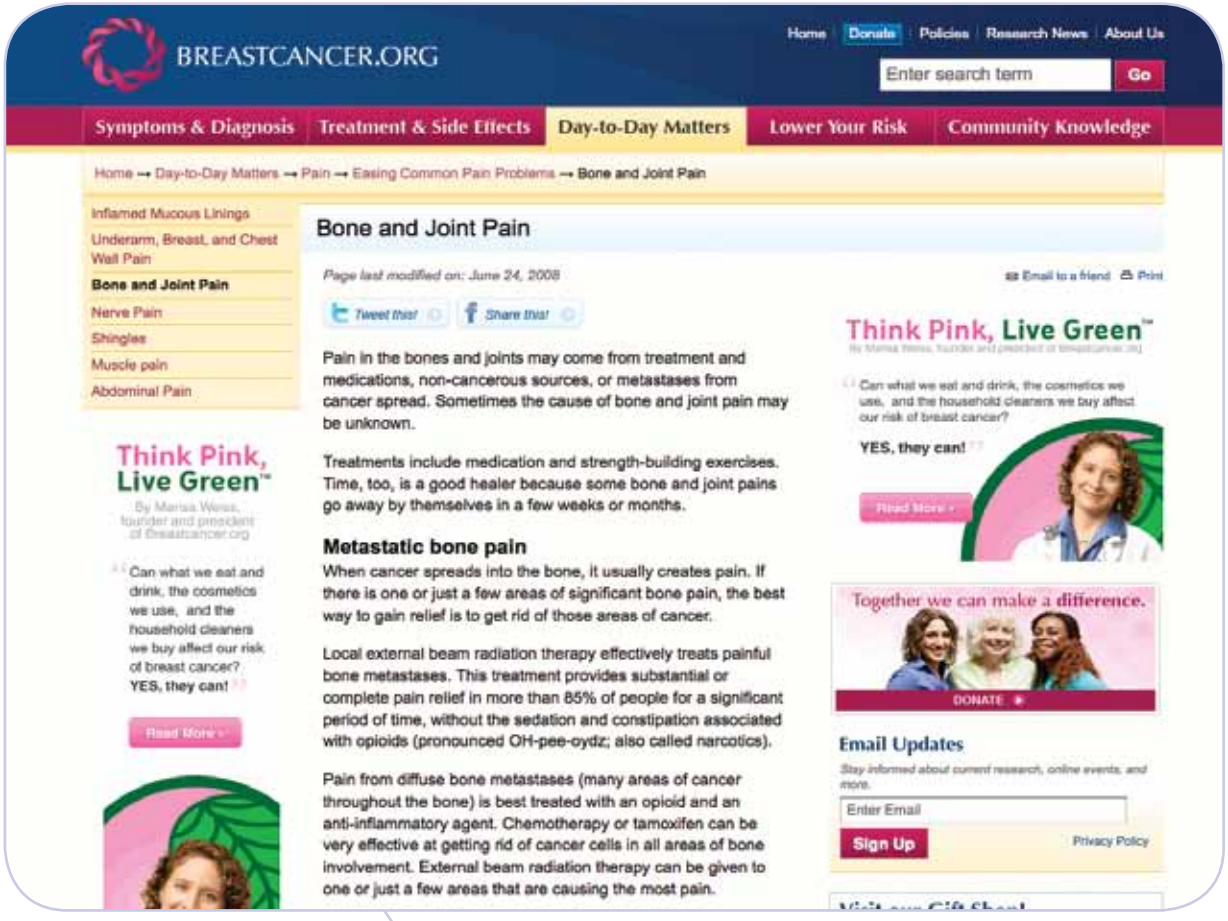
Breastcancer.org

www.breastcancer.org



ADDRESS:
7 E. Lancaster Ave.
3rd Floor
Ardmore, PA 19003

CONTACT INFO:
Phone: (610) 642-6550
E-mail: comments@breastcancer.org

Breastcancer.org is a nonprofit organization that provides accurate and up-to-date information to patients with breast cancer. A section on metastatic bone pain can be found by selecting Day-to-Day Matters at the top of the page, then clicking Pain in the side bar, followed by Easing Common Pain Problems (again in the side bar), and Bone and Joint Pain. This section explains metastatic bone pain and common treatments. Day-to-Day Matters also includes a section on Bone Health, tailored specifically to patients with cancer.

Breast Cancer Network of Strength

www.networkofstrength.org

ADDRESS:
135 S. LaSalle St.
Suite 2000
Chicago, IL 60603

CONTACT INFO:
Phone: (800) 221-2141
Spanish: (800) 986-9505
E-mail: yourshoes@networkofstrength.org

The Breast Cancer Network of Strength was developed to provide support and information to women with breast cancer. For information on bone metastasis, follow the Programs & Services link in the navigation bar, then select ShareRing Transcript Archives from the side menu. Here, you can download PDFs of teleconference transcripts, including Treating Metastatic Breast Cancer and Managing Bone Health and Bone Metastases. More information can be found by choosing the Information tab at the top, then selecting the following sequence of links: Breast Cancer Diagnosis, Recurrent and Advanced Breast Cancer, Treatment Options by Location, and Cancer in Bones.

Living Beyond Breast Cancer

www.lbbc.org

ADDRESS:
354 West Lancaster Ave.
Suite 224
Haverford, PA 19041

CONTACT INFO:
Phone: (610) 645-4567
E-mail: mail@lbbc.org

Living Beyond Breast Cancer (LBBC), founded in 1991 by radiation oncologist Marisa C. Weiss, MD, addresses a woman's need for breast-cancer-related information, connection and support after completing treatment. The foundation's mission is to empower all women affected by breast cancer to live as long as possible with the best quality of life. The website offers an array of information for breast cancer patients such as: Breast Cancer Basics, Beyond the Basics, Breast Cancer News, and information on clinical trials and research studies. In the Guides to Understanding Breast Cancer, you will find a full-color, downloadable guide on bone health with sections such as Bone Health Basics, How Treatments Affect Your Bones, Testing and Scores, Using Lifestyle Changes to Improve Bone Health, Medical Treatments for Bone Loss, and Moving Forward.

