Thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), are among the adverse events that can affect patients with multiple myeloma. Patients are at risk for the serious and potentially life-threatening events because of their disease, the presence of individual risk factors, and antimyeloma agents or other medications. Although use of the novel immunomodulatory drugs lenalidomide (Revlimid®, Celgene Corporation) and thalidomide (Thalomid®, Celgene Corporation) and the proteasome inhibitor bortezomib (Velcade®, Millennium Pharmaceuticals, Inc.) have increased response rates and survival times for patients with multiple myeloma in recent years (Ghobrial et al., 2007; Manochakian, Miller, & Chanan-Khan, 2007; Rajkumar et al., 2005; Richardson & Anderson, 2006; Richardson, Hideshima, Mitsiades, & Anderson, 2007), their use has been associated with an increased risk of thromboembolic events. The increase is related, in part, to administration of concomitant medications, including dexamethasone (Bennett et al., 2006; Celgene Corporation, 2007a, 2007b; Durie et al., 2006; Palumbo et al., 2008; Rajkumar et al.; Rajkumar & Gertz, 2006; Zonder et al., 2006). Thromboembolic events have been reported in patients receiving single-agent bortezomib, but at a much lower rate than that observed in patients with multiple myeloma treated with other agents, including lenalidomide or thalidomide (Celgene Corporation, 2007a, 2007b; Harousseau et al., 2006; Lonial et al., 2007). However, patients receiving bortezomib may be at risk for DVT and PE as a result of other risk factors, including some concomitant therapies.

At a Glance
- Patients with multiple myeloma are at risk for thromboembolic events (deep vein thrombosis and pulmonary embolism) because of the disease, individual risk factors, and treatment.
- Patients must be monitored and, if indicated, receive prophylaxis for thromboembolic events, which are serious and potentially life altering and life threatening.
- Measures to prevent thromboembolic events associated with novel therapies include mechanical, myeloma regimen related, and antithrombotic pharmaceutical and are based on individual patient-related and myeloma-related risk factors.

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The International Myeloma Foundation’s Nurse Leadership Board, in recognition of the need for specific recommendations on managing key side effects of the novel antimyeloma agents, developed this consensus statement for the assessment and prevention of thromboembolic events, including DVT and PE, associated with novel therapies. The recommendations are designed to be used by healthcare providers in any type of medical institution (Bertolotti et al., 2007, 2008).

**Issue Statement**

Certain populations are at increased risk for thromboembolic events, including DVT and PE. Patients with cancer are among those with an increased risk for thromboembolic events (Heit et al., 2000, 2002; Otten et al., 2004; Prandoni, 2005; Van Gerpen & Mast, 2004), and patients with multiple myeloma may incur an even higher incidence (Hussein, 2006; Palumbo et al., 2008). Some combination treatments and concomitant therapies for multiple myeloma also may increase the incidence of thromboembolic events (Palumbo et al.).

Disruption of the vascular endothelium by trauma, surgery, or disease can expose the subendothelium to clotting elements in the blood. In normal coagulation, platelet activation, granule secretion, and aggregation are followed by activation of the plasma coagulation cascade, ultimately leading to fibrin formation. Thrombosis can result from the unregulated activation of coagulation that occurs with continued endothelial damage, reduced blood flow in deep veins, and hypercoagulability. The resulting thrombus may obstruct blood vessels partially or completely or may dislodge from the site of formation to become an embolus (Handin, 2005; Story, 2006; Viale & Schwartz, 2004).

Thromboembolic events can produce life-altering complications, affecting physiologic functions such as breathing, cognition, and overall function, and should be considered medical emergencies. Thromboembolic events can permanently affect the lives of patients and their families. Impairment resulting from thromboembolic events can interfere with therapy, treatment options, drug combinations, and patient adherence.

