



PRODUCT PROFILER

Lenalidomide (Revlimid[®])

An Immunomodulatory Agent for the Treatment of
Multiple Myeloma and Myelodysplastic Syndromes

FDA-Approved Indications:

- Multiple Myeloma
- Myelodysplastic Syndromes

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THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

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PRODUCT PROFILER

Lenalidomide (Revlimid): An Immunomodulatory Agent for the Treatment of Multiple Myeloma and Myelodysplastic Syndromes

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Lenalidomide: An Immunomodulatory Agent for the Treatment of Multiple Myeloma and Myelodysplastic Syndromes

INTRODUCTION

This Product Profiler introduces health care professionals to a new drug, lenalidomide (Revlimid, Celgene), which has recently been approved by the Food and Drug Administration (FDA) for the treatment of a subset of patients with multiple myeloma (MM), a hematological cancer, and myelodysplastic syndromes (MDS), a group of diseases characterized in most patients by refractory peripheral blood cytopenias and hypercellular bone marrow.

Lenalidomide is an analogue of the established drug thalidomide, but it enjoys a better safety profile than thalidomide. Also, unlike many other agents used in the treatment of these diseases, it is available as an oral capsule.

A number of therapies are already on the market for MM and MDS, but their usefulness is limited by their efficacy and, at present, there is no cure for these conditions. We will provide a brief overview of MM and MDS and current treatment options, followed by a review of the evidence-based literature supporting the FDA-approved indications for lenalidomide.

DISEASE BACKGROUND

Multiple Myeloma

Multiple myeloma is a B-cell malignancy characterized by excessive monotypic plasma cells in the bone marrow associated with monoclonal protein in the serum and/or urine, reduced normal immunoglobulin concentrations, and lytic bone disease¹ (Figure 1). It is the third most prevalent blood cancer in the U.S., affecting about 50,000 people.¹ It represents approximately 1% of all cancers and 2% of all cancer deaths.²

The average age at diagnosis is about 68 years, and only 1% of cases are diagnosed in individuals younger than 40 years of age. African-Americans and Native Pacific Islanders have the highest reported incidence of this disease, and Asians have the lowest. The higher incidence of myeloma in African-Americans and the much less frequent occurrence in Asians suggest genetic factors.²

No cause of MM has been identified.² Age is

the most significant risk factor for MM, as 99% of cases are diagnosed in people over the age of 40, and more than 50% occur in people over the age of 71. Chromosomal changes including chromosomal translocations (generally involving the Ig heavy chain gene), and chromosomal gains and losses are very frequent in myeloma.² These abnormalities have an important influence on disease outcomes.

Etiology

The use of sensitive tests such as fluorescent *in situ* hybridization (FISH) has led to the detection of genetic abnormalities in at least 90% of patients with MM.³ Associated environmental factors include engine exhaust fumes, solvents (benzene, creosote), other chemicals, and ionizing radiation (in atomic bomb survivors, radiation workers, and patients undergoing radiotherapy for ankylosing spondylitis). People in agricultural occupations, petroleum workers, workers in leather industries, and cosmetologists all seem to have a higher-than-average chance of developing MM. Exposure to herbicides, insecticides, petroleum products, heavy metals, plastics, and various dusts, including asbestos, also appear to be risk factors.²

MM is characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of intact monoclonal immunoglobulin (IgG,

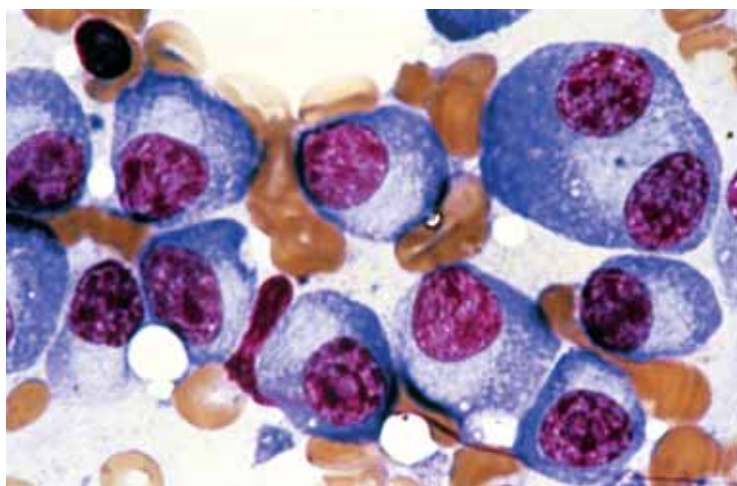


FIGURE 1 Myeloma cells. (From Vescio R. Multiple Myeloma & Amyloidosis Program, Jonsson Comprehensive Cancer Center/Cedars-Sinai Medical Center, 2005.²³)

IgA, IgD, or IgE) or Bence-Jones protein (free monoclonal κ and λ light chains). Hypercalcemia, anemia, renal damage, increased susceptibility to bacterial infection, and impaired production of normal immunoglobulin are common clinical manifestations of MM. It is often also characterized by diffuse osteoporosis, usually in the pelvis, spine, ribs, and skull.²

Pathophysiology

The plasma cells of patients with MM phenotypically express CD38+, CD56+, and CD138+, and about 20% of the cells express CD20. Overproduction of interleukin-6 (IL-6) (a plasma cell growth factor), tumor necrosis factor (TNF), and IL-1 are generally observed in MM.⁴ Deletions of p53, a tumor-suppressor gene, are also found in patients.

Cytogenetically, deletions of chromosome 13 are not infrequent; the deletions are observed in approximately 15% of patients and have been associated with adverse prognoses.⁵

Myeloma plasma cells, however, have specific adhesion molecules on their surface, allowing them to target bone marrow, where they attach to structural cells called *stromal cells*. Once the myeloma cells attach to bone marrow stromal cells, several interactions cause myeloma cells to grow. Chemical messengers called *cytokines* are produced by both myeloma cells and stromal cells. These cytokines, such as IL-6, stimulate the growth of myeloma cells and prevent apoptosis, leading to proliferation of myeloma cells and ultimately resulting in bone destruction.

Myeloma cells also produce growth factors that promote angiogenesis, the creation of new blood vessels that provide oxygen and nutrients that promote tumor growth.¹ Vascular endothelial growth factor (VEGF) plays a key role in angiogenesis. Angiogenesis encourages the reproduction of myeloma cells, which increase in number and begin to infiltrate the bone marrow, eventually constituting more than 10% of the cells present. Mature myeloma cells can grow unchecked.

As tumors grow, they invade the hard outer part of the bone, the solid tissue. In most cases, the myeloma cells spread into the cavities of all the large bones of the body by adhering to extracellular matrix proteins and stromal cells that localize tumor cells in the marrow milieu, leading to the secretion of inflammatory cytokines (TNF, VEGF).¹ Myeloma cells are identical and produce the same immunoglobulin protein, called monoclonal (M) protein or paraprotein, in large quantities. Although the specific M protein varies among patients, it is always exactly the same in any one patient.