Susan G. Komen for the Cure

ww5.komen.org

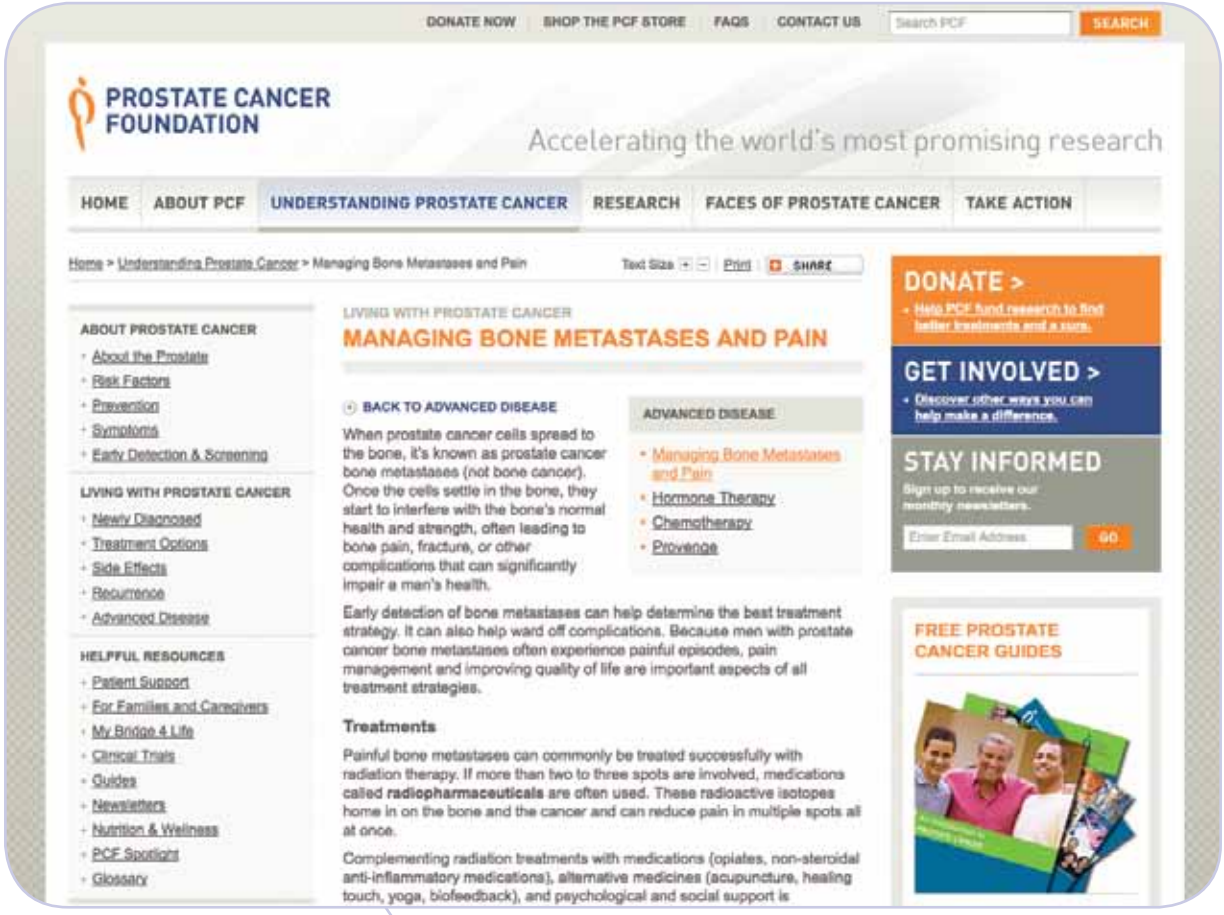
ADDRESS:
5005 LBJ Freeway
Suite 250
Dallas, TX 75244

CONTACT INFO:
Phone: (877) GO-KOMEN
(877) 465-6636
E-mail: Online

Susan G. Komen for the Cure provides information and support to women with breast cancer. For information on bone pain and bone metastases, highlight Understanding Breast Cancer, then select Understanding Breast Cancer Guide in the drop down menu. Toward the middle of the page, select Pain management related to metastatic breast cancer and Additional care for metastatic breast cancer under the "Metastatic Breast Cancer" section. To read about bisphosphonates and bone health, go to Komen Perspectives under the Research & Grants tab in the top navigation bar.

