National PBM Drug Monograph
Lenalidomide (Revlimid®)
July 2006
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Efficacy:

- Lenalidomide is an analogue of thalidomide. It is an immunomodulatory drug that inhibits proinflammatory cytokines, stimulates T-cell proliferation and NK cell activity, has antiangiogenic activity, and pro-apoptotic activity is some cell lines
- It metabolism has not been fully studied, but 2/3 of the drug is eliminated in the urine.
- In vitro studies with human liver cell lines indicate that lenalidomide is not affected by, does not inhibit or induce cytochrome P450 isoenzymes and therefore there is little chance for a drug interaction with this metabolizing pathway.
- Lenalidomide was studied in a single-arm, open label, multicenter study (003) in patients with myelodysplastic syndrome with a del 5q cytogenetic abnormality who were RBC transfusion dependent.
- In addition, patients had low or intermediate-1 risk IPSS scores.
- Lenalidomide, given at 10mg daily for 21 days every 28 days or 10mg daily eliminated transfusion dependence in 64% of patients for a median duration of 52 weeks.

Safety:

- A large percentage of patients experienced adverse events.
- The most common adverse events were neutropenia, thrombocytopenia, and infections.
- The most serious adverse events were neutropenia and thrombocytopenia
- Up to 80% of patients required at least one dose interruption or dose reduction during therapy
- A Black Box warning for 1) teratogenicity 2) neutropenia and thrombocytopenia and 3) deep vein thrombosis and pulmonary embolism are contained in the package insert.

Recommendations:

- Lenalidomide produces substantial benefit by eliminating RBC transfusion dependence in a large percentage of patients with MDS and a del 5q cytogenetic abnormality but with a large risk for and adverse event.
- Lenalidomide should not be added to the national formulary at this time. Criteria for use include patients with transfusion-dependent myelodysplastic syndrome with a deletion (5q) cytogenetic abnormality.

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of individual patient situations

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating lenalidomide for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2,3]

The mechanism of action of lenalidomide has not been fully characterized. Lenalidomide is a derivative of thalidomide and belongs to the novel class of derivatives known as immunomodulatory drugs. It has immunomodulatory properties through inhibition of proinflammatory cytokines like TNF-α, IL-6, and IL-12 and stimulation of T-cell proliferation and NK cell activity and number. Lenalidomide also possess antiangiogenic activity and has demonstrated inhibition of cell proliferation and pro-apoptotic activity in some cell lines.

Table #1 Pharmacokinetics

Parameter	Lenalidomide
Metabolism	Not fully studied
Elimination	About 2/3 eliminated in urine
Half-life	3 hours
Protein Binding	
Bioavailability	Absorption is rapid; food does not change the AUC but reduces peak plasma levels

Special Populations:

1. Renal Insufficiency: The pharmacokinetics of lenalidomide in MDS patients with renal insufficiency has not been well studied. In multiple myeloma patients, patients with mild renal impairment had a 56% increase in the AUC compared to patients with normal renal function.
2. Hepatic Disease: Pharmacokinetic parameters have not been studied in this population.
3. Age: The effects of age on lenalidomide pharmacokinetics have not been studied.
4. Pediatrics: There is no pharmacokinetic data in patients under the age of 18.
5. Gender: The effects of gender have not been studied.
6. Race: The effects of race on lenalidomide pharmacokinetics have not been studied.

FDA Approved Indication(s) and Off-label Uses

Treatment of patients with transfusion-dependent anemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a 5q deletion cytogenetic abnormality (with or without other cytogenetic abnormalities).

