About the International Myeloma Foundation

Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific charity in the world. With more than 350,000 members in 140 countries, the IMF serves myeloma patients, family members, and the medical community. The IMF provides a wide range of programs in the areas of Research, Education, Support, and Advocacy:

**RESEARCH**  The IMF is the leader in globally collaborative myeloma research. The IMF supports lab-based research and has awarded over 100 grants to top junior and senior researchers since 1995. In addition, the IMF brings together the world’s leading experts in the most successful and unique way through the International Myeloma Working Group (IMWG), which is publishing in prestigious medical journals, charting the course to a cure, mentoring the next generation of innovative investigators, and improving lives through better care.

**EDUCATION**  The IMF’s educational Patient & Family Seminars, Medical Center Workshops, and Regional Community Workshops are held around the world. These meetings provide up-to-date information presented by leading myeloma specialists and researchers directly to myeloma patients and their families. Our library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

**SUPPORT**  Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY**  The IMF Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

Learn more about the way the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 800-452-CURE (2873) or visit myeloma.org.

Improving Lives Finding the Cure®
The Understanding series and 10 Steps to Better Care

The IMF’s Understanding series of booklets is designed to acquaint you with treatments and supportive care measures for multiple myeloma (which will be referred to as “myeloma” for the sake of simplicity).

For a general overview of myeloma, the IMF’s Patient Handbook should be your first step, while the IMF’s Concise Review of the Disease and Treatment Options is a more in-depth overview designed for healthcare professionals and knowledgeable readers outside the medical community. Both of these publications, as well as the many booklets in the IMF’s Understanding series, are available on our website myeloma.org, where you will find a wealth of information. You can also order hard copies of our publications by calling the IMF at 800-452-CURE (2873) toll-free in the United States and Canada, or 818-487-7455 worldwide, or by sending an email to theIMF@myeloma.org.

To help you navigate through the IMF website, we have organized information according to the 10 Steps to Better Care® to guide you from diagnosis (Step 1) through clinical trials and how to find them (Step 10). Information relevant to each step along the way, including guidelines for testing, treating, transplanting, assessing response, managing side effects, monitoring, and treating relapsed disease, is available on the IMF website myeloma.org under the appropriate step on the path to better care.

Words appearing in bold type are explained in the “Terms and definitions” section at the end of this booklet.

What you will learn from this booklet

Velcade® (bortezomib) plays an important role throughout the disease course of the myeloma patient, from induction therapy for those who are newly diagnosed, to a possible role as part of conditioning for stem cell transplant, to consolidation and/or maintenance therapy, to treatment for those whose myeloma has become refractory to and/or relapsed on previous therapies. Thus, since Velcade is available as a treatment option throughout the disease, the Understanding VELCADE® (bortezomib) for injection booklet encompasses several of the 10 Steps to Better Care:

• Step 3 – Initial treatment options (frontline therapy)
• Step 4 – Supportive care and how to get it
• Step 5 – Transplant: Do you need one?
• Step 7 – Consolidation and/or maintenance
• Step 9 – Relapse: Do you need a change in treatment?

What is Velcade and how does it work?

Velcade is the first in a class of drugs called proteasome inhibitors. It was first approved by the US Food and Drug Administration (FDA) for the treatment of relapsed/refractory myeloma in May 2003. In June 2008, the FDA expanded Velcade’s approval to include the frontline setting. In January 2012, the FDA approved subcutaneous (SQ) administration of Velcade. In August 2014, the FDA expanded the Velcade label to allow for retreatment of patients who previously responded to Velcade and who relapsed at least six months after completing prior Velcade treatment.

Velcade can be used alone, in combination with dexamethasone, or as part of a more complex multi-drug regimen.

Velcade works by inhibiting enzyme complexes called proteasomes. Both normal cells and cancer cells contain proteasomes, which break down damaged and unwanted proteins into smaller components. Proteasomes also carry out the regulated breakdown of undamaged proteins in the cell, a process that is necessary for the control of many critical cellular functions. These smaller components are then used to create new proteins required by the cell. Proteasomes can be thought of as crucial to the cell’s “recycling” of proteins.

When Velcade inhibits proteasomes, the normal balance within a cell is disrupted. This disruption results in a number of effects on the cell, some of which are still being studied. When proteasomes are inhibited in laboratory tests, myeloma cells stop dividing.

Myeloma cells also stop producing chemicals to stimulate other myeloma cells: the autocrine feedback loop is interrupted. Myeloma cells are more sensitive to these effects than normal cells, so that myeloma cells die while normal cells can recover.