Prostate Cancer Foundation

www.pcf.org



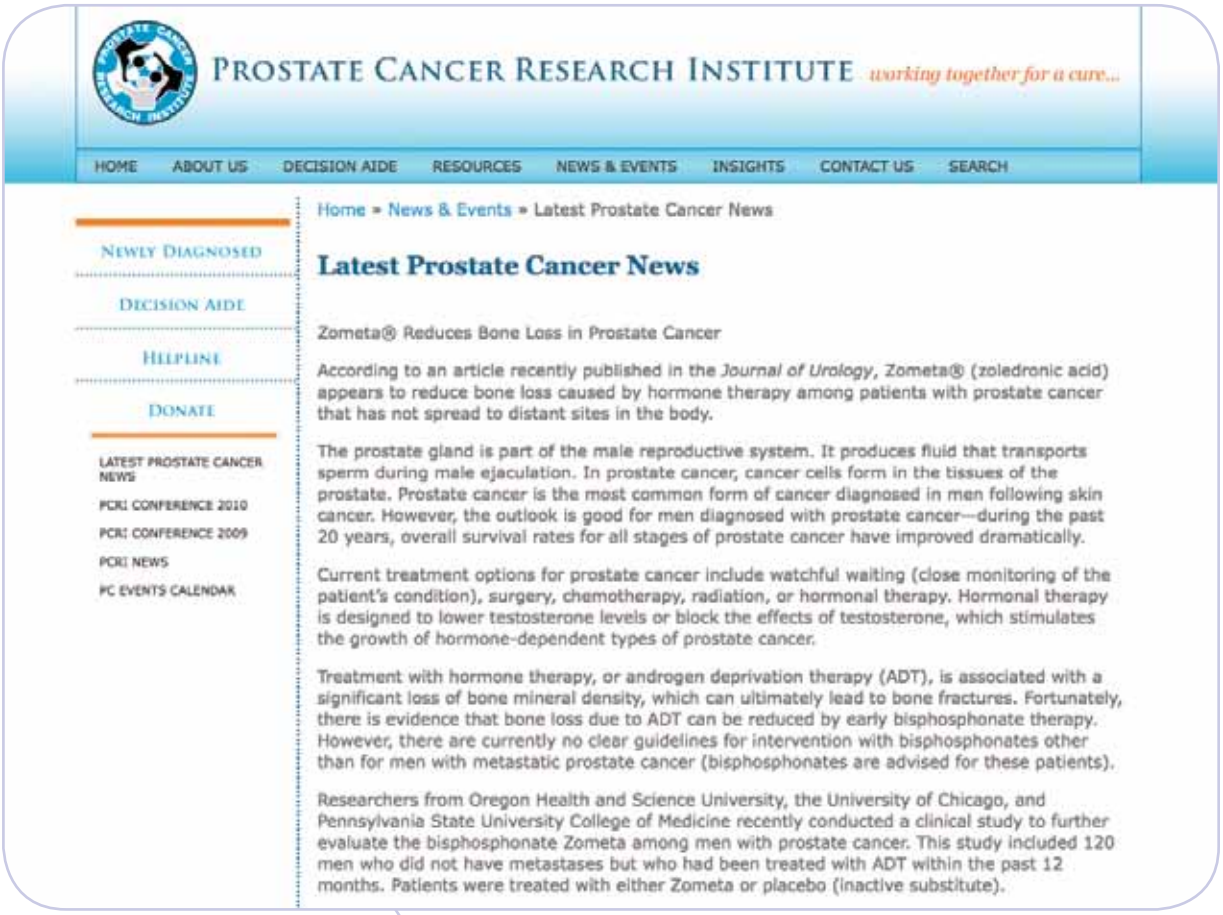
ADDRESS:
1250 Fourth Street
Santa Monica, CA 90401

CONTACT INFO:
Phone: 1(800)757-CURE [2873]
E-mail: info@pcf.org

The Prostate Cancer Foundation funds prostate cancer research worldwide and provides information for patients at its Web site. Highlighting Understanding Prostate Cancer on the home page brings up a drop-down menu. Selecting Advanced Disease will take you to a page that links to a section on Managing Bone Metastases and Pain. You can also find some discussion of bone complications under PSA Rising During Hormone Therapy, also found at Understanding Prostate Cancer.

Prostate Cancer Research Institute

www.prostate-cancer.org



ADDRESS:
5777 W. Century Blvd.
Suite 800
Los Angeles, CA 90045

CONTACT INFO:
Phone: (310) 743-2116
E-mail: info@pcri.org

The Prostate Cancer Research Institute was founded by medical oncologists to educate patients and their families about prostate cancer. By going to News & Events from the Home page, visitors can find the Latest Prostate Cancer News, which includes recent news and a Prostate Cancer News Archive, which separates recent news by topic. Some topics include information on screening and prevention, as well as articles geared toward early, locally-advanced, and metastatic prostate cancer.

Us TOO International

www.ustoo.org

ADDRESS:
5003 Fairview Avenue
Downers Grove, IL

CONTACT INFO:
Phone: (800) 808-7866
E-mail: ustoo@ustoo.org

Us TOO International is a prostate cancer education and support network. The organization, a 501-c-3, nonprofit organization, was started in 1990 by prostate cancer survivors for prostate cancer patients, survivors, their spouses/partners and families. If you select Post-Treatment Issues from the About Prostate Cancer section, then you can choose the Bone Health link at the top of the page to obtain information on bone metastases. Within the Bone Health section you will find links to information on spinal fractures, tips on bone health, and an article on dental health. There is a free, colorful brochure, "What You Need to Know for Better Bone Health" that includes information on signs and symptoms of bone metastases, treatment options, and recommendations for better care.

Lung Cancer Alliance

www.lungcanceralliance.org

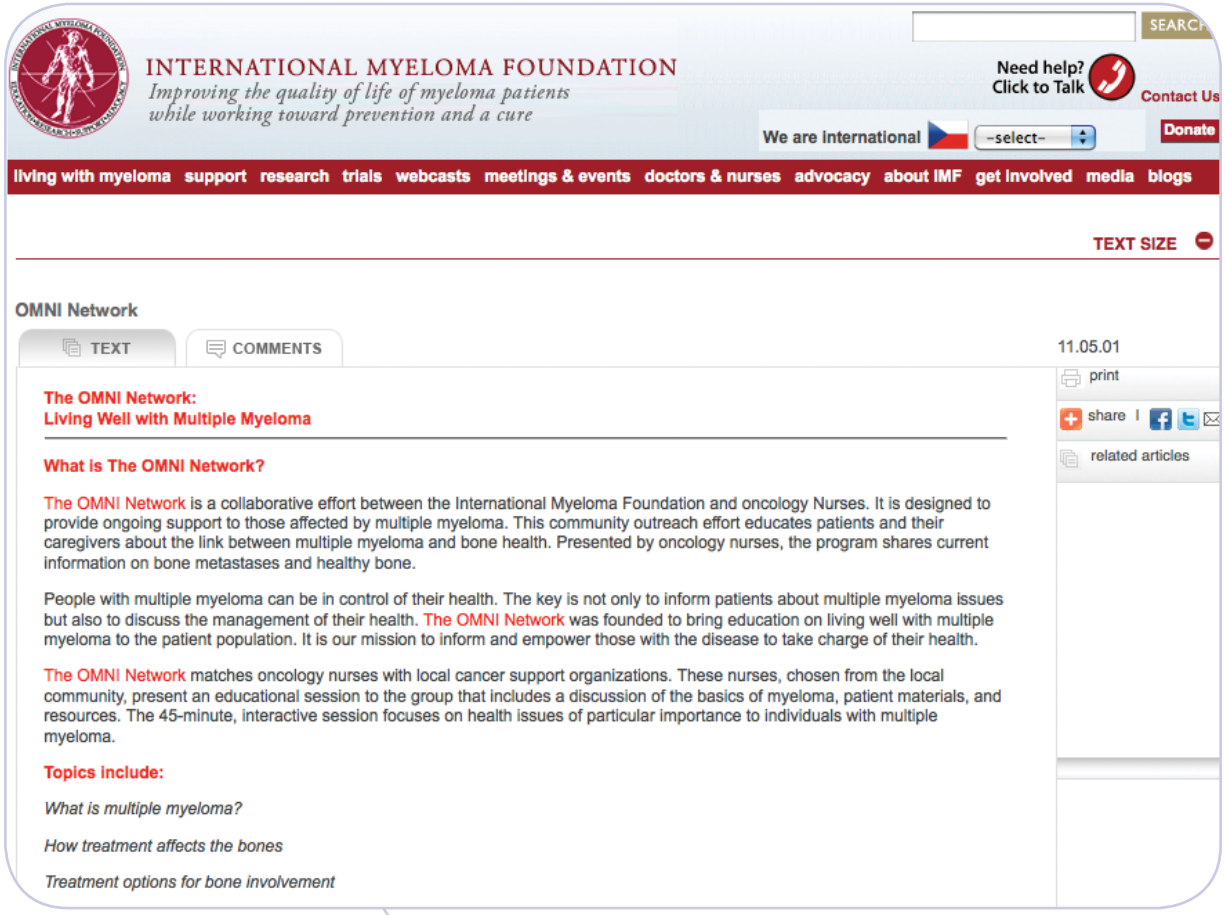
ADDRESS:
888 16th St. NW
Suite 150
Washington, DC 20006