Off-label use:

1. Transfusion-dependent MDS patients without a 5q deletion cytogenetic abnormality
2. Monotherapy or combination therapy for relapsed or refractory multiple myeloma
3. First-line therapy with dexamethasone for multiple myeloma

Current VA National Formulary Alternatives

Myelodysplastic syndrome:

Azacitidine given subcutaneously for 7 days every 4 weeks; restricted to criteria for use for all MDS subtypes regardless of cytogenetic abnormalities

Multiple Myeloma:
Various combination chemotherapy drugs

Nonformulary Drugs
Thalidomide

Dosage and Administration

1. Starting Dose
   Lenalidomide 10mg orally with water every day. Capsules should not be chewed or opened. Since this drug is excreted by the kidneys, there is a higher risk of adverse reactions in patients with impaired renal function (e.g. the elderly). In these patients, renal function and dose selection should be carefully monitored.
2. Dose Adjustments During Treatment

Table #2 If thrombocytopenia develops within 4 weeks of starting at 10mg

If baseline platelet count is ≥100,000/mcL	
If platelets:	Recommendations
Fall to < 50,000/mcL	INTERRUPT lenalidomide therapy
When they Return to ≥ 50,000/mcL	RESUME lenalidomide at 5mg every day
If baseline platelet count is < 100,000/mcL	
When Platelets:	Recommendations
Fall to 50% of baseline	INTERRUPT therapy
If baseline is ≥ 60,000/mcL and returns to ≥ 50,000/mcL	RESUME lenalidomide at 5mg every day
If baseline is < 60,000/mcL and returns to ≥ 30,000/mcL	RESUME lenalidomide at 5mg every day

Table #3 If thrombocytopenia develops AFTER 4 weeks of starting at 10mg

When Platelets:	Recommendations
Are < 30,000/mcL or <50,000/mcL requiring platelet transfusions	INTERRUPT lenalidomide therapy
Return to ≥ 30,000/mcL (without hemostatic failure)	RESUME lenalidomide at 5 mg every day

Table #4 If thrombocytopenia develops during treatment with 5mg every day

When Platelets:	Recommendations
Are < 30,000/mcL or <50,000/mcL requiring platelet transfusions	INTERRUPT lenalidomide therapy
Return to ≥ 30,000/mcL (without hemostatic failure)	RESUME lenalidomide at 5 mg every OTHER day

Table #5 If neutropenia develops within 4 weeks of starting at 10mg

If baseline ANC ≥ 1,000/mcL	
When Neutrophils:	Recommendations
Fall to < 750/mcL	INTERRUPT lenalidomide therapy
Return to ≥ 1,000/mcL	RESUME lenalidomide at 5mg every day
If baseline ANC < 1,000/mcL	
When Neutrophils:	Recommendations
Fall to < 500/mcL	INTERRUPT lenalidomide therapy
Return to ≥ 500/mcL	RESUME lenalidomide at 5mg every day

Table #6 If neutropenia develops AFTER 4 weeks of starting at 10mg

When Neutrophils:	Recommendations
< 500/mcL for ≥ 7 days or <500/mcL with fever ≥ 38.5°C	INTERRUPT lenalidomide therapy
Return to ≥ 500/mcL	RESUME lenalidomide at 5mg every day

Table #7 If neutropenia develops during treatment with 5mg every day

When Neutrophils:	Recommendations
< 500/mcL for ≥7 days or <500/mcL with fever ≥ 38.5°C	INTERRUPT lenalidomide therapy
Return to ≥ 500/mcL	RESUME lenalidomide at 5mg every OTHER day

Efficacy

Efficacy Measures

Primary Endpoint: RBC transfusion independence for at least 8 consecutive weeks.

Secondary Endpoints:
Cytogenetic Response
≥50% decrease in RBC transfusion requirements
Change of hemoglobin concentration from baseline
Platelet response
Neutrophil response
Bone marrow response
Duration of response
Safety

Summary of efficacy findings

Study 003 was a single arm, multicenter, phase II trial in transfusion dependent patients with Myelodysplastic Disease (MDS) with an International Prognostic Scoring System (IPSS)* of low or intermediate-1 risk with an associated del 5q (with or without other cytogenetic abnormalities).

