Understanding VELCADE® (bortezomib) for Injection

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07/08

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Sponsored by an unrestricted educational grant from Millennium Pharmaceuticals, Inc.

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Introduction

You have been given this booklet to learn more about a new drug called VELCADE® (bortezomib). After reading this booklet, you should know:

- What VELCADE® is
- How VELCADE® works
- The possible **side effects*** of VELCADE®
- How VELCADE® is given.

This booklet is meant to provide you with general information only. It is not meant to replace the advice of your doctor or nurse. Your doctor or nurse can answer questions related to your specific treatment plan.

WHAT IS MULTIPLE MYELOMA?

Multiple myeloma (synonymous with myeloma and plasma cell neoplasm) is a malignancy of **bone marrow** plasma cells. It is therefore a hematologic malignancy that most closely resembles leukemia. The malignant plasma cells, otherwise known as myeloma cells, accumulate in the bone marrow and only rarely enter the bloodstream as in a true leukemia. The major features of myeloma result from this progressive accumulation of myeloma cells within the marrow, causing:

- Disruption of normal bone marrow function, most commonly reflected by **anemia** (a low level of **red blood cells** in the bloodstream), although reduction in **white blood cell** and **platelet** counts can also occur

*Words appearing in **bold** are defined in the glossary at the end of the booklet.

- Damage to surrounding bone
- Release of **monoclonal protein (M protein)** from the myeloma into the bloodstream
- Suppression of normal immune function, reflected by reduced levels of normal immunoglobulins and increased susceptibility to infection.

Myeloma cells can also grow in the form of localized tumors or plasmacytomas. Such plasmacytomas can be single or multiple and confined within bone marrow and bone (medullary), or they can develop outside of bone in soft tissue. Plasmacytomas outside bone are called extramedullary plasmacytomas. When there are multiple plasmacytomas inside or outside bone, this condition is also called multiple myeloma.

Once a diagnosis of multiple myeloma has been made, it is important for a doctor to determine the stage of the disease. Disease staging will help determine what parts of the body have been affected and allow the doctor to decide the best treatment option. The stages of multiple myeloma are:

Stage I (low cell mass). The bone structure appears normal or close to normal on x-ray images. The number of red blood cells and amount of calcium in the blood are normal or close to normal, and the amount of M protein is very low.

Stage II (intermediate cell mass). An intermediate stage between stage I and III.

Stage III (high cell mass). One or more of the following are present:

- Anemia
- A high level of calcium in the blood
- Multiple lytic bone lesions
- A high level of M protein in the blood or urine.

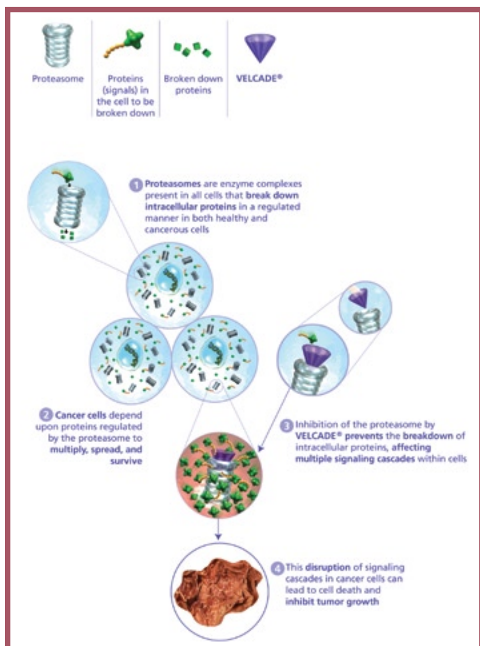
It is important to understand that, although multiple myeloma is a serious malignancy, it is a treatable disease; many patients experience a series of responses, relapses, and remissions. Additionally, the average survival of 5 years for patients diagnosed with multiple myeloma may potentially be extended with new treatment options.

Following diagnosis, several options, including VELCADE®, are available for initial or frontline therapy. For patients who may be candidates for therapy with transplant, various induction regimens can be considered including VELCADE® with dexamethasone, dexamethasone alone, or dexamethasone in combination with other novel agents. The combination of VELCADE® with the **alkylating agent** melphalan plus prednisone, or melphalan and prednisone alone, is an option for patients not considering transplant. At the time of relapse, different options and combinations are used to achieve further response. VELCADE® is an important new agent for use in this setting as well.