CONTACT INFO:
Phone: (202) 463-2080
(800) 298-2436
E-mail: info@lungcanceralliance.org

The Lung Cancer Alliance (LCA) is a national nonprofit organization dedicated to supporting patients with lung cancer and keeping them informed. Several resources on the Web site address how bone metastases might affect patients with lung cancer. Information can be found under the Facing Lung Cancer tab, in the About Lung Cancer section. You can also read about patients who have experienced bone metastases in Stories of Hope in the Support section. LCA helps match patients with lung cancer to appropriate clinical trials.

International Myeloma Foundation

www.myeloma.org

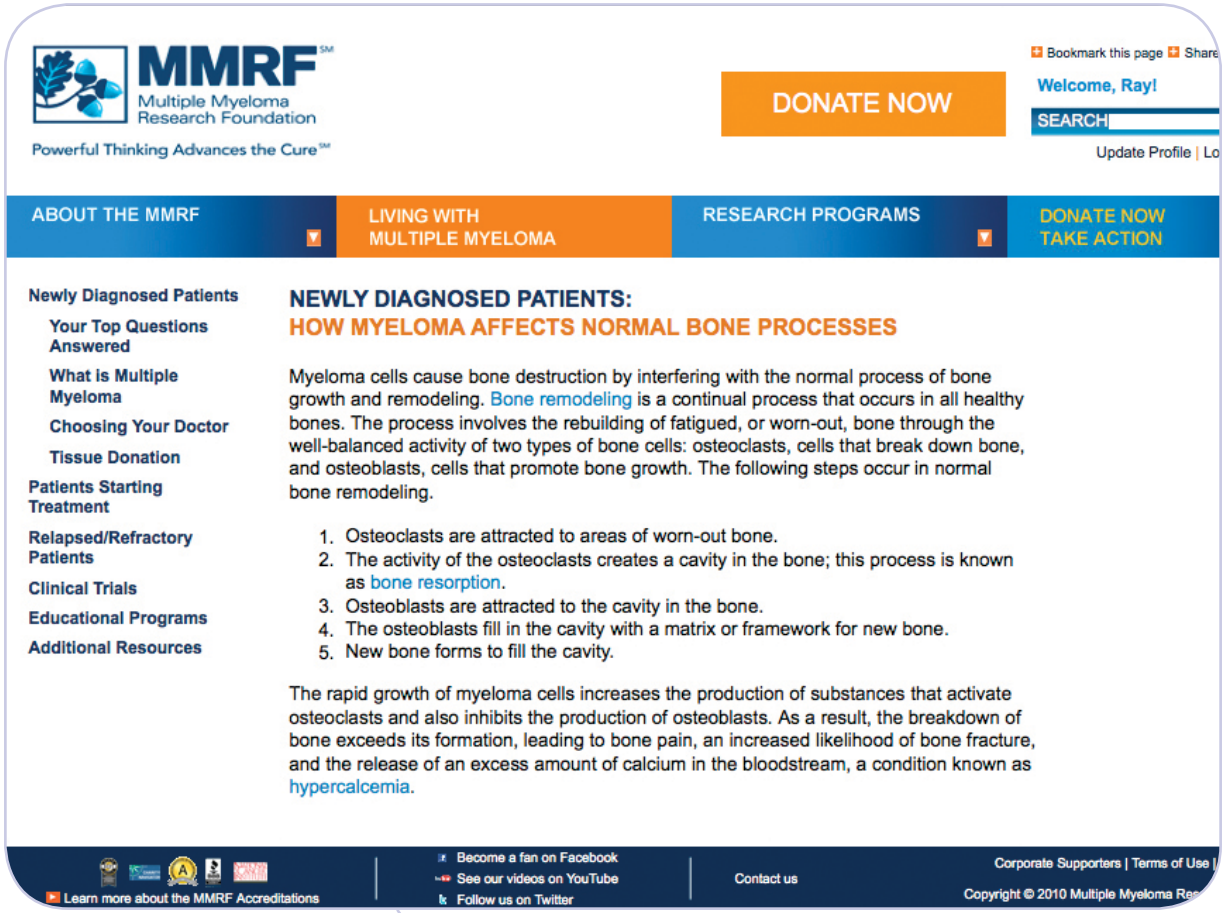


ADDRESS:
12650 Riverside Drive
Suite 206
North Hollywood, CA 91607
CONTACT INFO:
Phone: (800) 452-2873
(818) 487-7455
E-mail: TheIMF@myeloma.org

While multiple myeloma is not metastatic cancer, this hematologic malignancy is characterized by destructive, progressive bone diseases. In addition to supporting research on myeloma's causes and cures and advocating on behalf of patients, the International Myeloma Foundation provides overviews on every aspect of the disease. Typing "bone" into the search field at the top of the page brings up a list of resources, including a link to a section containing Bone Articles, which features Webcasts and discussions with physicians on bone disease in myeloma.