- Transfusion dependence was defined as 2 or more units of packed RBC units 8 weeks prior to starting study.
- ECOG Performance Status of 0-2
- Exclusions included: Pregnant or lactating females, inability to perform bone marrow aspirate, chronic myelomonocytic leukemia, ANC <500cells/mm^3, platelets <50,000/mm^3, serum creatinine >2.5gm/dL, serum AST/ALT > 3 X ULN, direct bilirubin >2 mg/dL, prior ≥ grade 3 allergic reaction/hypersensitivity to thalidomide, anemia due to other causes (iron, folate, or B12 deficiency, autoimmune or hereditary hemolysis, or GI bleed), chronic use of physiologic doses of steroids within 28 days, use of chemotherapy or immunosuppressive drugs for MDS within 28 days
- Dose: 10mg orally daily on days 1-21 every 28 days (N=45); amended later to continuous dosing regimen of 10mg orally every day (N=103). Dosing was amended based in information from the pilot study (001) that the onset of response was faster with continuous dosing.
- The median age of patients was 71 years old; 34.5% were male, 96.6% were white, 37.2% had a low IPSS score, 43.9% had a intermediate-1 risk IPSS score, 39.9% had an ECOG PS of 0, 50.7% ECOG PS=1, and 0.9% ECOG PS=2.

Table #8 Efficacy Endpoints

Outcome	10 mg Continuos dosing (N=103)	10 mg Synchronous dosing (N=45)	Overall (N=148)
% Transfusion Independent			
Overall (95%CI)	68 (58. 76.8)	55.6 (40, 70.4)	64.2 (55.9, 71.9)
Low IPSS (95%CI)	66.7 (50.5, 80.4)	84.6 (54.6, 98.1)	70.9 (57.1, 82.4)
Intermediate-1 IPSS (95%CI)	72.5(56.1, 85.4)	48 (27, 68.7)	63.1 (50.2, 74.7)
Duration of Response			
Patients Progressed	11.4%	11.8%	11.5%
Patients Censored	88.6	88.2	88.5
Median (min, max)	28.5 wks (8.1, 44)	40.7 wks (8.1, 48.1)	30 wks (8.1, 48.1)
Updated Data			
Patients Progressed			28.1%
Patients Censored			71.9

Median (min,max)			52.3 wks (8.1, 74.6)
Change in hemoglobin from baseline of ≥1 g/dL (95%CI)	N/A	N/A	(N=93) 73.1% (62.9, 81.8)
Decrease of ≥50% in RBC Transfusion requirements (95%CI)	74.6% (63,84)	72.4% (53, 87)	74% (64,82)
Cytogenetic Response % Major Minor			(n=72 evaluable) 44% 29

- Transfusion independence was consistent in other populations, i.e. isolated 5q deletion vs 5q plus other cytogenetic deletions
- The rate of RBC-transfusion independence was similar between major cytogenetic responders (95.8%) and minor cytogenetic responders (94.7%)
- There were no platelet responses in the FDA analysis of 14 eligible patients
- Of the 6 patients eligible for neutrophil response, there was one major response
- Granulocyte CSF was allowed in patients who developed neutropenia or fever and neutropenia.

*International Prognostic Scoring System

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	-	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	Grade 0/1	Grade 2/3			

Karyotypes: Good=normal; -Y, del(5q), del(20q); Poor=complex ≥3 abnormalities or chromosome 7 abnormality; Intermediate= all others

Risk group scores
Low= 0
Intermediate-1 = 0.5-1.0
Intermediate-2 = 1.5-2.0
High = ≥2.5

For further details on the efficacy results of the clinical trials, refer to Appendix on Page 11.

Supporting Data[4]
Study 001 was an open label, single center trial (phase 2) to evaluate efficacy and safety in patients with MDS who had symptomatic anemia or transfusion dependent anemia with no response to epoetin or high endogenous erythropoietin levels. Patients received lenalidomide at one of 3 doses: 25mg daily, 10 mg daily, or 10 mg daily for 21 days every 28 days.