Age is the only other factor that significantly affects outcome. Survival of more than five years is associated with ages younger than 60 years; survival for less

than two years is associated with ages above 60 years.¹⁵ Other correlations include platelet count below $130 \times 10^9/L$ and serum levels of lactate dehydrogenase (LDH) above normal.⁵

Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) are heterogeneous clonal hematopoietic stem-cell disorders characterized in most patients by refractory peripheral blood cytopenias associated with a hypercellular bone marrow and an increased risk of acute myelogenous leukemia (AML) transformation.⁶⁻⁹ Dysplasia, the morphological hallmark of MDS, refers to discordant nuclear-cytoplasmic maturation and accelerated apoptosis.¹⁰ The cytopenias that complicate these stem-cell disorders are the result of a diminished responsiveness of bone marrow progenitor cells to normal trophic signals, leading to premature hematopoietic progenitor cell loss and ineffective hematopoiesis.^{11,12}

Anemia is present at the initial diagnosis, although nearly 50% of patients present with no outward symptoms. Signs and symptoms indicative of MDS are cytopenia-related and may include fatigue, pallor, infection, and bleeding. Associated laboratory findings include anemia, neutropenia, and thrombocytopenia.¹³

A distinct MDS subtype, the 5q syndrome, as defined by the World Health Organization (WHO) classification, involves an isolated interstitial deletion of the long arm of chromosome 5.¹⁴ This subtype is associated with a better prognosis than other subtypes of MDS. Patients with an isolated del (5q) have a median survival of 107 months and are predominantly female, with a median age of 65 years.¹⁴

MDS patients may be stratified into two major risk groups:¹⁶

- Low-risk patients are in the International Prognostic Scoring System (IPSS) intermediate-1 (low) category.
- Higher-risk patients are in the IPSS intermediate-2 (high) category.

Low-intensity therapy utilizes non-chemotherapeutic agents such as lenalidomide, thalidomide, anti-thymocyte globulin, cyclosporine, and TNF receptor fusion protein.¹⁶

Incidence and Prevalence

MDS is a condition with a yearly incidence of about 2 to 13 per 100,000 people, with higher rates among older people and slightly higher rates among men. People older than 70 years of age have an incidence rate of MDS of about 20 to 50 cases per 100,000 people per year.¹⁷ Because of the problems of diagnosis and classification, precise data on the incidence and prevalence of MDS are still lacking.

Etiology and Risk Factors

From 80% to 90% of MDS cases occur *de novo* or with a known exogenous mutagenic event.^{6,29} The remaining 10% to 20% of cases are secondary and can be connected to a specific environmental exposure. Although the etiologic mechanism of MDS is not known, exposure to ionizing irradiation or bone marrow-damaging agents, including chemotherapeutic drugs, along with genetic factors, may enhance the risk of developing secondary MDS. One of the common chromosomal alterations found in MDS is del (5q).¹⁸⁻²¹

Cytogenetic abnormalities are found in the dysplastic clone in 40% to 75% of patients with MDS.²¹ Deletion of the long arm on chromosome 5—del (5q)—is the best described chromosomal aberration associated with MDS. The deletion accounts for about 22% of all cytogenetic abnormalities. The del (5q) cytogenetic abnormality is associated with transfusion-dependent anemia.^{21,22}

Patients with MDS are classified as having one of five subtypes of disease:¹⁶

- refractory anemia
- refractory anemia with ringed sideroblasts
- refractory anemia with an excess of blasts (RAEB)
- refractory anemia with an excess of blasts in transformation
- chronic myelomonocytic leukemia

Myelodysplastic syndromes are generally indolent, with blood counts staying relatively stable for at least several months. Each subtype is characterized by a different degree of disease severity along with variable patient survival rates. Several types of evaluations are needed to determine the clinical status of patients with MDS in order to prescribe the appropriate treatment.¹⁶

The WHO classification and the criteria for MDS have designated the 5q syndrome as a specific myelodysplastic syndrome: MDS associated with isolated (5q) together with characteristic features.²² It is important to distinguish patients with the del (5q) cytogenetic abnormality in selecting treatment because lenalidomide is effective in producing red blood cell (RBC) transfusion-independence in patients with transfusion-dependent anemia caused by low-risk or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Immunomodulatory agents (e.g., thalidomide and lenalidomide), are considered to be useful for low-intensity therapy for MDS,¹⁴ although thalidomide is limited because of its sedative and neurological effects.²⁰ Lenalidomide was added to the National Comprehensive Cancer Network's 2006 guidelines for the treatment of MDS in patients with deletion 5q chromosomal abnormalities.¹⁶

Current Drug Therapy Options

MULTIPLE MYELOMA

The standard approach for the initial treatment of patients with myeloma involves the use of conventional chemotherapy and bisphosphonates.²³ Conventional dose primary therapy consists of melphalan/prednisone (MP) (considered the gold standard), dexamethasone, vincristine/doxorubicin/dexamethasone (VAD), liposomal doxorubicin/vincristine/dexamethasone (DVD), or thalidomide/dexamethasone. If a response occurs, several approaches for further management based on age, characteristics, and preferences of the patient may be used: observation; maintenance therapy; autologous stem cell transplantation; or allogeneic stem cell transplantation.^{24,25}

Patients with progressive disease after primary therapy can be treated with salvage therapies. The initial induction therapy may be used again if relapse occurs at least six months after the primary therapy. Salvage therapies may consist of cyclophosphamide-VAD (C-VAD), etoposide/dexamethasone/cytarabine/cisplatin (EDAP), high-dose cyclophosphamide, thalidomide, thalidomide/dexamethasone, dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE), or bortezomib (Velcade), a protease inhibitor that degrades ubiquitinated proteins.²⁵

Remission rates and response duration with second-line therapies are not encouraging. Approximately 40% of resistant and relapsing patients may achieve a second remission with glucocorticoids. Second-line combination chemotherapy regimens (primarily those including alkylating regimens) may help a small percentage of patients: 8% of resistant patients and 22% of refractory patients. A slightly higher percentage of patients receiving doxorubicin-based regimens may respond. The duration of the second response may be less than one year.²⁶

Patients who fail to achieve remission on re-induction are considered refractory to treatment. Approximately one third of patients with myeloma do not respond to induction therapy, and eventually all patients who achieve remission will relapse. Patients refractory to initial chemotherapy as a result of drug-resistance have a poor prognosis, with few responding to other therapies. Patients who respond to chemotherapy initially but who relapse during the course of treatment or within the following few months are more likely than drug-resistant patients to respond to second-line therapy.²⁶