Multiple Myeloma Research Foundation

www.themmrf.org



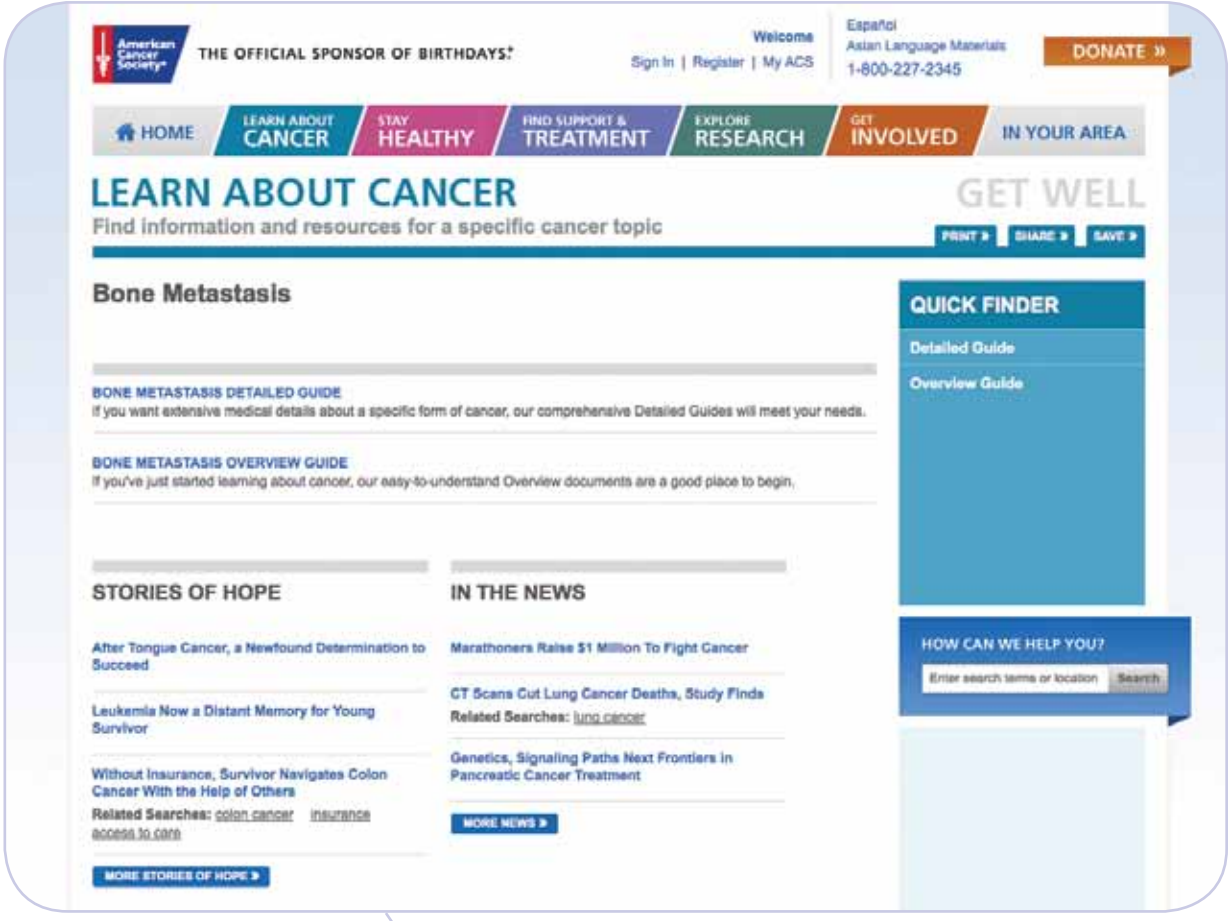
ADDRESS:
383 Main Avenue
5th Floor
Norwalk, CT 06851

CONTACT INFO:
Phone: (203) 229-0464
E-mail: info@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.