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### Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Vascular Toxicity Grades

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>GRADE 2 (MILD)</th>
<th>GRADE 3 (SEVERE)</th>
<th>GRADE 4 (LIFE THREATENING OR DISABLING)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis/embolism (vascular access related)</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anti-coagulation, lysis, filter, invasive procedure) not indicated</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anti-coagulation, lysis, filter, invasive procedure) indicated</td>
<td>Embolic event, including pulmonary embolism or life-threatening thrombus</td>
</tr>
<tr>
<td>Thrombosis/thrombus/embolism</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anti-coagulation, lysis, filter, invasive procedure) not indicated</td>
<td>Deep vein thrombosis or cardiac thrombosis; intervention (e.g., anti-coagulation, lysis, filter, invasive procedure) indicated</td>
<td>Embolic event, including pulmonary embolism or life-threatening thrombus</td>
</tr>
</tbody>
</table>

*Note:* Vascular toxicity has no grade 1 (mild).

*Note:* Based on information from National Cancer Institute, 2006.

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### Patient and Caregiver Educational Recommendations

Patient education, focused nursing assessment, and proactive prophylaxis against thromboembolic events may increase positive patient outcomes. Nursing opportunities include identifying and recommending prophylaxis against thromboembolic events in conjunction with the healthcare team and implementing prophylaxis algorithms such as those included in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ for venous thromboembolic disease (NCCN, 2007), the International Myeloma Working Group (IMWG) consensus statement recommendations (Palumbo et al., 2008), this consensus statement, and other nursing practices that have been identified to reduce the risk of thromboembolic events.

### Global Statement

Recommendations for prevention and prophylaxis of thromboembolic events in patients with multiple myeloma depend on institutional practices, drug therapies and combinations, and factors specific to individual patients (e.g., concomitant illnesses, medical history, cost of therapy, insurance, patient abilities, adherence, allergies and sensitivities).

### Tool for Grading Thromboembolic Events

Healthcare professionals can quantify the severity of thromboembolic events with the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). The NCI CTCAE are used for identifying treatment-related adverse events to facilitate the evaluation of new cancer therapies, treatment modalities, and supportive measures. For most adverse events, the NCI CTCAE defined grades 1 through 5 using unique clinical descriptions; each grade is assigned a severity: grade 1 is mild, grade 2 is moderate, grade 3 is severe, grade 4 is life threatening or disabling, and grade 5 is death related to the adverse event. Table 1 defines the NCI CTCAE version 3.0 vascular toxicity...
Individual Demographics
- Older age
- Obesity
- Immobilized, bed ridden, or low activity level (e.g., during prolonged air travel)
- Smoker or user of other forms of tobacco
- Varicose veins
- Pregnancy

Genetic Factors
- Strong family history of thromboembolic events
- Blood-clotting disorders
  - Factor V Leiden mutations
  - Factor VIII elevation
  - Prothrombin mutations
  - Protein C deficiency
  - Protein S deficiency
  - Antithrombin III deficiency
  - Hyperhomocysteinemia

Disease or Medical Condition
- Sickle cell disease and sickle cell trait
- Previous superficial vein thrombosis or venous thromboembolism
- Cardiac diseases, including myocardial infarction and congestive heart failure
- Chronic renal disease and nephrotic syndrome
- Neurologic disease or stroke with paralysis
- Hospitalization within previous three months with or without surgery
- Cancer with or without chemotherapy, including a diagnosis of myeloma
- Trauma
- Diabetes
- Acute infection
- Hepatic disease
- Regional bulky lymphadenopathy with extrinsic vascular compression
- Autoimmune diseases (e.g., rheumatologic and inflammatory bowel diseases)

Procedure-Related Factors
- Current or previous central venous catheter, IV catheter, or pacemaker
- Recent general, orthopedic, neurologic, or gynecologic surgery
- Anesthesia

Medications
- Chemotherapy for cancer, including some antimyeloma agents and supportive therapies
- Estrogenic agents, including
  - Hormone-replacement therapy
  - Oral contraceptives
  - Tamoxifen or raloxifene
  - Diethylstilbestrol
- Vitamin K
- Antimyeloma therapy and other myeloma medications (see Table 3)

Figure 1. General Risk Factors for Thromboembolic Events

Note: Based on information from Austin et al., 2007; Bauer, 2001; Heit et al., 2000, 2002; Joffe et al., 2004; Khorana et al., 2006; National Comprehensive Cancer Network, 2007; Palumbo et al., 2008; Prandoni, 2005; Prandoni et al., 2005; Spencer et al., 2007; Ven Gerpen & Mast, 2004.