How is Velcade given?

Velcade comes in the form of a lyophilized (freeze-dried) powder, which must be reconstituted before it is administered. As approved in 2003, Velcade is given as an intravenous (IV, into the vein) infusion injected through either a peripheral or central IV line. It is injected over a short period of 3 to 5 seconds.

In January 2012, the FDA approved a second method for administering Velcade to patients. In addition to the former method of giving Velcade as an IV infusion, it is possible to receive Velcade as a subcutaneous (SQ, under the skin) injection, commonly known as a “shot.” The SQ injection is given at the doctor’s office, at the same dose and on the same schedule as IV Velcade, and should be given alternating between the thighs and the abdomen. There is no data from clinical trials to support administration of SQ Velcade in the arm. Like IV Velcade, SQ Velcade is approved to be administered throughout the myeloma disease course.

Please refer to the IMF’s tip card on SQ Velcade for detailed information on approved injection locations and techniques. Adhering to these guidelines will help to prevent skin reactions at the site of the injection and will ensure proper absorption of the medication. SQ Velcade causes significantly less peripheral neuropathy (PN) than IV Velcade, and may also have reduced gastrointestinal side effects. If you have pre-existing neuropathy or GI problems, you should discuss using SQ Velcade with your doctor.
When is Velcade given, and at what dose?

In standard protocols, Velcade is given at the doctor’s office or a clinic at 1.3 mg per square meter of body mass twice per week for 2 weeks, followed by a 10-day rest period. Patients and their doctors typically choose a Monday/Thursday or Tuesday/Friday schedule. At least 72 hours are needed between doses, so that normal cells have a chance to recover from the effects of the drug. Therefore, changes in the administration schedule must be limited to delaying an injection for a day, rather than moving the injection up one day.

There are situations in which it may be necessary to reduce the dose of Velcade and/or administer it once, rather than twice, per week. Your doctor may order dose reductions and/or treatment schedule changes if you experience side effects. Schedule and dose changes can also be ordered preventively for patients with pre-existing medical problems or for patients who are elderly and frail.

In 2011, IMF International Myeloma Working Group (IMWG) members Dr. Antonio Palumbo and Dr. Kenneth Anderson published a dosing regimen for older and/or frail patients in the New England Journal of Medicine. Among that population of patients, Dr. Palumbo recommends that dosages of Velcade and the drugs with which it is commonly combined be adjusted according to the patient’s age and concurrent illnesses and/or tolerance.

Dr. Palumbo provides a helpful table for specific dose adjustments recommended for frail patients (see Table 1). His “go-go,” “moderate-go,” “slow-go” three-group system is now being used by many clinicians.

The specific treatment algorithm for Velcade dose reductions within combinations is summarized in Table 2, which includes (at dose level “–2”) dose reduction of Velcade to once per week (versus twice per week in the standard regimens).

Velcade is frequently given in combination with other anti-myeloma drugs, including dexamethasone, cyclophosphamide, lenalidomide (Revlimid®), thalidomide (Thalomid®), melphalan and prednisone, and pegylated liposomal doxorubicin (Doxil®). Velcade is a required component of the recently FDA-approved combination therapy Farydak® (panobinostat) plus Velcade and dexamethasone for patients who have had one to three prior therapies for myeloma, including Velcade and an immunomodulatory drug (IMiD®) such as (Thalomid®, Revlimid®, or Pomalyst®). Velcade is also being tested in combination with many other agents that are still in clinical trials. Details about therapy with dexamethasone, thalidomide, and Revlimid are discussed in separate IMF booklets.

Velcade in clinical trials

A wide range of clinical trials have been conducted with Velcade. Studies have demonstrated the efficacy of Velcade therapy for patients in the frontline, conditioning, relapsed/refractory, and maintenance settings.

Velcade has been demonstrated to help prevent bone loss in myeloma patients, and has been proven safe for use in patients with kidney dysfunction. Because of its effectiveness and broad use in myeloma, Velcade is often used as the standard of care in randomized clinical trials or as a platform drug for novel combinations in phase II clinical trials. Velcade is currently in hundreds of clinical trials, including:

- a study to determine if Velcade will help prevent bone-related events in patients with smoldering multiple myeloma (SMM);
- a study of Velcade as a single therapy once weekly in newly diagnosed myeloma;
- a study of allogeneic transplant followed by Velcade maintenance therapy for patients with high-risk myeloma.