American Cancer Society

www.cancer.org



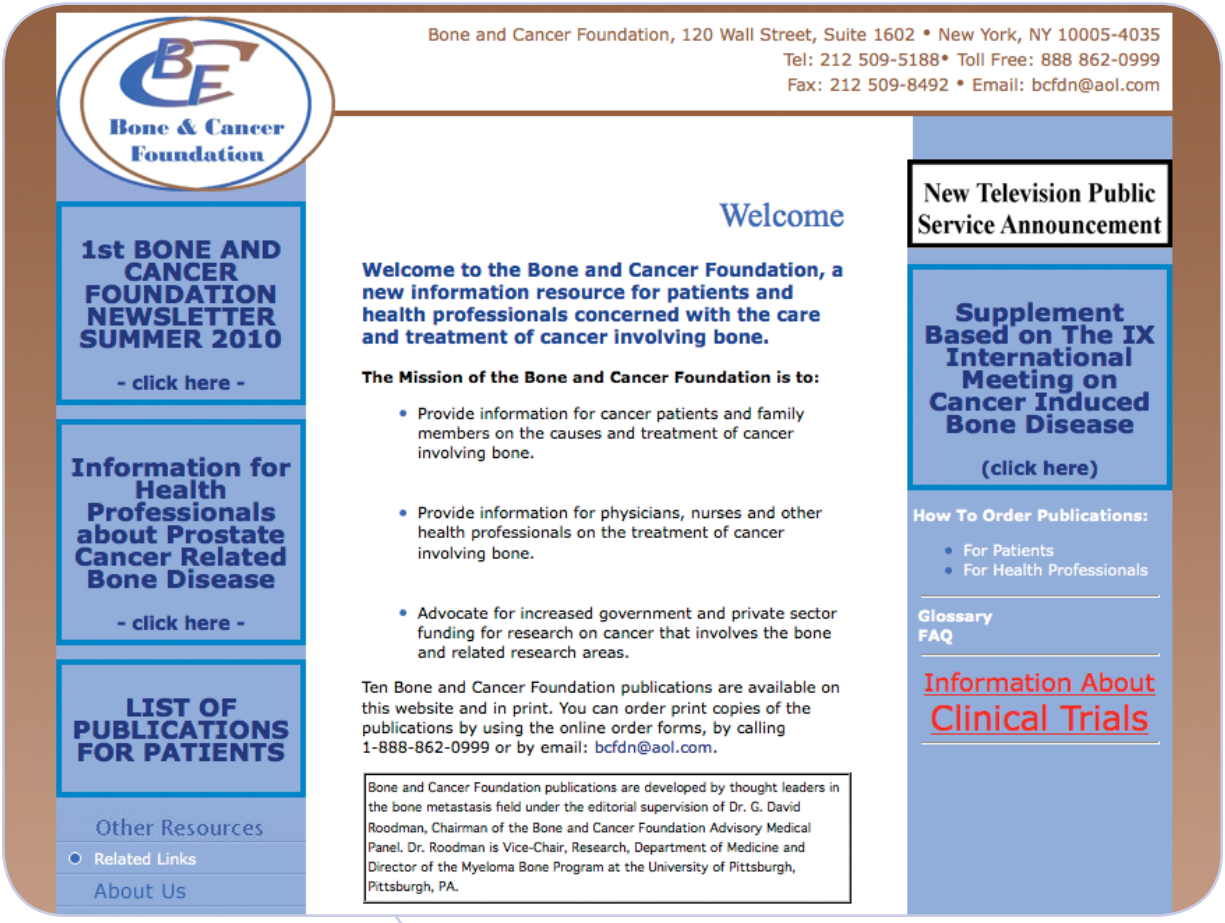
ADDRESS:
National Home Office
1599 Clifton Road NE
Atlanta, GA 30329-4251

CONTACT INFO:
Phone: (800) 227-2345
E-mail: Online

The American Cancer Society offers information and support to patients with every type of cancer and to caregivers. To find information on bone metastases, highlight Learn About Cancer in the navigation bar, click Show All Cancer Types, and select Bone Metastasis. This section offers a Bone Metastasis Overview Guide for patients who have just begun to learn about cancer and a Bone Metastasis Detailed Guide for patients seeking extensive medical information on this complication of cancer.

Bone and Cancer Foundation

www.boneandcancerfoundation.org



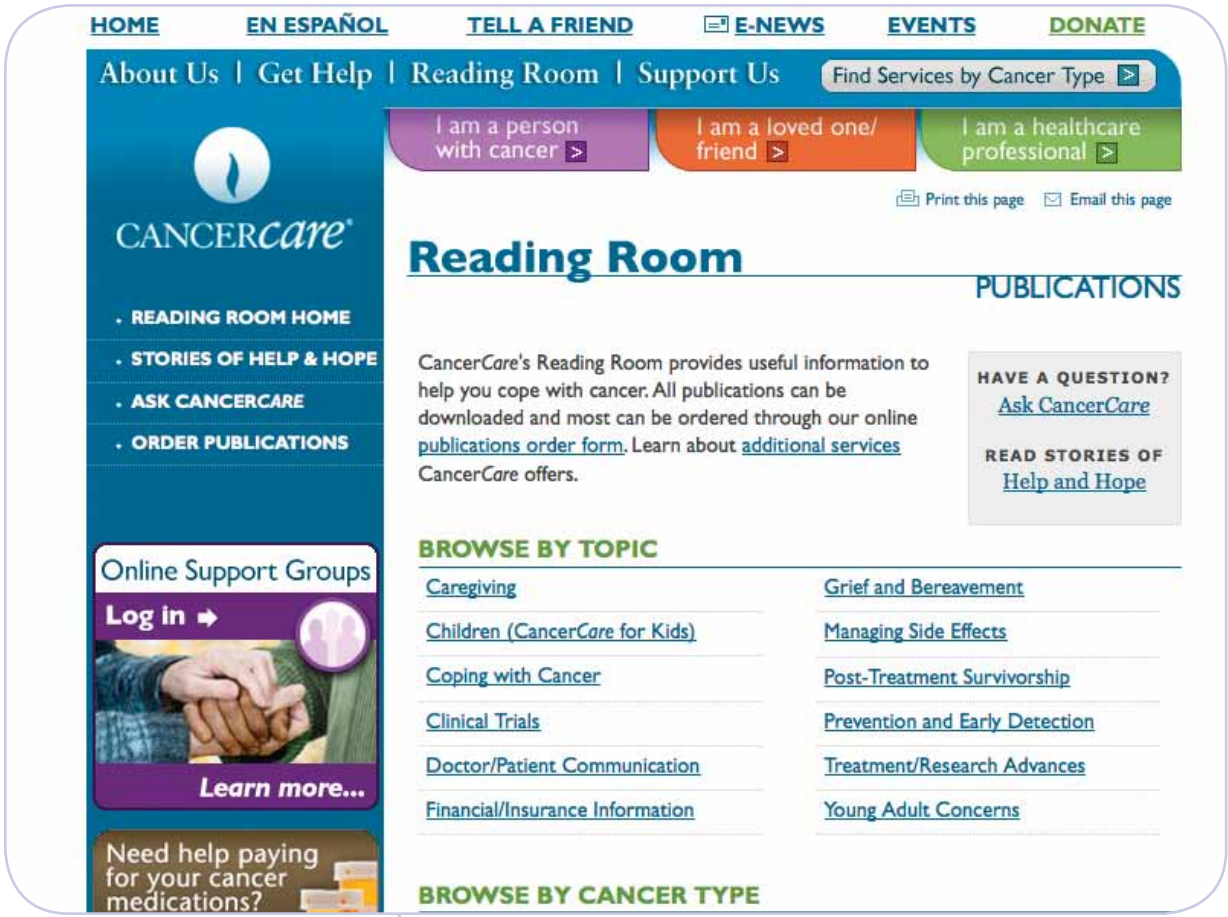
ADDRESS:
120 Wall Street
Suite 1602
New York, NY 10005-4035

CONTACT INFO:
Phone: (212) 509-5188
E-mail: bcfdn@aol.com

The Bone and Cancer Foundation serves as an information resource for patients and healthcare professionals on the treatment of bone cancer and bone metastases. The side bar includes a link to a List of Publications for Patients. This section features articles on Managing Pain Related to Cancer and Bone, Surgical Management of Cancer that Spreads to the Bone, and Questions & Answers About Prostate Cancer, Bone Metastases and Treatment-Related Osteoporosis, along with articles on bone complications associated with breast cancer, lung cancer, and myeloma bone disease.

