

Understanding Revlimid®

International Myeloma Foundation
12650 Riverside Drive, Suite 206
North Hollywood, CA 91607 USA

Telephone:

800-452-CURE (2873)

(USA & Canada)

818-487-7455

Fax: 818-487-7454

TheIMF@myeloma.org

www.myeloma.org



Table of Contents

Introduction	5
What is Revlimid® and How Does it Work?	6
Use of Revlimid® as Maintenance in the Post-Transplant Setting	9
What are the Possible Side Effects of Revlimid®?	11
Other Side Effects to be Aware of When Revlimid® is Combined with Dexamethasone	16
Dose Adjustments with Revlimid®	17
Will a Dose Reduction in Revlimid® Change the Effectiveness of Treatment?	18
How is Revlimid® Given?	18
About the IMF	19
Glossary	26



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.

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. A significant number of patients are living 10 and even 20 or more years with the disease.

Following diagnosis, several options are available for initial or front-line therapy. Various induction regimens can be considered, both for patients who are candidates for high-dose chemotherapy with stem cell transplant and those who are not. (see the IMF's *Patient Handbook*). At relapse, newer agents are frequently required to achieve

further response. Revlimid is an important novel agent for use in this setting.

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 myeloma in newly diagnosed patients and on in patients with relapsed and refractory myeloma. Clinical trials are also studying the use of Revlimid® for maintenance therapy.

Based on the data from two pivotal Phase III clinical trials of Revlimid® and high-dose dexamethasone versus high-dose dexamethasone alone in patients with relapsed or refractory myeloma, in June 2006, the FDA approved Revlimid® in combination with dexamethasone for use in patients who have had at least one prior therapy. This relapse setting approval is the norm for most countries, with specifics varying from country to country.

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



Findings in support of low-dose Dexamethasone

Many oncologists are now prescribing dexamethasone in a once-weekly cycle, often at a dose lower than 40 mg. Based upon ECOG trial E4A03, which compared Revlimid® plus standard high-dose dexamethasone versus Revlimid® plus low-dose dexamethasone (40 mg once weekly), the once-weekly dosing schedule is now the 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. 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® was reported to be effective in newly-diagnosed multiple myeloma in two Mayo Clinic trials in 2005 and 2007. (see E4A03, above). Currently there are many ongoing trials of Revlimid®, alone and in combination, in newly-diagnosed myeloma in the US and Europe.

In addition, Revlimid® is being investigated in various combinations, such as melphalan plus prednisone (MPR); Velcade® (bortezomib) plus low-dose dexamethasone (VRd), cyclophosphamide and dexamethasone (RCD), and Adriamycin and dexamethasone (RAD).

Current National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Multiple Myeloma include Revlimid®/dexamethasone as primary induction therapy for transplant candidates (category 1, or “recommendation based upon high-level evidence, e.g., randomized, controlled trials, and there is uniform NCCN consensus”), and Revlimid®/low-dose dexamethasone as primary induction therapy for non-transplant candidates (category 1).

Use of Revlimid® as Maintenance in the Post-Transplant Setting

At the annual meeting of the American Society of Hematology (ASH) in December 2010, two large randomized trials evaluating Revlimid® as a maintenance therapy after

high-dose melphalan with autologous stem cell transplant were presented. Results from both trials, IFM 005 and the CALGB, were very promising, with remissions twice as long with Revlimid® versus placebo (Progression Free Survival - PFS of 42 months versus 21 months). Further follow-up is necessary to assess overall survival benefit. Based upon the results of the further follow-up in these pivotal trials, treating physicians will be able to make appropriate recommendations concerning this treatment decision.

The NCCN includes Revlimid® as an option for post-transplant maintenance therapy, but in category 2A, which means that results of clinical trials have not yet undergone full peer review; and that the safety and efficacy data are still preliminary.



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. Animal studies conducted earlier showed evidence that Revlimid® caused the same type of severe birth defects as those in the past with thalidomide. 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)

In the prescribing information for Revlimid (March 2010) the Black Box Warnings include: the risk of birth defects or death to a developing baby; the risks of neutropenia and thrombocytopenia; and the increased risk of deep vein thrombosis and pulmonary embolism (the latter a blood clot that travels to the lung).

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. 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, *Understanding Dexamethasone and Other*

Steroids, available from the IMF. Remember to discuss any changes in your health with a doctor or nurse on your healthcare team.

Dose Adjustments with Revlimid®

The standard dose for Revlimid® is 25 mg each day for 21 days of a 28-day (one month) cycle. After 3-6 months of use, your physician may consider reducing the dose because of lowered white and/or red blood cell counts. In addition, there may be cumulative side effects such as fatigue or even slight neuropathy. Your physician may decide that dose reduction is appropriate, lowering first to 15 mg, then to 10 mg, and even to 5 mg if necessary.

Ongoing results from clinical trials show that with such dose reductions, treatment benefit is retained. Long remissions were reported in the MM-009 and -010 relapse trials and



patients were able to continue treatment beyond 10 months (with dose reductions) and achieve extended benefit.

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. Although 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 three goals of treatment, education, and research. He sought to provide a broad spectrum of services for patients and, their families, friends, and healthcare providers. Although Brian died four years after his initial diagnosis, his dream did not. Today, the IMF reaches out to an international membership of more than 195,000. 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.

MYELOMA MANAGER™ PERSONAL CARE ASSISTANT™

This software program was developed by the IMF and is designed specifically to help patients and caregivers to capture, display, and store laboratory test results, and to access important information. It is available free of charge on the IMF website at www.myeloma.org. Currently this program is only compatible with PCs.

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.

IMF 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 leaders of myeloma support group leaders.

RESEARCH

BANK ON A CURE®

This DNA bank will provides genetic data research in new drug development.

THE INTERNATIONAL STAGING SYSTEM (ISS)

This updated staging system for myeloma enhances 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; they have remained in the field and are actively pursuing a cure for this disease.

Glossary

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.

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.

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.

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

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.