

Understanding Revlimid®

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Introduction

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

- What Revlimid® is
- How Revlimid® works
- The possible side effects of Revlimid®
- How Revlimid® 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. All words that appear in **bold type** are defined in the glossary at the end of the booklet.

What is Multiple Myeloma?

Multiple myeloma (also known as myeloma and as plasma cell neoplasm) is a malignancy of the **immunoglobulin**-producing plasma cells found in the **bone marrow**. It is a hematologic malignancy resembling leukemia. However, the malignant plasma cells, or myeloma cells, rarely enter the blood stream as in a true leukemia. Instead, the myeloma cells accumulate in the bone marrow, causing:

- Disruption of normal bone marrow function, most commonly giving rise to anemia (a low level of **red cells** in the bloodstream), although reduction in

white blood cell and platelet counts can also occur

- Damage to bone surrounding accumulated myeloma cells
- Release of an abnormal protein, **monoclonal protein (M protein)**, into the bloodstream
- Suppression of normal immune function, observed as reduced levels of normal immunoglobulins and increased susceptibility to infection

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

Confronted with a diagnosis of multiple myeloma, it is important for your doctor to determine the stage of the disease. Disease staging will help determine what parts of the body have been affected and to what extent. This will allow the doctor to decide the best treatment option.

The Stages of Multiple Myeloma

Stage I (low cell mass): Early disease. 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): More advanced disease. One or more of the following are present:

- **Anemia**
- A high level of calcium in the blood
- More than 3 areas of advanced **lytic** bone lesions
- A high level of M protein in the blood or urine

Multiple myeloma is a serious malignancy, but it is treatable. Many patients experience a series of responses, relapses, and remissions. With new treatments, the average survival of 5 years for patients diagnosed with multiple myeloma may be extended.

Following diagnosis, several options are available for initial or frontline therapy. For patients who may be candidates for high-dose therapy with transplant, various induction regimens can be considered, including thalidomide with dexamethasone, dexamethasone alone, or other dexamethasone-containing combinations. The combination of the **alkylating agent** melphalan plus prednisone, a simple oral therapy, is an option for patients not considering transplant with intravenous high-dose melphalan. At the time of relapse, newer agents are



frequently required to achieve further response. Revlimid® is an important new agent available for use in this setting. Velcade® (bortezomib) is also an important new agent available for relapse in patients.

What is Revlimid® and How Does it Work?

Revlimid® is an **immunomodulatory agent**. It is a drug that can modify or regulate the functioning of the immune system. These agents appear to have multiple actions, including both anticancer and anti-inflammatory activities. Immunomodulatory agents induce immune responses, enhance the activity of immune cells, and inhibit inflammation. They are able to alter the levels of various growth factors, called

cytokines and/or **interleukins**, and affect cells of the immune system. Immunomodulatory agents enhance the activation of specialized white blood cells of the immune system – both the T-cell lymphocytes and T cells known as natural killer cells, or NK-cells – which help kill cancer cells.

Revlimid® is a **vascular endothelial growth factor inhibitor**. It belongs to a group of immunomodulatory agents with the ability to inhibit new blood vessel development on which cancer cells depend. Revlimid® is structurally related to thalidomide but has been modified by researchers to take advantage of the anticancer properties, and at the same time substantially reduce the likelihood of nerve or neurologic toxic side effects (**peripheral neuropathy**). Revlimid® has direct and indirect effects on myeloma cells, including the ability to induce programmed cell death of myeloma cells, inhibit myeloma cell growth, inhibit new blood vessel growth, and reduce adhesion of myeloma cells to bone marrow **stromal cells**. Moreover, Revlimid® can act synergistically with other antimyeloma agents and kill myeloma cells that are resistant to conventional therapy.

Clinical studies are investigating the effects of Revlimid® on newly diagnosed patients and on patients with relapsed and refractory myeloma.

Two pivotal Phase III clinical trials of Revlimid® and high-dose dexamethasone versus high-dose dexamethasone alone in patients with

relapsed or refractory myeloma exceeded the prespecified interim efficacy end point for disease progression. Because of these data, the trials were unblinded many months earlier than anticipated, and all patients not on Revlimid® had the opportunity to add Revlimid® to their dexamethasone regimen if needed.