Table#9 Study 001 Results

Response	25 mg/day N=13	10mg/day N=13	10mg/d for 21 days N=17	Total N=43
Erythroid Response Major Minor Total	 6 0 6	 6 1 7	 9 2 11	 21(49%) 3 (7%) 24 (56%)
Weeks to Response Median ±SD Range	 9±5.8 2.5-18.5	 10.5±6.4 2-17.5	 11.5±10.3 6-24	NA

Adverse Events (Safety Data)[5]

Table #10 Adverse Events in ≥5% of lenalidomide patients

System/Organ Class	10mg dose Overall %
Blood and lymph Thrombocytopenia	 61.5

Neutropenia	58.8
Anemia	11.5
Leukopenia	8.1
Febrile Neutropenia	5.4
Skin	
Pruritus	41.9
Rash	35.8
Dry skin	14.2
Contusion	8.1
Night sweats	8.1
Increased sweating	6.8
Ecchymosis	5.4
Erythema	5.4
GI Disorders	
Diarrhea	48.6
Constipation	23.6
Nausea	23.6
Abdominal pain	12.2
Vomiting	10.1
Abdominal pain upper	8.1
Dry mouth	6.8
Loose stools	6.1
Respiratory/ thoracic	
Nasopharyngitis	23
Cough	19.6
Dyspnea	16.9
Pharyngitis	15.5
Epistaxis	14.9
Exertional dyspnea	6.8
Rhinitis	6.8
Bronchitis	6.1
General Disorders	
Fatigue	31.1
Pyrexia	20.9
Peripheral edema	20.3
Asthenia	14.9
Edema	10.1
Pain	6.8
Rigors	6.1
Chest pain	5.4
Musculoskeletal	
Arthralgia	21.6
Back pain	20.9
Muscle cramp	18.2
Pain in limb	10.8
Myalgia	8.8
Peripheral swelling	8.1
Nervous System	
Dizziness	19.6
Headache	19.6
Hypoasthesia	6.8
Dysgeusia	6.1
Peripheral neuropathy	5.4
Infections	
URT Infection	14.9
Pneumonia	11.5
UTI	10.8
Sinusitis	8.1
Cellulitis	5.4
Metabolism/nutrition	
Hypokalemia	10.8
Anorexia	10.1
Hypomagnesemia	6.1
Hepatic	
Increased alanine aminotransferase	8.1
Psychiatric	
Insomnia	10.1
Depression	5.4
Vascular	

Hypertension	6.1
Renal and Urinary Dysuria	6.8
Cardiac Palpitations	5.4
Endocrine Acquired hypothyroidism	6.8

There is some data of a relationship to the dose and toxicity; there was more neutropenia, pneumonia, and diarrhea in the continuous dose group vs. the syncopated dose group. There was no difference in anemia, thrombocytopenia, febrile neutropenia, pancytopenic sepsis, and pyrexia.

Deaths and Other Serious Adverse Events

Table #11 Most Frequent Grade 3 and 4 Adverse Events

Event	10mg dose Overall %
Neutropenia	53.4
Thrombocytopenia	50
Pneumonia	7.4
Rash	6.8
Anemia	6.1
Leukopenia	5.4
Fatigue	4.7
Dyspnea	4.7
Back Pain	4.7
Febrile Neutropenia	4.1
Nausea	4.1
Diarrhea	3.4
Pyrexia	3.4
Sepsis	2.7
Granulocytopenia	2.0
Pulmonary embolism	2.0
Multi-organ failure	1.4

Serious adverse events reported in other clinical trials of lenalidomide:
Blood: warm type hemolytic anemia, bone marrow depression, coagulopathy, hemolysis, hemolytic anemia

Cardiac: Congestive heart failure, atrial fibrillation, angina, cardiac arrest, cardiomyopathy, myocardial infarction, pulmonary edema, supraventricular arrhythmia, ventricular dysfunction

GI: GI hemorrhage, ischemic colitis, intestinal perforation, rectal hemorrhage, dysphagia, gastritis