WHAT IS VELCADE® AND HOW DOES IT WORK?

VELCADE® is the first in a new class of drug called **proteasome inhibitors**. In June 2008, VELCADE® was approved for use in the front-line setting. VELCADE® is also an important treatment option for patients who have become refractory to and or relapsed on previous therapies.

How VELCADE® works.



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, cancer cells stop dividing. They also stop producing chemicals to stimulate other cancer cells. In addition, inhibition of proteasomes has caused cancer cells to die. Cancer cells appear to be more sensitive to these effects than normal cells, so that cancer cells die while normal cells can recover.

Clinical studies have investigated the effects of VELCADE® therapy on patients in both the relapsed/refractory and front-line settings.

Melphalan/Prednisone/VELCADE Trial

One study enrolled newly diagnosed patients at least 65 years of age (median for the study population was 75). They were given VELCADE® at a dose of either 1.0 or 1.3 mg/m^2 on days 1, 4, 8, 11, 22, 25, 29, and 32, followed by a ten-day rest period, for a total of 4 cycles (equivalent to 8 regular cycles of VELCADE®). This was followed by five maintenance cycles of VELCADE® given at 1.0 or 1.3 mg/m^2 once a week for four

weeks followed by a 13-day rest period. Both series included melphalan at 9 mg/m^2 and prednisone at 60 mg/m^2 given on the first four days of each cycle.

A total of 89% of the 53 enrolled patients responded, including 32% complete responses (CR) and 11% near complete responses (nCR). Compared to the historical data for 6 cycles of melphalan/prednisone (MP) regimen, the overall response rate more than doubled (42% to 89%), while the CR/nCR rate improved from 3% to 43% with the addition of VELCADE®. Furthermore, 12 of the 17 patients with complete responses were tested for evidence of residual disease: 6 of these 12 achieved molecular remission as judged by strict laboratory criteria. At 16 months, 91% of patients were free of disease progression.

Apex Trial

Another study, updating the results of the previously published APEX trial, showed that the overall median survival rate for patients receiving single agent VELCADE® was 30 months compared to 24 months for those receiving high-dose dexamethasone. In this study, patients received VELCADE® on days 1, 4, 8, and 11 followed by a 10-day rest period (the standard VELCADE® cycle) for 8 cycles followed by 3 cycles of maintenance VELCADE® given on days 1, 8, 15, and 22 followed by a 13-day rest. Out of 315 evaluable patients, 135 patients (or 43%) achieved at least a partial response, with 27 patients achieving a complete response. This new data demonstrates an improvement in response from 38% in the initial reported data to 43% with longer follow-up. For the subset of VELCADE®-treated patients that had only one prior therapy, 51% achieved at least a partial response.

The median time to first response with VELCADE is 6 weeks. Of the 135 responders in the APEX study, 66% of responding patients achieved maximum M-protein reduction in or after cycle 4. Hence the best response to therapy often comes with continued treatment (responding patients in this study received a median of 10 cycles).

Duration of response was improved in the APEX study for those who achieved a 100% M-protein reduction compared to those who achieved a reduction greater than 50% but less than 100%. Researchers who

conducted the trial, and who now have almost two years of mature data, concluded that patients achieve a better response with longer VELCADE® therapy duration.

Previously Untreated Myeloma Trial

Fifty patients were enrolled in a clinical trial for patients with previously untreated multiple myeloma. At the time of the study, 50% of the patients were classified at Durie-Salmon Stage III. They were given VELCADE® 1.3 mg/m^2 on days 1, 4, 8, and 11 followed by a 10-day rest period for a maximum of 6 cycles. 40 mg of dexamethasone was added on the day of, and the day after, each VELCADE® dose if less than a partial response was achieved after two cycles, as well as if less than a complete response was achieved after four cycles.

This study concluded that VELCADE® alone and in combination with dexamethasone is an effective therapy in cases of newly diagnosed myeloma. The response rate (with and without the dexamethasone) was 90%, and the total of complete responders and near complete responders was 19%. Furthermore, the study showed that VELCADE® is a feasible option for induction therapy; that stem-cell harvest was successful and engraftment was prompt; and that adverse events were predictable and manageable, with the most frequent being **neuropathy** (35% at grade 2 or 3) and fatigue (20% at grade 2 or 3).