![Image](image602x392-769x550)

### Table 1: Frail Patient’s Treatment Algorithm

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Dose level 0</th>
<th>Dose level –1</th>
<th>Dose level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 years</td>
<td>1.0–1.3 mg/m²</td>
<td>1.3 mg/m²</td>
<td>1.0–1.3 mg/m²</td>
</tr>
<tr>
<td>Mild, moderate, or severe frailty</td>
<td>days 1, 4, 8, 11 3 weeks</td>
<td>days 1, 4, 8, 11 3 weeks</td>
<td>days 1, 8, 15, 22 5 weeks</td>
</tr>
<tr>
<td>Comorbidities and organ dysfunction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cardiac, pulmonary, hepatic, renal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go-go</td>
<td>Dose level 0</td>
<td>Dose level –1</td>
<td>Dose level –2</td>
</tr>
<tr>
<td>Moderate-go</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow-go</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose level 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one risk factor + any G 3-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hematologic AE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If a Grade 3-4 AE (adverse event, or side effect) occurs:
1. discontinue therapy; 2. wait for a Grade 1 AE; 3. restart at a lower dose
Use of Velcade in clinical practice in 2015

In the frontline setting

Numerous studies have demonstrated the efficacy of Velcade in combination with:
- melphalan and prednisone;
- dexamethasone (VD);
- cyclophosphamide plus dexamethasone (VCD, also known as CyBorD);
- Doxil plus dexamethasone (VDD);
- thalidomide plus dexamethasone (VTD);
- Revlimid plus dexamethasone (VRD).

It is important to discuss with your physician the most appropriate combination and strategy in your case. The choice is determined by several factors, including plans for autologous transplantation or not; presence or absence of high-risk chromosome features (t(4;14); t(14;16); t(14;20); del 17p), and the presence or absence of kidney problems, underlying neuropathy, or any tendency for blood clot formation. In addition, personal preference is always a key component.

Other disease settings, including consolidation, maintenance, and relapse

In these settings various combinations and sequences have been demonstrated to be effective. Details should be discussed with your physician.

It is important to note that Velcade is active and well-tolerated in patients with relapsed myeloma with varying degrees of renal (kidney) insufficiency. Efficacy/safety in clinical trials were not substantially affected by severe-to-moderate versus no/mild kidney impairment. Several trials have confirmed the safety and efficacy of Velcade for patients with renal impairment.

In addition, several clinical trials using various treatment strategies incorporating Velcade have shown that Velcade can help overcome the poor-risk features of the t(4;14) genetic mutation and significantly improve overall survival.

There is low risk of venous thromboembolism (VTE) with Velcade, and Velcade may even provide a protective effect against VTE in combination with IMiD-based regimens.

What are the possible side effects of Velcade?

Most of the side effects associated with Velcade are manageable and predictable. The most important side effects are described here. Your doctor or nurse can provide more information in greater detail about these and other possible side effects. Speak with your doctor or nurse if you notice ANY changes in your health.

Peripheral neuropathy

Peripheral neuropathy (PN) is a serious condition in which treatment affects nerves in the hands, feet, legs, and/or arms. Symptoms of PN include numbness, tingling, or even pain in the hands, feet, legs, and/or arms. Some patients may have experienced PN from the effects of the monoclonal protein itself and/or from previous treatments for myeloma. If you begin taking Velcade with this pre-existing condition, it is especially important that you pay particular attention to the extent of your discomfort, so that you can rapidly report a worsening of your condition to your doctor. If detected and managed appropriately, the neuropathy is often reversible.

Subcutaneous (SQ) Velcade causes significantly less PN than IV Velcade. Patients who received SQ Velcade in the Intergroupe Francophone du Myélome (IFM) trial in which it was compared to IV Velcade had an incidence of PN of any severity of 38%, while those who received IV Velcade had a 53% incidence of any grade of PN. Only 6% of the patients who received SQ Velcade had PN of Grade 3 or 4 (on a scale where 1 is the lowest and 4 the highest grade), while 16% of the IV patients had Grade 3 or 4 PN. SQ Velcade may also have reduced side effects on the gastrointestinal system (nausea, constipation/diarrhea).

Prevention and treatment of PN

You are strongly advised to contact your physician if you experience new or worsening symptoms of PN, as early detection and dose modification may prevent progression of this condition. Notifying your physician also allows for appropriate modifications of the Velcade dose and/or schedule.