The identical North American and international trials enrolled a total of 705 patients and are being conducted in 97 sites in the United States, Europe, Israel, and Australia. Patients were randomized to receive Revlimid® (25 mg/day) and high-dose dexamethasone or an identically appearing placebo and high-dose dexamethasone.

Patients all received standard high-dose dexamethasone at a dose of 40 mg daily on days 1–4, 9–12, and 17–20 every 28 days and were randomized to receive either Revlimid® 25 mg daily orally on days 1–21 every 28 days, or placebo. One cycle was



28 days. Beginning at cycle 5, the dose intensity of dexamethasone was reduced to 40 mg daily on days 1–4 only, every 28 days. Patients resistant to dexamethasone were excluded. Patients were stratified with respect to bone-marrow involvement, previous stem-cell transplant, and number of previous regimens.

The trials included a primary end point of time-to-disease progression, calculated as the time from randomization to the first documentation of progressive disease. The definition of a complete response (CR) is the disappearance of M protein in serum and urine and less than 5% plasma cells in the bone marrow, confirmed at 2 separate time points 6 weeks apart. The definition of a partial response (PR) is at least a 50% reduction in the level of the serum M protein. Patients achieving a response or stable disease continue on therapy.

The international study enrolled 351 patients from 50 clinical sites, and the North American study enrolled 354 patients from 47 clinical sites. In both studies, the responses exceeded the preestablished efficacy stopping rule for the primary end point: time-to-disease progression. Response data were available on all 691 eligible patients of the 705 enrolled in the study.

Response rates achieved with the combination were about 60%: more than double that seen with dexamethasone alone. Together, these data confirm a significant clinical benefit for

patients receiving Revlimid® plus dexamethasone. Data from these studies will continue to be collected on an ongoing basis.

In both trials, patients treated with the combination had an increase in **side effects** compared with patients receiving dexamethasone alone. The side effects were generally manageable and included constipation, **neutropenia**, diarrhea, **thrombocytopenia**, rash, fatigue, and deep vein thrombosis (blood clot).

New findings in support of low-dose Dexamethasone

However, many oncologists are now prescribing dexamethasone in a once-weekly cycle, often at a dose lower than 40 mg. Based upon recent ECOG trial data the once-weekly dosing schedule is now more of a preferred approach. The ECOG trial evaluated the Revlimid/dexamethasone (high- and low-dose) combinations in the frontline setting. The once per week schedule “low-dose” proved to be more effective (better survival at 1 year) and had significantly fewer side effects. Results were presented at ASCO 2007. Your doctor will work with you to find a dosing schedule that is well tolerated and appropriate to treat your multiple myeloma.

Additional findings for Revlimid® and newly-diagnosed Myeloma

Revlimid® has been reported to be effective in newly-diagnosed multiple myeloma. In a clinical trial, 34 patients received Revlimid® at a dose of 25 mg daily on days 1–21 of



a 28-day cycle. Dexamethasone was given orally at a dose of 40 mg daily on days 1–4, 9–12, 17–20 of each cycle. The dose of dexamethasone was reduced to 40 mg on days 1–4 of each cycle for patients continuing therapy beyond 4 months. Patients also received an aspirin once daily to decrease the risk of a blood clot.

All patients were evaluated for response and toxicity. Of the 34 patients, 31 (91%) had an objective response (a response confirmed by a health-care provider), including 2 patients (6%) who achieved a complete response (CR), 11 patients (32%) who achieved a near complete response/very good partial response (nCR/VGPR), and 18 patients (53%) who achieved a partial response (PR).

Of the 3 patients not achieving an objective response, 2 met criteria for minor response, and one had stable disease. The median time to response was 1 month. Adequate stem cells (>3.0 million stem cells [CD34 cells]/kg body weight) were obtained in all patients who proceeded to autologous stem cell transplantation. The side effect profile was manageable, but there was a 47% incidence of grade 3 (out of 4 possible grades) or higher nonhematologic toxicity: most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (lung inflammation) (6%), and rash (6%). One patient died while participating in the study; the death was considered unrelated to therapy. One patient developed a pulmonary embolism (blood clot that

travels to the lung) but recovered with therapy. Two large cooperative group trials are currently testing Revlimid®/dexamethasone as initial therapy for multiple myeloma in the United States.