WHAT ARE THE POSSIBLE SIDE EFFECTS OF VELCADE®?

Generally, 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.

Remember, speak with your doctor or nurse if you notice ANY changes in your health.

Peripheral Neuropathy

Peripheral neuropathy is a serious condition in which treatment affects nerves in the hands, feet, legs, and/or arms. Symptoms of peripheral neuropathy include numbness, tingling, or even pain in the hands, feet, legs, and/or arms. Some patients may have experienced peripheral neuropathy from previous treatments for multiple 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.

Prevention and Treatment of Peripheral Neuropathy

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

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.

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 antiemetic medication 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.

Prevention and Treatment of Diarrhea

Precautions should be taken to prevent 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 antidiarrheal medication or intravenous hydration as required.

Decreased Platelet Levels

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 returns 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

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), 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.

Other Side Effects of VELCADE®

Other side effects may occur with VELCADE® and include headache, insomnia, occasional rash, fever, cough, back pain, and muscle cramps. Remember to discuss ANY changes in your health with a doctor or nurse on your health care team.

WILL A REDUCTION IN DOSE OF VELCADE® CHANGE THE EFFECTIVENESS OF TREATMENT?

It is important to communicate openly with your doctor or health care 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/m^2. However, a lower dose of 1.0 mg/m^2, which is the first dose reduction your doctor is likely to try, has also been found active against multiple 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.

HOW IS VELCADE® GIVEN?

VELCADE® is a lyophilized (freeze-dried) powder, which must be reconstituted before injection. VELCADE® may be injected through either a peripheral or central intravenous line. VELCADE® is injected over a short period of 3 to 5 seconds. As with all treatments, a doctor or nurse will closely monitor you if you are receiving VELCADE® for the first time.

VELCADE® is given 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 is needed between doses, so that normal cells have a chance to recover from the effects of the drug. Therefore, changes in the administration schedule are limited to delaying an injection for a day, rather than moving the injection up one day.

About the IMF

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

Brian D. Novis
IMF Founder

Myeloma is a little-known, complex, and often misdiagnosed bone marrow cancer that attacks and destroys bone. Myeloma affects approximately 75,000 to 100,000 people in the United States, with more than 20,000 new cases diagnosed each year. While there is presently no known cure for myeloma, doctors have many approaches to help myeloma patients live better and longer.

The International Myeloma Foundation (IMF) was founded in 1990 by Brian and Susie Novis shortly after Brian's myeloma diagnosis at the age of 33. It was Brian's dream that future patients would have easy access to medical information and emotional support throughout their battle with myeloma. He established the IMF with the 3 goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients, their families, friends, and health care providers. Although Brian died 4 years after his initial diagnosis, his dream didn't. Today the IMF reaches out to an international membership of more than 185,000. The IMF was the first organization dedicated solely to myeloma, and today it remains the largest.

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

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

How Can the IMF Help You?

PATIENT EDUCATION

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

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

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

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

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

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

MYELOMA TODAY NEWSLETTER
Our quarterly newsletter is available free of charge by subscription.

SUPPORT

MYELOMA HOTLINE: 800-452-CURE (2873)
Toll-free throughout the United States and Canada, the IMF Hotline is staffed by trained information specialists and is in frequent interaction with members of our Scientific Advisory Board.

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

RESEARCH

BANK ON A CURE®
This DNA bank will provide genetic data research in new drug development.

THE INTERNATIONAL STAGING SYSTEM (ISS)
This updated staging system for myeloma will enhance physicians' ability to select the most appropriate treatment for each patient.

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

Glossary

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

Anemia: A low level of red blood cells in the bloodstream.

Bone marrow: A soft, spongy tissue found in most large bones that produces red and white blood cells and platelets.

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

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

Monoclonal protein (M protein): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. A high level of M protein indicates that myeloma cells are present in large numbers.

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

Neuropathy: Numbness, tingling, and/or pain in the hands, feet, legs, and/or arms.

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

Plasmacytoma: A tumor made up of cancerous plasma cells.

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.

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

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.

Thrombocytopenia: A low level of platelets in the blood. These low levels can cause bruising or bleeding as well as a delay in the injury healing process.

White blood cell: A cell made by the bone marrow that helps fight infection and/or disease.