Recommendations for Prophylaxis

Clearly, recognizing factors that put patients at risk for thromboembolic events and instituting preventive measures are better than attempting to treat adverse events after they occur.
Prophylactic measures against thromboembolic events may be categorized as mechanical, myeloma regimen related, and antithrombotic pharmaceutical (clot-preventing agent). Figure 3 describes recommendations for thromboembolic prophylaxis in each of the categories. Prophylaxis should take into account the patient’s risk based on individual factors and the patient’s antimonyeloma and other therapeutic regimens. For example, measures to reduce the risk of thromboembolic events that are not related to myeloma or its therapy but are associated with individual patient factors (e.g., diet, exercise, lowering of cholesterol, weight reduction) may be recommended. Some antithrombotic agents may be contraindicated in the presence of thrombocytopenia, renal impairment, or other comorbidities in patients with multiple myeloma because of their disease or antimonyeloma therapy. For patients with a platelet count of 50 x 10^9/L or less, aspirin and other anticoagulants generally should be held. Prophylaxis for thromboembolic events related to high-dose dexamethasone might consist of administration of low-molecular-weight heparin or heparin only on the days that dexamethasone is given. Less aggressive dosing schedules and lower doses of thalidomide and steroids alone or in combination may decrease incidence of thrombotic events; therefore, judicious dose reductions may increase quality of life and adherence to the therapeutic regimen.

The recommendations for prophylaxis presented in this article are made in consideration of the IMWG consensus statement (Palumbo et al., 2008). The IMWG’s recommendations for thrombotic prophylaxis that take into account individual or myeloma-related risk factors, such as those listed in Figure 1 and Table 3, are as follows.

- Aspirin for patients with zero or one individual or myeloma-related risk factor
- Low-molecular-weight heparin or full-dose warfarin for patients with two or more individual or myeloma-related risk factors

Figure 2. Signs and Symptoms of Thromboembolic Events

Low-molecular-weight heparin or full-dose warfarin for all patients with therapy-related risks, including high-dose dexamethasone, doxorubicin, or multiagent chemotherapy

The labeling for thalidomide and lenalidomide recommends monitoring for signs and symptoms of thromboembolic events. According to the thalidomide label, preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylaxis with aspirin or an anticoagulant (Celgene Corporation, 2007b). The lenalidomide label states that the decision to use prophylaxis should be made after assessment of each patient’s risk factors (Celgene Corporation, 2007a).

Individual patient risk factors, the presence of multiple myeloma, and the use of antimyeloma therapies or other medications all contribute to the risk of serious and life-threatening thromboembolic events in patients with myeloma. Prophylactic measures based on individual and myeloma-related risk factors can reduce or eliminate the risk.

### Table 3. Therapy-Related Risk Factors for Thromboembolic Events

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>FACTORS ASSOCIATED WITH INCREASED RISK</th>
<th>FACTORS ASSOCIATED WITH NO OR DECREASED RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>Administration in combination with high-dose dexamethasone (defined as ≥ 480 mg per month), dexamethasone plus erythropoietin, erythropoietin, cyclophosphamide, or combinations containing doxorubicin (including liposomal doxorubicin)</td>
<td>Administration in combination with bortezomib or low-dose dexamethasone</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Administration in combination with high-dose dexamethasone, erythropoietin, melphalan, melphalan plus prednisone, or doxorubicin (including liposomal doxorubicin) with or without dexamethasone, or in combination with two or more chemotherapy agents with or without a corticosteroid</td>
<td>Administration in combination with low-dose dexamethasone</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Administration in combination with some multidrug therapies</td>
<td>Administration in combination with erythropoietin with or without high-dose dexamethasone or with liposomal doxorubicin, in combination with lenalidomide, or in combination with VDT-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide)</td>
</tr>
</tbody>
</table>

### Mechanical Prophylaxis

Sequential compression devices
Antiembolism stockings
Exercise regimens

**Myeloma Regimen–Related Prophylaxis**
Reduce thalidomide from 100 mg PO to 50 mg PO daily, or reduce by 50 mg increments from current dosage.
Administer dexamethasone 20–40 mg once weekly.
Administer dexamethasone 20 mg days 1–4 only (monthly cycle) versus standard pulse (days 1–4, 9–12, and 17–20).