On the basis of the poor disease-free outcomes and the low overall survival rate with these older drugs

used for induction therapy, newer drugs are definitely needed. Bortezomib has been found to be superior to high-dose dexamethasone for patients with MM who experience relapse after one to three previous therapies.²⁷ Despite serious adverse effects, more patients were alive after one year of treatment with bortezomib than was the case with patients receiving the standard treatment.²⁹

Thalidomide has been shown to exert effectiveness in one-third of patients with recurrent or refractory MM, although patients exhibited major nonhematological adverse effects (e.g., fatigue/sedation, constipation, skin toxicity or rash, and peripheral neuropathy).²³ Thalidomide/dexamethasone treatment in patients with newly diagnosed multiple myeloma resulted in a better response rate than did dexamethasone alone.²⁸

MYELOUDYPLASTIC SYNDROMES

A combination of cytarabine (Ara-c) and an anthracycline has been the cornerstone of intensive chemotherapy.²⁹ Variable complete remission rates have been reported with the use of these regimens (13% to 60%), but median remission duration and survival times are minimal, usually less than one year. The death rate from toxic events, such as bleeding and infection from induction therapy, was 5% to 20%.²⁹

Intermediate or high doses of cytarabine combined with idarubicin (Idamycin) or fludarabine (Fludara) in induction protocols have brought about higher rates of a complete response when compared with conventional protocols. However, the toxicity is higher, and not all of the patients, especially those older than 60 years of age, can tolerate the intensive regimens.¹⁵

Azacitidine, which has been used in intermediate-2 and high-risk MDS patients, was found to be partially effective, although treatment was associated with neutropenia and thrombocytopenia. Azacitidine is indicated for patients with all five MDS subtypes described on page 4: refractory anemia or refractory anemia with ringed sideroblasts [if accompanied by neutropenia or thrombocytopenia or requiring transfusions]; refractory anemia with excess blasts; refractory anemia with excess blasts in transformation; and chronic myelomonocytic leukemia.

Other therapies include hematopoietic growth factors, such as recombinant human erythropoietin, granulocyte colony-stimulating factor, and granulocyte/macrophage colony-stimulating factor. These agents have been shown to improve white blood cell

(WBC) counts and to reduce infections in MDS patients; however, the effects are transient.²⁹

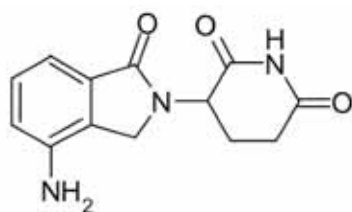
On May 3, 2006, the FDA approved decitabine (Dacogen) for Injection. Decitabine is indicated for the treatment of patients with MDS, including previously treated and untreated *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia), and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups.³⁰

Supportive care remains the mainstay of treatment for low-risk or elderly MDS patients, whether or not additional treatments are administered. Supportive therapies include leuko-reduced RBC transfusions for symptomatic anemia, antibiotics for bacterial infections in neutropenic patients, and antifibrinolytic agents or platelet transfusions for those with thrombocytopenia and refractory bleeding.³¹ Patients receiving blood transfusions may experience transfusion-related reactions, including allergic or febrile reactions, acute immune hemolytic reactions, and other blood-borne infections.

Chemistry and Pharmacokinetics

CHEMICAL AND PHYSICAL PROPERTIES⁴

Lenalidomide (Revlimid, Celgene), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic and anti-neoplastic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C₁₃H₁₃N₃O₃, and the gram molecular weight is 259.3.



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl)
piperidine-2,6-dione

MECHANISM OF ACTION AND CLINICAL PHARMACOLOGY⁴

The mechanism of action of lenalidomide is not fully characterized. Lenalidomide has anti-neoplastic, immunomodulatory and anti-angiogenic properties; it inhibits the secretion of pro-inflammatory cytokines and increases the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. The drug inhibits cell proliferation with varying effectiveness in some, but not all, cell lines. It inhibits the expression of cyclooxygenase-2 (COX-2) but not COX-1 *in vitro*.

Lenalidomide is effective in inhibiting the growth of MM cells obtained from patients as well as MM.1S cells (a human MM cell line). It also blocks the production of cytokines, which are important for cell growth in MM, including TNF- α and IL-6.

PHARMACOKINETICS AND DRUG METABOLISM⁴

Absorption

In healthy volunteers, lenalidomide is rapidly

absorbed following oral administration. Maximum plasma concentrations (C_{max}) occur between 0.625 and 1.5 hours after the dose is given. Coadministration with food does not alter the extent of absorption (the area under the curve [AUC] concentration), but it does lower the C_{max} by 36%.

The pharmacokinetic disposition of lenalidomide is linear. The C_{max} and AUC concentration increase proportionately with the increase in dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

Pharmacokinetic sampling was not performed in MDS patients. In MM patients, the C_{max} occurred between 0.5 and four hours after the dose was given on both Days 1 and 28. AUC and C_{max} values increased proportionally with the dose following single and multiple doses. AUC value in multiple myeloma patients was 57% higher than in healthy male volunteers.

Pharmacokinetic Parameters

Distribution. *In vitro* (¹⁴C)-lenalidomide binding to plasma proteins is approximately 30%.

Metabolism and Excretion. The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide was eliminated unchanged through urinary excretion. The process exceeded the glomerular filtration rate and therefore was partially or entirely active. The half-life of elimination was approximately three hours.

Special Populations

Patients with Renal Insufficiency. The pharmacokinetics of lenalidomide in MDS patients with renal dysfunction has not been determined. In patients with MM, those with mild renal impairment had an AUC 56% greater than those with normal renal function.

Patients with Hepatic Disease. The pharmacokinetics of lenalidomide in patients with hepatic impairment has not been studied.

Pediatric Patients. No pharmacokinetic data are available in patients younger than 18 years of age.

Clinical Trials

MULTIPLE MYELOMA⁴

Two randomized studies (Studies 1 and 2) were conducted to evaluate the efficacy and safety of lenalidomide. These multicenter, multinational, double-blind, placebo-controlled studies compared lenalidomide plus oral pulse high-dose dexamethasone therapy with dexamethasone therapy alone in patients with MM who had received at least one prior treatment.^{4,32}

In both studies, patients in the lenalidomide/dexamethasone group received 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took one placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups received 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first four cycles of therapy. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first four cycles of therapy. In both studies, treatment was to continue until disease progression.

Dose adjustments in each study were allowed based on clinical and laboratory findings. The primary efficacy endpoint in both studies was time to progression (TTP) (Figure 2). Figure 3 summarizes the response rates based on the best response assessments for Studies 1 and 2.

Three hundred forty-one patients were evaluated in Study 1: 170 in the lenalidomide/dexamethasone group and 171 in the placebo/dexamethasone group. Three hundred fifty-one patients were evaluated in Study 2: 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group (Table 1). In the two studies, base-

line demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups.