Revlimid® is also being tested for use as a single agent. A multicenter, Phase II, open-label study is ongoing to evaluate the effectiveness and safety of single-agent Revlimid® administered at a dose of 30 mg once a day for 21 days every 28 days. The study enrolled 222 patients, all of whom had received at least 2 previous treatments for myeloma. Preliminary results show that a PR or better occurred in 25% of patients and stable disease or better in 71%. Time-to-progression was a median of 22.4 weeks (range 1.8–66 weeks). The most common treatment-related side effects included upper respiratory tract infection, neutropenia, and thrombocytopenia. Side effects have been manageable with a very low incidence of deep vein thrombosis (DVT) and minimal treatment-caused neuropathy.

What are the Possible Side Effects of Revlimid®?

Most of the side effects associated with Revlimid® 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.

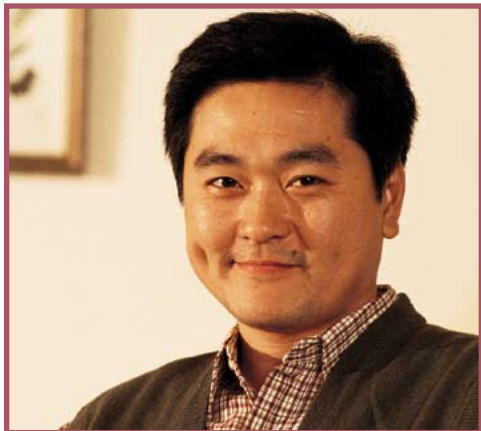


In clinical trials conducted to date, Revlimid® has a different safety profile from thalidomide. Significant sleepiness, constipation, or neuropathy – common side effects seen with thalidomide therapy – are much less frequent. Revlimid® does not appear likely to cause the type of severe birth defects noted in the past with thalidomide, but nonetheless is an analogue of thalidomide. Additional studies are ongoing to determine the risk of birth defects. While these studies are being conducted, a risk-management plan called RevAssist is designed to prevent exposure during pregnancy. With RevAssist, only registered pharmacists and clinicians can prescribe and dispense Revlimid®. The plan requires patients, including female patients of child-bearing potential, to undergo mandatory pregnancy testing, and to give informed consent before taking Revlimid®. Female patients of child-bearing potential and all

male patients are required to complete a monthly phone survey. Clinicians must check pregnancy tests, limit prescriptions to a 28-day mail supply, and report any pregnancies to the FDA.

Safety information about Revlimid® is derived from clinical trials, and as many clinical trials are ongoing, no definitive conclusions can yet be made. The events that have been observed are listed below, from most frequent to least frequent.

- Constipation
- Neutropenia
- Diarrhea
- Thrombocytopenia
- Rash
- Fatigue
- Deep-vein thrombosis (DVT)



Recently, the FDA approved Revlimid® for the treatment of patients with myelodysplastic syndromes, a disorder in which the bone marrow does not function normally, and a sufficient number of normal blood cells are not produced. With this approval, Black Box Warnings have been included to address the prevention of exposure during pregnancy and the potential need to modify the dose due to lowered blood counts and an increased risk of blood clots.

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

Decreased Platelet Levels – thrombocytopenia

Patients taking Revlimid® may 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.

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.

Decreased White Blood Cell Levels – neutropenia

Patients taking Revlimid® may experience a condition called neutropenia: a lowered level of white cells (neutrophils) in the blood. Neutrophils help blood to fight infection; fewer neutrophils can lead to a “cold” with fever, sore throat, and mouth sores.

Prevention and Treatment of Decreased White Blood Cell Levels

You should inform your physician if you experience fever, sore throat, or mouth sores. Fever is the symptom that usually indicates infection in a person who has neutropenia. It is an important sign that immediate medical attention is needed. The treatment of neutropenia depends on its cause and severity. Sometimes the bone marrow recovers by itself without treatment. The neutropenia accompanying viral infections (such as influenza) may be transient and resolve after the infection has cleared. Mild neutropenia generally has no symptoms and may not need treatment.