Hepatic: hyperbilirubinemia, cholecystitis

Nervous system: cerebrovascular accident, aphasia, cerebellar infarction, TIA

Renal: Renal failure, hematuria, azotemia

Respiratory: exacerbation of COPD, respiratory failure, exacerbation of dyspnea, interstitial lung disease

Table#12 Differences in frequency of Grades 3 and 4 AE in Studies 003 and 002*

Organ System	Study 003 N=148	Study 002 N=215
Neutropenia	53.4%	26.5%
Thrombocytopenia	50.0	21.4
Infections- All Pneumonia	16.2 8.9	12.1 3.7
Rash	6.8	4.2
Fatigue	4.7	3.3
Pyrexia	3.4	0.9
Bleeding, all types	2.7	2.8
Pulmonary Embolism	2.0	0

Deep Vein Thrombosis	3.5	0.9

*Study 002 population did not have a 5q deletion

Common Adverse Events
The most common adverse events were: thrombocytopenia, neutropenia, diarrhea, and fatigue

Tolerability

Table #13 Reasons for Discontinuation of lenalidomide

Primary reason for discontinuation	Overall MDS studies at 10mg (N=395) %
Adverse Event	19
Lack of therapeutic effect	14.9
Withdrew consent	4.6
Lost to follow-up	0.6
Death	3.8
Protocol violation	0.3
Other	2.3

Dose interrupted or reduced at least once due to an adverse event: 79.7% of patients
Second dose interruption or reduction due to an adverse event: 33.8% of patients

Precautions/Contraindications

Black Box Warnings

1. **Potential for Human Birth Defects**
   Lenalidomide is an analogue of thalidomide, a known human teratogen that causes severe life-threatening human birth defects. If taken during pregnancy, lenalidomide may cause birth defects or death to an unborn child. Females should be advised to avoid pregnancy while taking lenalidomide. Because of the potential for toxicity, lenalidomide will only be available under a special distribution program to patients, physicians, and pharmacists registered with the program.

2. **Hematologic Toxicity (Neutropenia and Thrombocytopenia)**
   Patients with 5q deletion Myelodysplastic Syndrome (MDS) have significant neutropenia and thrombocytopenia associated with the use of lenalidomide. Eighty percent of patients required a dose delay or reduction. Thirty-four percent required a second delay or dose reduction. Patients should have blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Patients may require dose delay, dose reduction, blood product support, or growth factors.

3. **Deep Vein Thrombosis and Pulmonary Embolism**
   Patients with multiple myeloma treated with lenalidomide combination therapy experienced an increased risk of deep vein thrombosis and pulmonary embolism. Patients and physicians should observe for signs and symptoms of thromboembolism and patients should seek medical care if they develop shortness of breath, chest pain, and arm or leg swelling. It is unknown if prophylactic anticoagulation or antiplatelet therapy lessens t the potential for thromboembolic events.

Precautions

1. This drug is excreted by the kidneys. The risks of adverse events may be increased in patients with renal impairment, but no studies have been conducted in this population.
2. Patients should be counseled on the risk of teratogenicity, and female patients should be counseled on the precautions to be taken to preclude fetal exposure as set forth in the RevAssist™ educational materials.

Contraindications

1. Pregnancy: Category X (Black Box Warning)
2. Hypersensitivity to lenalidomide or its components.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic

and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name lenalidomide: thalidomide, Leflunomide, leuprolide, finasteride, temozolomide
LA/SA for trade name Revlimid: Revatio, Thalomid, Revia

Drug Interactions

Drug-Drug Interactions

1. Human In vitro metabolism studies and other non-clinical studies show that lenalidomide is not metabolized by, does not inhibit, and does no induce the cytochrome P450 isoenzymes and therefore is unlikely to cause or be subject to P450 drug interactions.
2. Co-administration of multiple 10mg doses of lenalidomide had no effect on single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25mg dose of warfarin did not affect the pharmacokinetics of multiple dose lenalidomide. Changes in the INR and PT after warfarin were as expected and not affected by lenalidomide.