Preplanned interim analyses of both studies showed

Table 1 Studies 1 and 2: Patient Characteristics

	Study 1		Study 2	
	Len + Dex	Dex	Len + Dex	Dex
n	170	171	176	175
Male	60%	59%	59%	59%
Median age, yr	64	62	62	63
ECOG PS ≤1	89%	95%	85%	82%
DS stage III	66%	67%	65%	63%
Lytic lesions	69%	77%	77%	80%
Mean marrow plasmacytosis	33%	31%	33%	30%
Mean time from Dx to Tx, yr	3.6	3.9	4.2	4.6
≥1 prior SCT	61%	58%	56%	54%
≥2 prior MM regimens	56%	54%	64%	64%

Data from Revlimid product information;⁴ Weber D. ASCO Annual Meeting, June 2–6, 2006;³⁴ available at: <http://ir.celgene.com>; and Dimopoulos MA. 11th Congress of the European Hematology Association Meeting, June 15–18, 2006.³³ DS = Durie-Salmon (baseline MM stage); ECOG PS = Eastern Cooperative Oncology Group performance status; Len = lenalidomide; Dex = dexamethasone; MM = multiple myeloma; SCT = stem-cell transplantation.

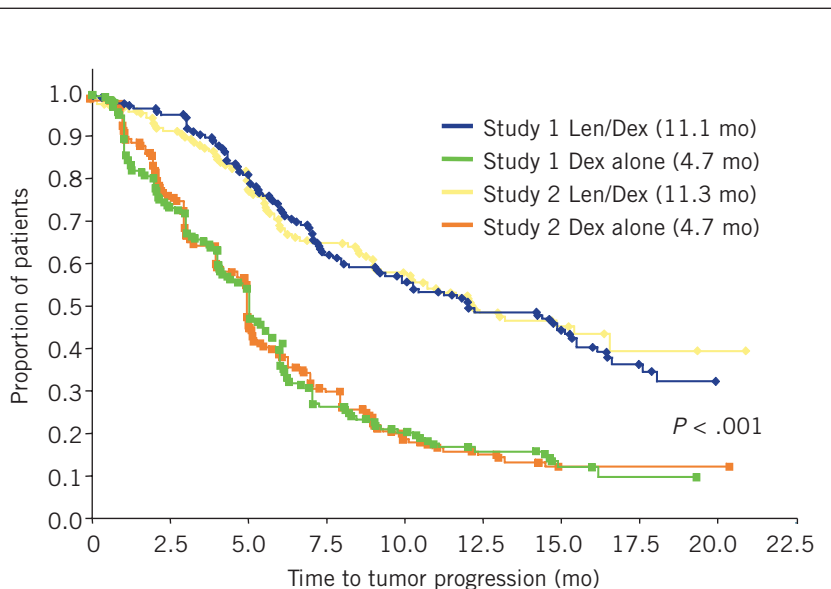


FIGURE 2 Studies 1 and 2, time to progression. Len = lenalidomide; Dex = dexamethasone. (Data from Dimopoulos MA. 11th Congress of the European Hematology Association, June 15–18, 2006.³³)

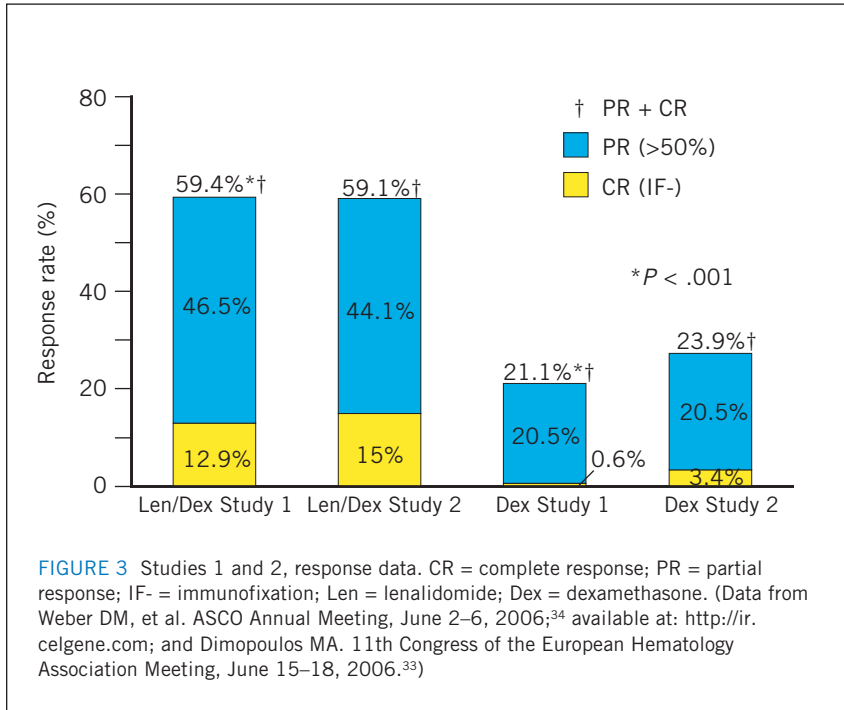


FIGURE 3 Studies 1 and 2, response data. CR = complete response; PR = partial response; IF- = immunofixation; Len = lenalidomide; Dex = dexamethasone. (Data from Weber DM, et al. ASCO Annual Meeting, June 2–6, 2006;³⁴ available at: <http://ir.celgene.com>; and Dimopoulos MA. 11th Congress of the European Hematology Association Meeting, June 15–18, 2006.³³)

In another clinical trial, lenalidomide was used in combination with melphalan and prednisone (R-MP) in patients older than 65 years with newly diagnosed symptomatic MM. The patients received nine courses of lenalidomide (5–10 mg/day for 21 days every four to six weeks) plus melphalan 0.18–0.25 mg/kg and prednisone 2 mg/kg for four days every four to six weeks.

After three cycles of R-MP, myeloma protein was reduced by 75% to 99% in one patient (11.1%), responses of 50% to 74% were reported for eight patients (55.6%), and responses of less than 50% were noted for five patients (33.3%). No disease progressions were observed. Grade 3 or 4 adverse events were reported in nine patients (35%).

The investigators concluded that significant response rates were observed and that the combination

that lenalidomide/dexamethasone was significantly superior ($P < .0001$) to dexamethasone alone for the primary efficacy endpoint, TTP. The studies were unblinded to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination. Complete response and overall response rates in the lenalidomide/dexamethasone arm were significantly higher than those in the dexamethasone-alone arm in both studies.