Fatigue

Fatigue is commonly associated with Revlimid® 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 provider to discuss fatigue issues

Deep Vein Thrombosis

Deep vein thrombosis (DVT) is a serious condition and is potentially life threatening. DVT is a



blood clot in a deep vein of the lower extremities (usually occurring in the leg or thigh, and very occasionally in the neck or upper arm). A blood clot from a DVT can break loose (embolize) and travel to the heart or lungs. An embolus is very dangerous. If you start taking Revlimid® and experience warmth, swelling, redness, difficulty breathing, and/or pain in an extremity, notify your doctor as soon as possible.

Prevention and Treatment of DVT

You are strongly advised to contact your physician if you experience swelling and/or redness and/or pain in a leg or thigh. Your doctor will diagnose your condition to determine whether or not it is a DVT. Treatment of a DVT may depend upon both its location and underlying cause. Your doctor may prescribe a blood thinner to keep the clot from getting larger.

Rash

Rash is a serious concern. Although it seldom occurs, it is potentially dangerous, as a rash may be mild initially and then escalate in severity. Drug rashes vary in severity from mild redness with tiny bumps over a small area to peeling of the entire skin. Rashes may appear suddenly within minutes after a person takes a drug, or they may be delayed for hours or days.

Prevention and Treatment of Rash

You are strongly urged to notify your doctor if you experience any rash. Proper evaluation of a skin rash requires a visit to a doctor or other healthcare professional. If detected and managed appropriately, a rash is reversible.

Other Side Effects to be Aware of When Revlimid® is Combined with Dexamethasone

The major studies mentioned above, indicating benefit of Revlimid® in the relapse setting, used a combination of Revlimid® with dexamethasone. It is important to be aware that additional toxicities can occur with this combination versus Revlimid® alone.

Side effects that may occur with Revlimid® plus dexamethasone include muscle weakness, anxiety, agitation, cardiac arrhythmias, nausea, increased blood sugar, elevated liver enzymes, and constipation and/or diarrhea. Full details with regard to dexamethasone are discussed in a separate booklet. Remember to discuss any changes in your health with a doctor or nurse on your healthcare team.

Will a Dose Reduction in Revlimid® Change the Effectiveness of Treatment?

It is important to communicate openly with your doctor or healthcare professional and keep regular appointments to maintain your Revlimid® treatment schedule. Your doctor may choose to modify your dose of Revlimid® as part of an overall plan to manage a particular side effect that you experience. The dose used in the Phase III clinical studies is 25 mg per day. If you experience a severe

side effect, your doctor may modify your dose in either amount or schedule to reduce the severity of the side effect while maintaining treatment.

How is Revlimid® Given?

Revlimid® is given as capsules. The most common dosing used in multiple myeloma is 25 mg given orally daily on days 1–21 and repeated every 28 days (days 22–28 are rest days). Doses are then modified based on side effects.

IMF Hotline:

USA & Canada only: 800-452-CURE (2873)

Elsewhere: 818-487-7455

IMF Web site: www.myeloma.org

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 according to recent data. 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 165,000. 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.

Antibody: A protein produced by some of the body's white blood cells that helps fight infection.

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 body organ.

Cytokine: A growth factor produced by T-cells that stimulates the growth of T cells and B cells.

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

Febrile neutropenia: Presence of a low neutrophil count in the blood that is associated with fever; may indicate the presence of infection.

Immunoglobulin: An antibody.

Immunomodulatory agent: Drug that affects, enhances, or suppresses the immune system.

Interleukin: Various cytokines involved in the growth and survival of myeloma cells.

Lymphocyte: A type of white blood cell, mainly B-cells that produce immunoglobulins and T-cells that produce cytokines and interleukins. Also includes natural killer cells (**NK-cell**). A type of lymphocyte with enzymes that can kill tumor cells or microbial cells.

Lysis (lytic): Dissolution or destruction of cells

Monoclonal protein (M protein): An abnormal protein produced by myeloma cells that accumulate 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.

Neutrophil: A white blood cell.

Neutropenia: A low level of white blood cells in the bloodstream.

Peripheral 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.

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 the treatment with a drug. The term usually refers to an unwanted effect, but some side effects may be beneficial.

Stromal cell: Structural cells of the bone marrow that help support and nourish the blood-producing cells.

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

Vascular endothelial growth factor (VEGF): A growth factor that promotes the growth of new blood vessels (angiogenesis).

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