Acquisition Costs

Table #14 Acquisition Cost Comparison

Drug	Dose	Cost/Day/patient ($)	Cost/month (28 days)/patient ($)
Lenalidomide	10mg per day	168.42	4715.70
Lenalidomide	5mg per day	160.93	4506.11
Azacitidine	75mg/m^2 X 7 days		3891.44
Thalidomide	100 – 400 mg/day	28.86 – 95.70	808.08 – 1339.80

Conclusions

Clinical Efficacy: In the ITT analysis, 64.2% of patients were transfusion independent for at least 56 days. Responses were seen in both low risk and intermediate-1 risk patients and in both dosing schemas. Transfusion independence occurred in patients with an isolated del 5q and in patients with del 5q plus other cytogenetic abnormalities. The duration of the response during the study was 30 weeks, with a large percentage of patients censored on the day of analysis. Updated analysis data showed a median duration of response of 52 weeks, suggesting a clinical benefit. Responses were also accompanied by cytogenetic responses in 43% of patients. By the FDA analysis, only 96 patients met the strict definition of major eligibility criteria.

Clinical Safety: A large percentage of patients experienced an adverse event; 79.7% experienced a grade 3 or 4 adverse event. Neutropenia and thrombocytopenia can have rapid onset and resolution is unpredictable. It is difficult to assess if this is due to the drug or the disease or both as there is no comparator. A substantial number of patients required a dose interruption or dose reduction at least once during therapy due to neutropenia or thrombocytopenia.

Other important adverse events included infections, bleeding events, diarrhea, rash, pruritus, fatigue, peripheral edema, pyrexia, respiratory symptoms, musculoskeletal symptoms, headache, dizziness, and anorexia. Patients >65 years old experienced a higher frequency of adverse events.

Patients with a 5q deletion experienced more neutropenia, thrombocytopenia, and infections than similar patients without a del 5 q, although this data is from two different studies. Approximately 14 deaths are possibly or probably related to drug-induced neutropenia or thrombocytopenia.

Recommendations and Place in Therapy

Lenalidomide reduces or eliminates RBC transfusion dependence in a large proportion of patients with del 5q myelodysplastic syndrome, but also produces a high frequency of adverse events. Patients with the del 5q appear to be more sensitive to lenalidomide with an increased incidence of neutropenia, thrombocytopenia, and infections. Because the benefit of lenalidomide is substantial and the incidence of severe adverse events is high, careful medical evaluation of the patient prior to therapy and vigilant monitoring during therapy is required.

Without comparators, it is difficult to assess its place in therapy compared to the only other drug approved for MDS, azacitidine. The 10mg dose in patients with del 5q may be too high a starting dose; a phase III trial is comparing 5 mg to 10mg and to placebo to assess for efficacy and toxicity in this population. The use of lenalidomide for multiple myeloma will generate more interest in this drug in the near future.

Recommend that lenalidomide not be added to the national formulary at this time. Due to the extensive risk management program required by the FDA with physician, pharmacist, and patient's registration and on-going assessment, criteria are not needed at this time.

Criteria for Use include:
1. Low or Intermediate-1 risk transfusion-dependent Myelodysplastic Syndrome with a deletion (5q) cytogenetic abnormality
2. ECOG performance 0-2

N.B. Use in Low or Intermediate-1 risk transfusion-dependent Myelodysplastic Syndrome patients without a deletion (5q) cytogenetic abnormality must take into account the lower hematologic response rate and lack of published data. In these cases the patient and prescriber should weigh the benefits and risks versus alternative therapies.

Exclusion Criteria:
1. Baseline ANC < 500/mcL or platelets <50,000/mcL
2. Baseline serum creatinine > 2.5 g/dL
3. Pregnant or lactating female
4. Nutritional anemia (uncorrected)
5. Ongoing thrombosis

Prepared May 2006. Contact person: Mark C. Geraci, Pharm.D., BCOP Clinical Specialist

References:

[1] Teo SK. Properties of thalidomide and its analogues: implications for anticancer therapy. The AAPS Journal 2005;7(1) Article 3.