The overall response rates for lenalidomide/dexamethasone were 59.4% and 59.1% in Studies 1 and 2, respectively, as opposed to 21.1% and 23.9%, respectively, in patients treated with placebo/dexamethasone in these studies.^{33,34}

As reported at the 2006 American Society of Clinical Oncology (ASCO) Scientific Symposium, the primary endpoint of time to disease progression in the lenalidomide/dexamethasone arm was 11.1 months (11.3 months, International), compared with a median time to disease progression of 4.7 months for the dexamethasone-alone arm ($P = .0001$). Overall response rates with lenalidomide/dexamethasone were 59.4% (59.1%, International) and 21.1% (23.9%, International) with dexamethasone alone ($P = .0001$). From the investigators' assessment, the complete response rates in Studies 1 and 2, respectively, were 12.9% and 15% with lenalidomide/dexamethasone versus 0.6% and 3.4% with dexamethasone alone.^{33,34} An increased number of adverse effects was noted in the combination arm, compared with the dexamethasone/placebo arm, particularly grades 3 and 4 neutropenia and thrombocytopenia.^{33,34}

represents a reasonable and hopeful approach for newly diagnosed MM in patients who are not candidates for transplantation; however, more trials are needed.³⁵

MYELODYSPLASTIC SYNDROMES⁴

The efficacy and safety of lenalidomide were evaluated in patients with transfusion-dependent anemia in low-risk or intermediate-1-risk MDS with a 5q (q31-33) cytogenetic abnormality in isolation or with additional cytogenetic abnormalities, at a dose of 10 mg once daily or 10 mg once daily for 21 days every 28 days in an open-label, single-arm, multicenter study (Table 2 and Figure 4A–C). The major study was not designed or powered to prospectively compare the efficacy of the two dosing regimens. Sequential dose reductions to 5 mg daily and 5 mg every other day, as well as dose delays, were allowed for toxicity.

This major study enrolled 148 patients who had RBC transfusion-dependent anemia. *RBC-transfusion dependence* was defined as having received 2 or more units of RBCs within eight weeks prior to study treatment. Granulocyte colony-stimulating factor was permitted for patients who developed neutropenia or fever in association with neutropenia. The frequency of RBC-transfusion independence was modified from the International Working Group (IWG) response criteria for MDS. *RBC-transfusion independence* was defined as the absence of any RBC transfusion during any consecutive "rolling" 56 days (eight weeks) during the treatment period.

Table 2 Baseline Demographic and Disease-Related Characteristics

	Overall (N = 148)	
Age (years)		
Median	71.0	
Min, Max	37.0, 95.0	
Gender	<i>n</i>	(%)
Male	51	(34.5)
Female	97	(65.5)
Race	<i>n</i>	(%)
White	143	(96.6)
Other	5	(3.4)
Duration of MDS (years)		
Median	2.5	
Min, Max	0.1, 20.7	
Del 5 (q31-33) cytogenetic abnormality	<i>n</i>	(%)
Yes	148	(100.0)
Other cytogenetic abnormalities	37	(25.2)
IPSS Score [a]	<i>n</i>	(%)
Low (0)	55	(37.2)
Intermediate-1 (0.5-1.0)	65	(43.9)
Intermediate-2 (1.5-2.0)	6	(4.1)
High (>=2.5)	2	(1.4)
Missing	20	(13.5)
FAB Classification [b] from central review	<i>n</i>	(%)
RA	77	(52.0)
RARS	16	(10.8)
RAEB	30	(20.3)
CMML	3	(2.0)

[a] IPSS Risk category: low (combined score = 0), intermediate-1 (combined score = 0.5 to 1.0), intermediate-2 (combined score = 1.5 to 2.0), high (combined score >= 2.5); combined score = (marrow blast score + karyotype score + cytopenia score)

[b] French-American-British (FAB) classification of MDS. CMML = chronic myelomonocytic leukemia; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; RA = rheumatoid arthritis; RAEB = refractory anemia with excess blasts; RARS = refractory anemia with ringed sideroblasts.

From Revlimid (lenalidomide) product information. Summit, NJ: Celgene.⁴

A Erythroid Response [del 5q] Intent-to-Treat Analysis

Feature	Total	(%)	[CI]
Patients, n	148		
Erythroid response			
Txf. Indep.	99	(67)	[59, 74]
Minor (>50%↓)	14	(9)	
Txf. Indep. + Minor	113	(76)	[67-82]
Time to response			
Median	4.4 weeks		
Range	(3.6-5.3)		

B Response (TI) Characterization [del 5q]

Variable	Median Value [Range]
Maximum hemoglobin (g/dl)	
Baseline	7.8 [5.3-10.4]
Lenalidomide	13.4 [9.2-18.6]
Median hemoglobin ↑	5.3 g/dl [1.1-11.4]
Txf. Indep.	
Week 24	99/148
Sustained (3-31-05)	71 (73%)

C Cytogenetic Response [del 5q]

Variable	Patients, n (%)	[95% CI]
Evaluable, n	115	
Cytogenetic response	81 (70)	[61%-79%]
Complete (CCR)	51 (44)	[35%-54%]
Minor (≥50%↓)	30 (26)	[18%-35%]

FIGURE 4A-C Results of studies evaluating the 5 q abnormality and lenalidomide in the treatment of transfusion-dependent, low/intermediate-1 risk myelodysplastic syndromes. CCR = complete cytogenetic response; Txf. Ind. = transfusion-independent. (From Revlimid (lenalidomide) product information⁴ and Giralat AA. Internet Advisory Board. March 30, 2006.¹⁴)

Transfusion independence was seen in 99/148 (67%) patients (95% confidence interval [CI] [59, 74]) (see Figure 4A). The median duration from the date when the RBC transfusion independence was first declared (i.e., the last day of the 56-day RBC transfusion-free period) to the date when an additional transfusion was received after the 56-day transfusion-free period among the 99 responders was 44 weeks (range, 0 to more than 67 weeks). Of those patients who achieved a transfusion benefit, 99% did so by the completion of three months in the study. RBC transfusion independence rates were unaffected by age or sex.

The dose of lenalidomide was reduced or interrupted at least once because of an adverse event in 118 (79.7%) of the 148 patients; the median time to the first dose reduction or interruption was 21 days (mean,

35.1 days; range, 2–253 days), and the median duration of the first dose interruption was 22 days (mean, 28.5 days; range, 2–265 days). A second dose reduction or interruption attributed to adverse events was required in 50 (33.8%) of the 148 patients.

The median interval between the first and second dose reduction or interruption was 51 days (mean, 59.7 days; range, 15–205 days) and the median duration of the second dose interruption was 21 days (mean, 26 days; range, 2–148 days). Granulocyte colony-stimulating factors were permitted for patients who developed neutropenia or fever in association with neutropenia.

Table 3 (see page 17) shows acceptable dose adjustments during treatment with lenalidomide in patients with MDS.

Safety

BOXED WARNINGS⁴

The product carries three boxed warnings regarding (1) the potential for human birth defects, (2) hematological toxicity (neutropenia and thrombocytopenia), and (3) deep vein thrombosis and pulmonary embolism.

Lenalidomide is an analogue of thalidomide, a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females should be advised to avoid pregnancy while taking lenalidomide.