You should be aware that very detailed recommendations for Velcade dose and schedule modifications are available (see Tables 1 and 2). These are the key principles:

- Avoid progressive PN, especially if any significant pain develops (what is called Grade 2). Although PN can be reversible, it may be partly but not fully reversible. Prevention is the best approach. This requires early, proactive dose and/or schedule modifications.
- Discuss options for dose/schedule/method of administration changes with your doctor. The main types of modification are:

  1. Dose reduction. This is done in step-wise fashion:
     - full dose: 1.3 mg/m² body surface area.
     - first dose reduction: 1.0 mg/m²
     - half dose: 0.7 mg/m²

  2. One day per week option. Several recent studies have shown that using Velcade 1 day/week instead of the standard...
Fatigue

Fatigue is a common side effect associated with Velcade therapy. Although fatigue is generally not severe, caution is advised if you are operating machinery, including automobiles. Please see the IMF publication Understanding Fatigue for further information on this debilitating side effect and how to manage it.

Prevention and treatment of fatigue

Management of fatigue may include supportive care as determined by your physician. The effects of fatigue may be minimized by maintaining:

• a moderate level of activity;
• a healthy diet and proper fluid intake;
• a consistent sleeping schedule with enough rest;
• regularly scheduled visits with your doctor or health care professional.

Nausea

Nausea may occur while taking Velcade and may be associated with dizziness, light-headedness, or fainting if it leads to dehydration. Medical treatment may be required for dehydration.

Prevention and treatment of nausea

Precautions should be taken to prevent dehydration caused by vomiting. You should drink a sufficient amount of water and other fluids and seek medical advice if you experience dizziness, light-headedness, or fainting. Your physician may administer anti-emetic medication (to prevent vomiting) or intravenous hydration, as required.

Diarrhea

Diarrhea may occur while taking Velcade. Dizziness, light-headedness, or fainting may occur due to dehydration caused by either excessive or persistent diarrhea. You should maintain a proper level of hydration by drinking a sufficient amount of water and seek medical advice if you experience dizziness, light-headedness, or fainting. Your physician may administer anti-diarrheal medication or intravenous hydration, as required.

Decreased platelet levels

Myeloma patients taking Velcade often experience a condition called thrombocytopenia – a lowered level of platelets in the blood. Platelets help blood to clot; fewer platelets can lead to bruising, bleeding, and slower healing. The platelet level falls with treatment but, after the required interval between doses, should return to the baseline level by the beginning of the next cycle.

Prevention and treatment of decreased platelet levels

You should inform your physician if you experience excessive bruising or bleeding. Management may include platelet transfusions at the discretion of your physician.

Low blood pressure (hypotension)

A drop in blood pressure may occur after receiving Velcade. If you have a history of fainting or low blood pressure or are taking medication that can cause low blood pressure (such as antihypertensive medication, that is, medication to treat high blood pressure), it is important that you tell your doctor about your condition before you begin receiving Velcade. Dizziness, especially when it occurs after rapidly sitting up or standing from a lying-down position, may be a sign of low blood pressure.

Prevention and treatment of low blood pressure

You should seek medical advice if you experience dizziness, light-headedness, or fainting. Caution is advised when operating machinery, including automobiles. You should take precautions to prevent dehydration (drinking plenty of water, for example), and your physician may administer medication for the treatment of low blood pressure. It is also important to inform your doctor about any additional medications you are taking, particularly for the treatment of hypertension (high blood pressure).

Will a reduction in dose of Velcade change the effectiveness of treatment?

It is important to communicate openly with your doctor or healthcare professional and keep regular appointments to maintain your Velcade treatment schedule. Your doctor may choose to lower your dose of Velcade as part of an overall plan to manage a particular side effect you experience. The recommended initial dose of Velcade is 1.3 mg/m². However, a lower dose of 1.0 mg/m², which is the first dose reduction your doctor is likely to try, has also been found active against myeloma. In the small study that examined both of these doses, there was no significant difference in effectiveness between the two doses. Your doctor may also choose to skip a scheduled dose to reduce the severity of a side effect before continuing treatment.
Studies have shown that administration of Velcade on a weekly schedule in combination with other anti-myeloma agents is associated with a reduction in side effects, particularly peripheral neuropathy, without significant reduction in efficacy.

Terms and definitions

**Autocrine:** Autocrine refers to the process whereby a growth factor is both produced by a cell (such as myeloma) and can also stimulate myeloma cell growth, creating a positive autocrine loop. In a similar fashion, in a paracrine loop, factors produced by the microenvironment surrounding myeloma can stimulate myeloma. Stimulated myeloma cells produce factors which can in turn stimulate microenvironmental cells.