CancerCare

www.cancercare.org



ADDRESS:
275 Seventh Avenue
Floor 22
New York, NY 10001

CONTACT INFO:
Phone: (212) 712-8400
(800) 813-HOPE
E-mail: info@cancercare.org

CancerCare is a national nonprofit organization dedicated to providing information and support to patients with cancer and their loved ones. The Reading Room link at the top of the page brings up an archive of downloadable publications, sorted by category. The Prostate section under "Browse by Cancer Type" contain articles on bone health. To find podcasts on bone health, select I am a person with cancer or Get Help on the home page, followed by Find Help by Diagnosis in the menu on the left, then navigate to the prostate and breast cancer pages.

Compass

www.CompassSupportProgram.com

ADDRESS:
One Health Plaza
East Hanover, NJ 07936-1080

CONTACT INFO:
Phone: (866) 496-6382
E-mail: Online

Compass is an online resource on bone metastases created by Novartis Oncology, makers of ZOMETA®. Clicking Enroll Now calls up a screen for patients to input details on their condition and receive e-mailed information from the Compass program specific to their situation, as well as a *Personalized Doctor Discussion Guide*. Visitors can explore the Web site according to their health status: Diagnosed with cancer, but not with bone metastases, Prescribed ZOMETA, or Diagnosed with bone metastases or multiple myeloma, *but not taking* ZOMETA.

Indication

ZOMETA 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.

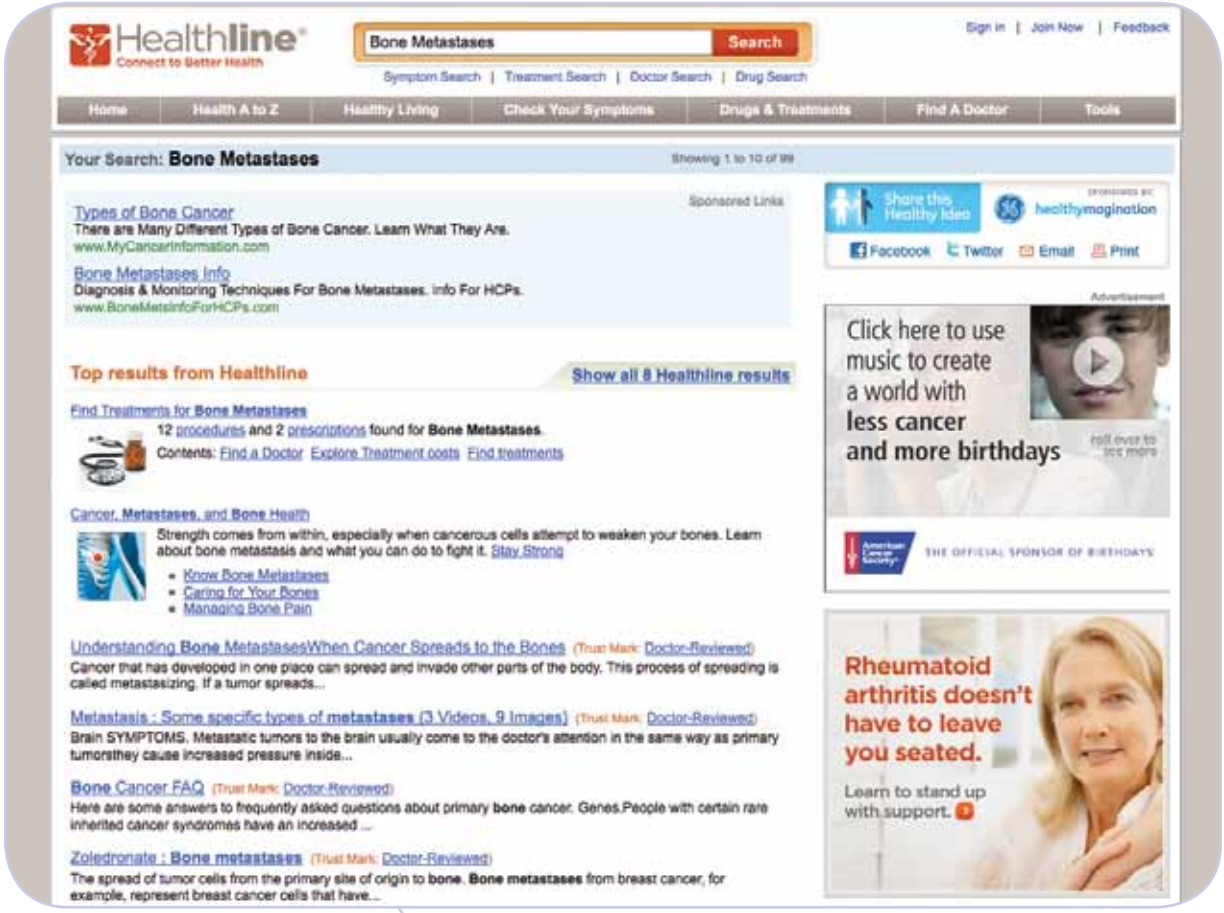
Eye-related side effects may occur with bisphosphonates, including ZOMETA. Cases of swelling related to fluid build-up in the eye, as well as inflammation of the uvea, sclera, episclera, conjunctiva, and iris of the eye have been reported.

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.