Special Prescribing Requirements⁴

Because of lenalidomide's potential toxicity and in order to avoid fetal exposure to this agent, it is available only under a special restricted distribution program, called "RevAssistSM." Only prescribers and pharmacists registered with the program are able to prescribe and dispense the product. Furthermore, lenalidomide must be dispensed only to patients who are registered in the program and who meet all of its criteria.

Celgene's RevAssist Program⁴

Prescribers

Lenalidomide can be prescribed only by licensed prescribers who are registered in the RevAssist program and who understand the potential risk of teratogenicity if lenalidomide is used during pregnancy. Effective contraception must be used by female patients of childbearing potential for at least four weeks before beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions, and for four weeks following discontinuation of lenalidomide therapy.

Reliable contraception is indicated even when there has been a history of infertility, unless the infertility is the result of a hysterectomy or because the patient has been postmenopausal naturally for at least 24 consecutive months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method of birth control.

Females of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature females who have not undergone a hysterectomy, who have not had a bilateral

oophorectomy, or who have not been postmenopausal naturally for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be females of childbearing potential.

Before lenalidomide is prescribed, females of childbearing potential should have two negative pregnancy tests (sensitivity of at least 50 mIU/ml). The first test should be performed within 10 to 14 days, and the second test within 24 hours prior to prescribing lenalidomide. A prescription for lenalidomide for a female of childbearing potential must not be issued by the prescriber until negative pregnancy tests have been verified by the prescriber.

It is not known whether lenalidomide is present in the semen of patients receiving the drug. Therefore, males receiving lenalidomide must always use a latex condom during any sexual contact with females of childbearing potential even if they have undergone a successful vasectomy.

Once treatment has started and during dose interruptions, pregnancy testing for females of childbearing potential should occur weekly during the first four weeks of use, then pregnancy testing should be repeated every four weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every two weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her pregnancy test or in her menstrual bleeding. Lenalidomide treatment must be discontinued during this evaluation.

The prescriber and the pharmacist should verify any pregnancy test results before dispensing any prescriptions. If pregnancy does occur during lenalidomide treatment, lenalidomide must be discontinued immediately.

Any suspected fetal exposure to lenalidomide should be reported to the FDA via the MedWatch phone number at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436. The patient should be referred to an obstetrician/ gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Female Patients

Lenalidomide should be used in females of childbearing potential only when the patient meets all of the following conditions (i.e., she is unable to become pregnant while receiving lenalidomide therapy):

- She understands and can reliably carry out instructions.
- She is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey, as described in the RevAssist program.
- She has received and understands both oral and written warnings of the potential risks of taking lenalidomide during pregnancy and of exposing a fetus to the drug.
- She has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method of birth control.
- Sexually mature females who have not undergone a hysterectomy, who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months), or who have had a bilateral oophorectomy are considered to be females of childbearing potential.
- She acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for four weeks prior to beginning lenalidomide therapy, during lenalidomide therapy, during dose interruptions, and for four weeks after discontinuation of lenalidomide therapy.
- She has had two negative pregnancy tests with a sensitivity of at least 50 mIU/mL, within 10 to 14 days, and 24 hours prior to beginning therapy.
- If the patient is between 12 and 18 years of age, her parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

Male Patients

Lenalidomide should be used in sexually active males when the patient meets all of the following conditions:

- He understands and can reliably carry out instructions.
- He is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey, as described in the RevAssist program.
- He has received and understands both oral and written warnings of the potential risks of taking lenalidomide and exposing a fetus to the drug.
- He has received both oral and written warnings of the risk of possible contraception failure and that it is unknown whether lenalidomide is present in semen. He has been instructed that he must

always use a latex condom during any sexual contact with females of childbearing potential, even if he has undergone a successful vasectomy.

- He acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with females of childbearing potential even if he has undergone a successful vasectomy. Females of childbearing potential are considered to be sexually mature females who have not undergone a hysterectomy, who have not had a bilateral oophorectomy, or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months).
- If the patient is between 12 and 18 years of age, his parent or legal guardian must have read the educational materials and agreed to ensure compliance with the above.

Hematological Toxicity (Neutropenia and Thrombocytopenia)⁴

Lenalidomide is associated with significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q MDS had to have a dose delay or reduction during the major study. Thirty-four percent of patients had to have a second dose delay or reduction. Grade 3 or 4 hematological toxicity was seen in 80% of patients enrolled in the study. Patients receiving therapy for del 5q MDS should have their complete blood counts monitored weekly for the first eight weeks of therapy and at least monthly thereafter.

Patients may require dose interruption and/or reduction. Patients may also require the use of blood product support and/or growth factors.

Deep Venous Thrombosis and Pulmonary Embolism⁴

Lenalidomide has demonstrated a significantly increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients with MM who were treated with lenalidomide combination therapy.

Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with lenalidomide may lessen the potential for venous thromboembolic events.

The decision to take prophylactic measures should be done carefully after an assessment of an individual patient's underlying risk factors.

CONTRAINDICATIONS⁴

Because lenalidomide is similar in structure to thalidomide, a known human teratogen, lenalidomide is contraindicated in pregnant women and in women capable of becoming pregnant. When there is no alternative, females of childbearing potential may be treated with lenalidomide, provided that adequate precautions are taken to avoid pregnancy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, including at least one highly effective method (e.g., intrauterine device [IUD], hormonal contraception, tubal ligation, or a partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning four weeks prior to initiating treatment with lenalidomide, during therapy with lenalidomide, during therapy delay, and continuing for four weeks following discontinuation of lenalidomide therapy. If hormonal or IUD contraception is medically contraindicated, two other effective or highly effective methods may be used.

Females of childbearing potential being treated with lenalidomide should have pregnancy testing (sensitivity of at least 50 mIU/mL). The first test should be performed within 10 to 14 days and the second test within 24 hours prior to beginning lenalidomide therapy and then weekly during the first month of lenalidomide, then monthly thereafter in women with regular menstrual cycles or every two weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy occurs, lenalidomide must be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

PRECAUTIONS⁴

No formal studies have been conducted in patients with renal impairment. Lenalidomide is known to be excreted by the kidneys, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.

DRUG INTERACTIONS⁴

Findings from human *in vitro* metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway, suggesting that lenalidomide is not likely to cause or to be subject to P450-based metabolic drug interactions in humans.

Coadministration of multiple doses of 10 mg of

lenalidomide had no effect on the single-dose pharmacokinetics of R- and S-warfarin. Coadministration of single 25-mg dose warfarin had no effect on the pharmacokinetics of total lenalidomide. Expected changes in laboratory assessments of prothrombin time (PT) and the International Normalized Ratio (INR) were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration.

When digoxin was coadministered with lenalidomide, the digoxin AUC was not significantly different; however, the digoxin C_{max} was increased by 14%.

Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during the administration of lenalidomide.

ADVERSE REACTIONS⁴**Multiple Myeloma**

Data were evaluated from 691 patients who received at least one dose of lenalidomide/dexamethasone (346 patients) or placebo/dexamethasone (345 patients) in Studies 1 and 2. The addition of lenalidomide to dexamethasone did not result in any major increase in toxicity compared with dexamethasone alone.