**Antithrombotic Pharmaceutical Prophylaxis**
Salicylic acid (aspirin): low (81 mg) or standard dose (325 mg) PO daily

**Antithrombotic Pharmaceutical Prophylaxis (Continued)**
Unfractionated heparin: 5,000 IU subcutaneously twice daily (Baxter Healthcare, 2004)
Low-molecular-weight heparin (e.g., enoxaparin, dalteparin): enoxaparin 40 mg subcutaneously daily (sanofi-aventis, 2007); dalteparin 200 IU/kg total body weight subcutaneously daily for 30 days, then reduce to 150 IU/kg subcutaneously daily (Pfizer, Inc., 2007)
Fondaparinux (inhibitor of activated factor X = factor Xa): 2.5 mg subcutaneously daily (GlaxoSmithKline, 2005)
Warfarin: oral or IV formulation at a dose to achieve and maintain an international normalized ratio of 2.0–3.0 (Bristol-Myers Squibb, 2007); weight-based dosing: 1 mg if body weight < 70 kg and 2 mg if body weight 70 kg or more (Miller et al., 2006)

**Note.** Based on information from Barlogie et al., 2005; Bennett et al., 2006, 2007; Celgene Corporation, 2007b; Harousseau et al., 2006; Hussein, 2006; Knight et al., 2006; Lonial et al., 2007; Manochakian et al., 2007; Millennium Pharmaceuticals, Inc., 2007; Offidani et al., 2005; Ortho Biotech Products, L.P., 2007; Palumbo et al., 2008; Richardson et al., 2007; Zangari et al., 2002.
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Patients with cancer are at increased risk for developing blood clots (thromboembolic events). Patients with multiple myeloma may have an even higher risk of developing blood clots. Novel therapies used to treat myeloma include thalidomide and lenalidomide. These drugs, in combination with other medications, may increase the incidence of clots. Prevention of blood clots can reduce complications and contribute to successful treatment. Changes in your medication may be made by a healthcare provider based on your symptoms.

### Types of Thromboembolic Events
- Deep vein thrombosis (DVT): a small blood clot in the arm, leg, hand, or foot; DVT is the most common thromboembolic event.
- Pulmonary embolus (PE): a blood clot that travels to the lungs.
- Cerebral infarction (stroke): a blood clot that travels to the brain.

### Symptoms of Deep Vein Thrombosis
- Swelling, aching, pain, tightness, or a hard or soft lump in the arm, leg, hand, or foot.
- Fast heartbeat.
- Veins larger than usual (distended).

### Symptoms of Pulmonary Embolus
- Anxiety.
- Fast heartbeat and fast breathing.
- Chest pain or new onset of shortness of breath.
- Coughing up blood.

### Symptoms of Stroke
- Change in emotional or mental behavior and confusion.

### TREATMENT
- DVT, PE, and stroke are considered medical emergencies.
- Report any symptoms to your healthcare provider immediately.
- You will need regular examinations and may need to receive medications to prevent clots.
- The treatments or medications you receive will be based on your individual risk factors.
- Low-dose aspirin may be suggested if you have no risk factors or only one risk factor.
- Pills or injectable anticlotting drugs may be prescribed if you have more than one risk factor.

### Risk Factors for Clot Formation
- Lack of activity.
- Obesity.
- Smoking.
- History of blood clots in you or your family.
- Taking estrogen compounds (hormone replacement).
- Taking drugs to increase the amount of red blood cells, such as erythropoietin, epoetin alfa, or darbepoetin alfa.
- Recent surgery.
- Prolonged air travel.

### Ways to Reduce Clot Risk
- Exercise, such as walking, ankle circles, and knee to chest lifts.
- Lose weight.
- Stop smoking.
- Take medications prescribed by your healthcare providers.

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**Note.** For more information, please contact the International Myeloma Foundation (1-800-452-CURE; www.myeloma.org). The foundation offers the Myeloma Manager™ Personal Care Assistant™ computer program to help patients and healthcare providers keep track of information and treatments. Visit http://manager.myeloma.org to download the free software.

**Note.** Patient education sheets were developed in June 2008 based on the International Myeloma Foundation Nurse Leadership Board’s consensus guidelines. They may be reproduced for noncommercial use.