Healthline

www.healthline.com



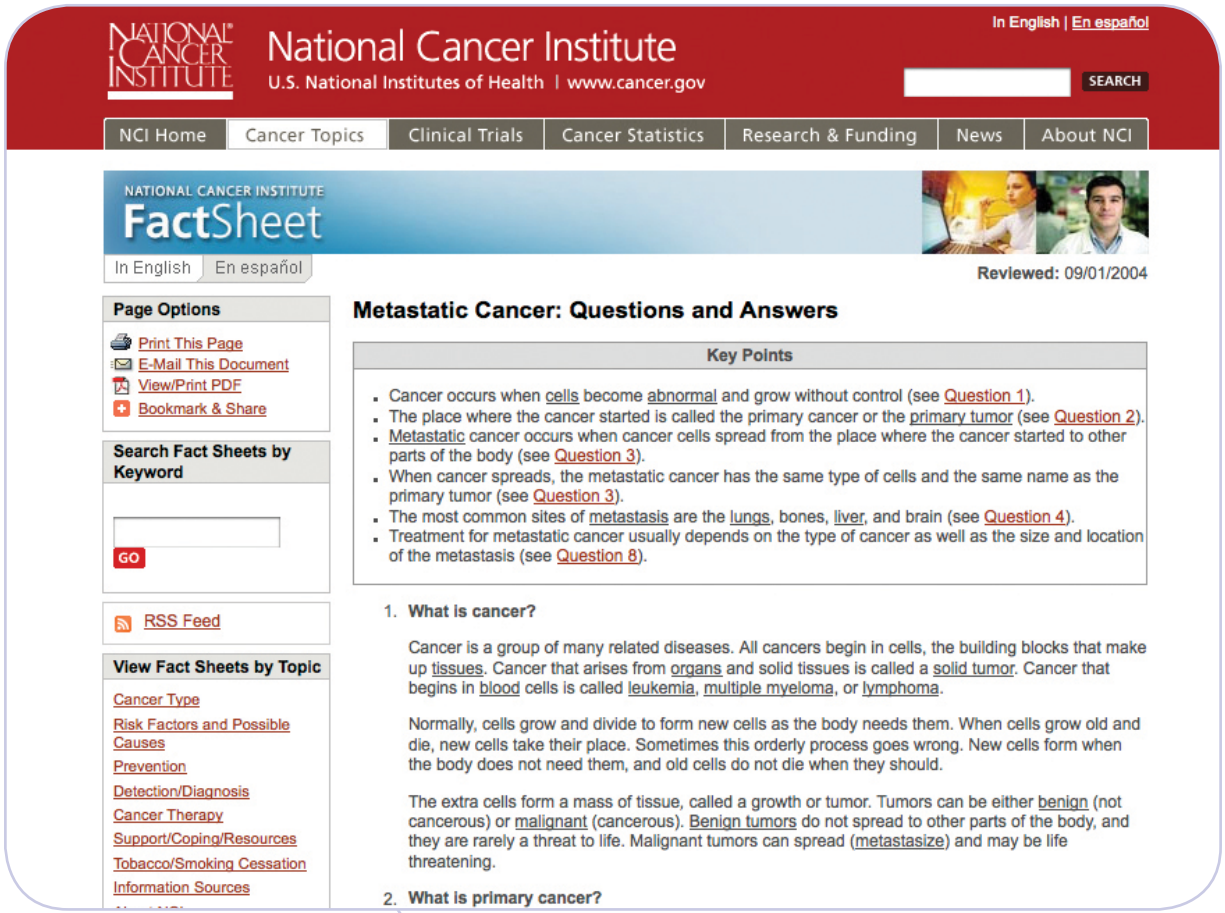
ADDRESS:
660 Third Street
San Francisco, CA 94107

CONTACT INFO:
Phone: (415) 281-3100
E-mail: Online

Healthline is an online medical database designed to help consumers find accurate information on any health-related topic. To retrieve information on bone metastases, type "bone metastases" in the search bar at the top of the page. This brings up a list of physician-reviewed articles, videos, and images. Some of these include: Understanding Bone Metastasis: When Cancer Spreads to the Bones; Bone Cancer FAQ; and Zoledronate: Bone Metastasis.

National Cancer Institute

www.cancer.gov



ADDRESS:
6116 Executive Blvd.
Suite 300
Bethesda, MD 20892-8322

CONTACT INFO:
Phone: (800) 422-6237
(800) 4-CANCER
E-mail: Online

The National Cancer Institute (NCI) is a part of the National Institutes of Health. In addition to supporting and coordinating cancer research, NCI offers information on virtually all things related to cancer. To find information on bone metastases, click on Cancer Topics in the navigation bar, then select NCI Fact Sheets under the Cancer Library section. From there, click Cancer Type, then choose Metastatic Cancer: Questions and Answers. Here you can also find links to related information and relevant clinical trials.

Notes

Helping to make access to the therapies you need easier

Novartis Oncology is committed to helping patients living with cancer receive the medicines they need. **Patient Assistance NOW Oncology** offers quick and easy access to information about the many reimbursement and support programs available.

You can get information about our **Patient Assistance NOW Oncology** support programs in two ways:

- Call **1-800-282-7630** to speak to one of our knowledgeable staff dedicated to making access to our programs as simple and convenient as possible; or
- Visit our web site at: **www.PatientAssistanceNow.com/oncology**

Support for Patients Includes:

- Insurance verification
- Medicare education
- Assistance with denials/appeals
- Therapy-specific support programs for out-of-pocket costs
- Assistance searching for other sources of coverage/funding that could alleviate or reduce costs for patients.
- Referrals to Independent Charitable Foundations for assistance with co-pay costs
- Patient assistance for low-income and uninsured patients
- Patients pre-qualified via phone screening for the Patient Assistance Program (PAP) will be sent a 30-day supply of their needed medication while completing the application

NOVARTIS ONCOLOGY

Patient Assistance NOW ONCOLOGY

Intellisphere®
Oncology Specialty Group

02/11

This Resource Guide was sponsored by Novartis Pharmaceuticals Corporation. The information is designed to be a summary of information and not an exhaustive clinical review.

ZOM-1007218