Neutropenia, thrombocytopenia, leukopenia, constipation, and rash not otherwise specified (NOS) were reported more frequently in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group. Tremor, dysgeusia, muscle cramp, dyspnea, and DVT were also reported more frequently in this group. Other adverse effects were reported in comparable proportions of patients in each treatment group.

The following adverse effects were reported in more than 10% of lenalidomide/dexamethasone patients: constipation, fatigue, insomnia, muscle cramp, diarrhea, neutropenia, anemia NOS, asthenia, pyrexia, nausea, headache, peripheral edema, dizziness, dyspnea NOS, tremor, weight loss, thrombocytopenia, rash NOS, back pain, hyperglycemia NOS, muscle weakness NOS, blurred vision, cough, dyspepsia, anorexia, upper respiratory tract infection NOS, dysgeusia, paraesthesia, hypokalemia, pneumonia NOS, arthralgia, and emesis.

The incidence of individual grade 3 and 4 adverse events was generally comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups, demonstrating that the addition of lenalidomide to dexamethasone was accomplished with a minimal increase in toxicity. Grade 3 and 4 neutropenia, thrombocytopenia, anemia NOS, leukopenia NOS, and DVT were reported in a significantly greater proportion of lenalidomide/dexamethasone-treated patients than in placebo/dexamethasone-treated subjects. However,

these events were mostly grade 3 in severity.

Thrombotic or thromboembolic events, including DVT, pulmonary embolism, thrombosis, and thromboembolism, were reported more frequently in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group. The incidence of thrombotic events was significantly higher among the lenalidomide/dexamethasone-treated patients who received erythropoietic agents concomitantly than among those who did not receive such agents concomitantly.

The incidence of serious adverse events was generally low both in the lenalidomide/dexamethasone group and in the placebo/dexamethasone group. With the exception of serious DVT, serious pulmonary embolism and serious atrial fibrillation, the incidence of serious adverse events was generally comparable between treatment groups, demonstrating that the addition of lenalidomide to dexamethasone was accomplished with a minimal increase in toxicity.

Myelodysplastic Syndromes⁴

A total of 148 patients received at least one dose of lenalidomide 10 mg in the del 5q MDS clinical study. At least one adverse event was reported in all of the 148 patients who were treated with the 10-mg starting dose of lenalidomide. The most frequently reported adverse

events were related to blood and lymphatic system disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, and general disorders and administrative-site conditions.

Thrombocytopenia and neutropenia were the most frequently reported adverse events observed. The next most common adverse events observed were diarrhea, pruritus, rash, and fatigue. In the single-arm studies conducted, it is often not possible to distinguish adverse events that are drug-related from those that reflect the patient's underlying disease.

In other clinical studies of lenalidomide in MDS patients, the following serious adverse events were reported: blood and lymphatic system disorders; cardiac disorders; ear and labyrinth disorders; endocrine disorders; gastrointestinal disorders; general disorders and administration-site conditions; hepatobiliary disorders; immune system disorders; infections and infestations; injury, poisoning and procedural complications; metabolism and nutrition disorders; musculoskeletal and connective tissue disorders; neoplasms, benign, malignant, and unspecified; nervous system disorders; psychiatric disorders; renal and urinary disorders; reproductive system and breast disorders; respiratory, thoracic, and mediastinal disorders; skin and subcutaneous tissue disorders; and vascular system disorders.

Indications, Dosage, and Administration

MULTIPLE MYELOMA⁴

Lenalidomide in combination with dexamethasone is indicated for the treatment of patients with MM who have received at least one previous therapy. It is also indicated for patients with transfusion-dependent anemia caused by low-risk or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

Lenalidomide is available in 5-mg, 10-mg, 15-mg, and 25-mg capsules. The recommended starting dose is 25 mg/day with water orally, administered as a single 25-mg capsule, on Days 1–21 of repeated 28-day cycles. Patients should not break, chew, or open the capsules. The recommended dose of dexamethasone is 40 mg/day on Days 1–4, 9–12, and 17–20 of each 28-day cycle for the first four cycles of therapy and then 40 mg/day orally on Days 1–4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings. The effect of substituting lesser strengths of lenalidomide to achieve a 25-mg capsule dose is unknown.

Dose Adjustments During Treatment

Dose modification guidelines are recommended to

manage grade 3 or 4 neutropenia or thrombocytopenia or other grade 3 or 4 toxicity judged to be related to lenalidomide. Administration of colony-stimulating factor (Neupogen) may be used to alleviate neutropenia.

MYELODYSPLASTIC SYNDROMES⁴

The recommended starting dose of lenalidomide is 10 mg with water daily. Patients should not break, chew, or open the capsules. Dosing is continued or modified based upon clinical and laboratory findings. Lenalidomide is known to be substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it would be prudent to monitor renal function.

Dose Adjustments During Treatment

The dosage should be adjusted for patients who start with a dose of 10 mg and who experience thrombocytopenia and neutropenia. In such cases, the dose may be reduced to 5 mg (see Table 3).

Table 3 Dose Adjustments During Treatment with Lenalidomide for Myelodysplastic Syndromes

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

Platelet Counts

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg daily

<i>When Platelets</i>	<i>Recommended Course</i>
Fall to <50,000/mcL	Interrupt REVLIMID® treatment
Return to ≥50,000/mcL	Resume REVLIMID® at 5 mg daily

<i>When Platelets</i>	<i>Recommended Course</i>
Fall to 50% of the baseline value	Interrupt REVLIMID® treatment
If baseline ≥60,000/mcL and returns to ≥50,000/mcL	Resume REVLIMID® at 5 mg daily
If baseline <60,000/mcL and returns to ≥30,000/mcL	Resume REVLIMID® at 5 mg daily

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg daily

<i>When Platelets</i>	<i>Recommended Course</i>
<30,000/mcL or <50,000/mcL and platelet transfusions	Interrupt REVLIMID® treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID® at 5 mg daily

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily

<i>When Platelets</i>	<i>Recommended Course</i>
<30,000/mcL or <50,000/mcL and platelet transfusions	Interrupt REVLIMID® treatment
Return to ≥30,000/mcL (without hemostatic failure)	Resume REVLIMID® at 5 mg at every other day

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

Neutrophil counts [Absolute Neutrophil Count (ANC)]

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg daily

<i>When Neutrophils</i>	<i>Recommended Course</i>
Fall to <750/mcL	Interrupt REVLIMID® treatment
Return to ≥1,000/mcL	Resume REVLIMID® at 5 mg daily

<i>When Neutrophils</i>	<i>Recommended Course</i>
Fall to <500/mcL	Interrupt REVLIMID® treatment
Return to ≥500/mcL	Resume REVLIMID® at 5 mg daily