**Autologous transplantation:** A procedure in which stem cells are removed from a patient’s blood and then are given back to the patient following intensive treatment.

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

**Clinical trial:** A research study of new treatment that involves patients. Each study is designed to find better ways to prevent, detect, diagnose, or treat cancer and to answer scientific questions.

• **Control group** – The arm of a randomized clinical trial that gets the standard treatment.

• **End point** – The goal of the trial; what a clinical trial is trying to measure or find out. Typical end points include measurements of toxicity, response rate, and survival.

• **Experimental group** – The arm of a randomized trial that gets the new treatment.

• **Randomized clinical trial** – A research study in which subjects are randomly assigned to receive a particular treatment.

• **Phase I trial** – A trial designed to determine the maximum tolerated dose (MTD) of a new drug or a new combination of drugs. It is usually the first human testing of a new treatment, although in phase I trials of combination therapies, the individual elements may already have been well tested. Patients in phase I trials must have advanced cancer that is refractory to any standard treatment. In a typical phase I trial, successive groups (“cohorts”) of 3 to 6 patients are given the treatment. All patients in a cohort get the same dose. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience dose-limiting toxicity (DLT). The dose level used for the previous cohort is then taken to be the MTD. This dose is then used in a phase II trial.

• **Phase II trial** – A trial designed to determine the response rate of a new therapy that has already been tested in phase I trials. Typically, 14 to 50 patients with one type of cancer are treated to see how many have a response. Patients are usually required to have advanced cancer that is refractory to any standard treatment, and in addition, they must have measurable disease. If results from a phase II trial are promising enough, the treatment may then be tested in a phase III trial. If the results are obviously much better than the standard treatment, then it may not be necessary to do a phase III trial, and the treatment may become standard based on phase II trial results.

• **Phase III trial** – A trial designed to compare two or more treatments for a given type and stage of cancer. The end point of a phase III trial is usually survival or disease-free survival. Phase III trials are usually randomized, so patients don’t choose which treatment they receive. A typical phase III trial has 50 to thousands of patients. Some phase III trials compare a new treatment that has had good results in phase II trials with an older, well known, standard treatment. Other phase III trials compare treatments that are already in common use. Some treatments in phase III trials may be available outside the clinical trial setting.

**Conditioning:** A treatment regimen given to a patient to destroy cancer cells prior to stem cell transplant. The most common conditioning regimen given to myeloma patients is 200mg of melphalan per square meter of body mass.

**Enzyme:** A type of protein that causes chemical reactions of other substances without undergoing change in the process.

**Gastrointestinal side effects:** Side effects of medication that affect the digestive tract, such as nausea, vomiting, diarrhea, and constipation.

**Immunomodulatory drug (IMiD):** Drug that affects, enhances, or suppresses the immune system.

**Induction therapy:** The initial treatment used in an effort to achieve remission in a newly diagnosed myeloma patient.

**Multiple myeloma:** A cancer arising from the plasma cells in the bone marrow. The plasma cells in patients with myeloma form abnormal antibodies, which can damage the bone, bone marrow, and other organs.

**Peripheral neuropathy (PN):** Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

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

**Platelet:** An element in the blood that helps with clotting, which in turn helps repair damaged blood vessels.

**Proteasome:** A joined group (or complex) of enzymes that destroy damaged or unwanted proteins and undamaged proteins that require degradation in the cell. This turnover or “recycling” of proteins is important to maintain balance within the cell and helps to regulate several functions including cell growth.

**Proteasome inhibitor:** Any drug that interferes with the normal function of the proteasome.

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

**Side effect:** An effect caused by treatment with a drug. The term usually refers to an unwanted effect, but some side effects may be beneficial.
One of the most daunting aspects of being diagnosed with multiple myeloma (MM) is learning about – and understanding – an unfamiliar disease that is quite complicated. From diagnosis to long-term survival, the 10 Steps to Better Care® will guide you through the MM journey:

1. Know what you’re dealing with. Get the correct diagnosis.
2. Tests you really need.
3. Initial treatment options.
4. Supportive care and how to get it.
5. Transplant: Do you need one?
6. Response Assessment: Is treatment working?
7. Consolidation and/or maintenance.
9. Relapse: Do you need a change in treatment?

Visit 10steps.myeloma.org to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your MM. Visit the IMF website myeloma.org or call the IMF InfoLine at 800-452-CURE (2873), which is staffed by trained information specialists, with your questions or concerns. The IMF is here to help.