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg daily

<i>When Neutrophils</i>	<i>Recommended Course</i>
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID® treatment
Return to ≥500/mcL	Resume REVLIMID® at 5 mg daily

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily

<i>When Neutrophils</i>	<i>Recommended Course</i>
<500/mcL for ≥7 days or <500/mcL associated with fever (≥38.5°C)	Interrupt REVLIMID® treatment
Return to ≥500/mcL	Resume REVLIMID® at 5 mg every other day

From Revlimid (lenalidomide) product information. Summit, NJ: Celgene.⁴

P&T Committee Considerations

P&T committees should consider several important factors before deciding whether to add or remove a drug from the formulary and in developing health plan coverage policies for new therapies. Drug safety, efficacy, tolerability, enhancement or improvement over currently available therapies, and cost-effectiveness are key P&T committee considerations in the evaluation of lenalidomide for possible inclusion on formularies.³⁶

MULTIPLE MYELOMA

Few therapeutic options are currently available for patients with MM who relapse after autologous or allogeneic stem-cell transplantation or for patients who are not responsive to conventional chemotherapy and who are not eligible for salvage high-dose therapy.

The efficacy and safety of lenalidomide in combination with dexamethasone have been evaluated in patients with MM who had received at least one prior treatment. Historically, treatment has relied on the combination of an alkylating agent and prednisone.

In the two clinical studies discussed in this Product Profiler, the interim analysis of both studies showed that lenalidomide/dexamethasone was superior ($P < .0001$) to dexamethasone alone for the primary efficacy endpoint: time to progression. In both studies, the complete response and overall response rates in the lenalidomide/dexamethasone arm were significantly higher than those in the dexamethasone-alone arm.

Several years ago, thalidomide was found to improve the response rate and overall survival in patients with advanced relapsed or refractory MM. It was used in combination with dexamethasone as salvage therapy in treating refractory MM. In May 2006, thalidomide was approved, in combination with dexamethasone, for the treatment of newly diagnosed MM.³⁷

Lenalidomide is a novel 4-amino-glutarimide analogue of thalidomide. Both are immunomodulatory drugs, but lenalidomide inhibits several cytokines with a much higher potency. In addition, lenalidomide has fewer adverse effects compared with thalidomide. Neuropathy, constipation, and fatigue were less common with lenalidomide. Myelosuppression was greater with lenalidomide than with thalidomide, but it was manageable with dose reduction. Thrombosis may be a problem, but it is manageable when anticoagulants are used prophylactically.

MYELODYSPLASTIC SYNDROMES

MDS represents many different hematopoietic stem-cell disease forms, and the pathophysiological pathways in MDS are currently under intense investigation. Thus far, no treatment option has altered the natural history of MDS. Supportive therapy with anemia management, including administration of erythropoietin-stimulating proteins, transfusions, and antibiotics, is still considered to be the standard of care. Before lenalidomide was approved for patients with MDS, azacitidine was the only approved treatment for the underlying pathology in MDS.

Thalidomide improves transfusion dependence in MDS patients, but long-term treatment and dose-escalation strategies are limited. The FDA has approved lenalidomide for the treatment of transfusion-dependent anemia caused by low-risk or intermediate-risk MDS associated with a deletion 5q cytogenetic abnormality with or without other additional cytogenetic abnormalities. Because of the marked improvement in efficacy and safety, lenalidomide appears to be a welcome and necessary new treatment option for MDS. Although it has the potential for serious adverse effects, they are manageable when the dose is reduced and therapy is temporarily discontinued. In addition, safety concerns regarding lenalidomide are being addressed through the RevAssist program.

The RevAssist program requires that patients, pharmacists, and physicians follow very specific protocols in conjunction with lenalidomide use. This restrictive distribution program was instituted to avoid fetal exposure to lenalidomide. Prescribers must be registered with this program, and only RevAssist contract pharmacies can dispense the drug. The authorization number and prescription are valid for only seven to 14 days; to receive lenalidomide, patients must enroll in the RevAssist program and must agree to adhere to its requirements.

COMPLIANCE

Patient compliance is always a challenge with any drug, and lenalidomide must be taken exactly as prescribed. Patients may find compliance with lenalidomide easier than with other therapies, however, because of its oral formulation.

COST CONSIDERATIONS

Finally, cost is an important factor when any new drug is being considered for health plan coverage. The

cost of lenalidomide in the treatment of MM is comparable to the acquisition cost of bortezomib (Velcade). Because lenalidomide is an oral agent, its lack of infusion costs (nursing time, physician time, and other administrative expenses) may offer cost advantages to payers.

Lenalidomide is also cost-effective compared with the current standard of care in the treatment of transfusion-dependent MDS in the U.S. An economic model demonstrated that, within the first year of treatment, the costs of lenalidomide therapy were largely offset by savings in blood transfusion and other standard, supportive care costs. Cost-effectiveness data illustrating this point were presented in a poster presentation at the 2006 meeting of the American Society of Clinical Oncology.³⁸

The estimated budget impact of lenalidomide on

health plans should take into consideration the relatively low prevalence of MM and transfusion-dependent low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality. P&T committees should also consider the cost offsets related to transfusion independence associated with lenalidomide therapy.

The actual costs of lenalidomide, best supportive care, and other therapies are contained in an economic model within the Revlimid Academy of Managed Care Pharmacy (AMCP) Dossier. Readers can obtain a copy of the dossier via an online request form at www.ptcommunity.com/requestinformation.

Updated prices for lenalidomide can also be obtained from online sources such as ReadyPrice®, Thomson Micromedex, Greenwood Village, Colorado.³⁹

Conclusion

To date, no treatment options have altered the natural history of MM or MDS, and better treatments are desperately needed. Lenalidomide represents an important advancement to improve outcomes for patients with MM and MDS.

Lenalidomide has been shown to reduce the need for transfusions in patients with low-risk or low-to-intermediate risk MDS who have a cytogenetic 5q deletion abnormality. Many patients experience a cytogenetic response, with the result that their chromosomes are considered “normal” after four to eight weeks of use. The specific role of this agent in the treatment of MDS alone, or in combination with azacitidine, remains to be determined.

In combination with dexamethasone, lenalidomide has also been effective in the treatment of MM patients who had received at least one previous treatment.

Lenalidomide may be better received, by both doctors and patients, than other therapeutic options that require frequent infusions, blood transfusions, or bone marrow/stem-cell transplants. Health care professionals may find that lenalidomide is cost-effective compared with other therapies that involve various administrative costs. As the first oral agent indicated for both diseases, it is a welcome and necessary addition to the armamentarium in the treatment of MM and MDS.

Like many drugs and biologic agents, lenalidomide may exhibit serious side effects, but these are manageable with dose reduction and temporary discontinuation of therapy.

Finally, its safety concerns are being addressed through the RevAssist program, which is managed by a broad network of contracted specialty pharmacies.

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