[2] Mitsiades CS, Mitsiades N. CC-5013 Celgene. Current Opinions in Investigational Drugs 2004; 5:635-647.

[3] Center for Drug Evaluation and Research Application number 21-880. Medical Review. 2005.

[4] List A, Kurtin S, Roe DJ, Buresh A, Mahadevan D, Fuchs D, et al. Efficacy of lenalidomide in myelodysplastic syndromes. NEJM 2005; 352:549-57.

[5] Revlimid® (lenalidomide) Product Package Insert. Celgene Corporation, Summit, NJ 2006.

Appendix Table: Clinical Trials with lenalidomide

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
Study 003 Single-arm Open label Multicenter	Inclusion criteria 1. low or intermediate risk-1 IPSS MDS with del 5q cytogenetics 2. RBC transfusion dependent anemia (≥2 units of RBC's in previous 8 weeks) 3. ECOG PS 0-2 4. Women of child bearing years with negative serum or urine pregnancy test agreeing to adequate contraceptive methods Exclusion criteria 1. Pregnant or lactating female 2. unable to aspirate bone marrow 3. proliferative CMML 4. ANC<500, plts<50K, Creatinine >2.5, AST/ALT>3X ULN, D.Bili >2.0 5. Prior ≥grade 3 toxicity to thalidomide 6. nutritional anemias 7. epoetin use within 7 days 8. chronic	Lenalidomide 10mg daily for 21 days , repeat every 28 days (N=45) Amended to: Lenalidomide 10mg daily (N=103)	Age, med:=71 Sex: M 34.5% Race: white 96.6% IPSS low: 37.2% IPSS intmed-1: 43.9 IPSS interm-2: 4.1 IPSS High: ¼ Missing: 13.5 ECOG 0: 39.5% 1: 50.7 2: 9.4	N_R =148 Outcome / 10mg Overall % Transfusion Independence: 64.2 Low IPSS: 70.9 Inter-1 IPSS: 63.1 Duration of response: 30 wks Updated: 52.3 wks Progression %: 11.5 Updates: 28.1 Change in Hgb ≥1: 73.1% Decrease of ≥50% in RBC transfusion req't: 74% Cytogenetic responses Major: 44% Minor: 29	Most common: neutropenia, thrombocytopenia, diarrhea Serious: Neutropenia, thrombocytopenia, pneumonia, rash, fatigue, pulmonary embolism, deep vein thrombosis Black Box Warning 1. Potential teratogen 2. neutropenia and thrombocytopenia 3. Deep vein thrombosis and pulmonary embolism

<table>
<tr><th>Citation
Design
Analysis type
Setting</th><th>Eligibility Criteria</th><th>Interventions</th><th>Patient Population Profile</th><th>Efficacy Results</th><th>Safety Results</th></tr>
<tr><td></td><td>>physiologic doses of steroids</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Study 001
Single arm
Open label
Single Center</td><td>Inclusion:
1. MDS
2. baseline hemoglobin <10 or transfusion dependent (at leas 4 units PRBC's in 8 weeks)
3. ECOG PS 0-2
4. Adequate renal and hepatic function
5. Adequate birth control for women of childbearing years

Exclusion:
1. Myelofibrosis >30% of bone marrow
2. Grade 4 neutropenia or thrombocytopenia
3. Clinically significant pulmonary, CV, endocrine, neurologic, GI, GU disease unrelated to hematologic disorder
4. Pregnant or lactating females
5. ongoing steroid treatment
6. known hep-B surface antigemia
7. bone marrow</td><td>Lenalidomide 25mg daily
Or
Lenalidomide 10mg daily
Or
Lenalidomide 10mg daily for 21 days repeat every 28 days</td><td>Age, med: 72
M: 60.5%
Race: white 88.4%
Del 5q: 30.2%
ECOG 0: 44.2%
1: 51.2
2: 4.7
IPSS low: 32.9%
Inter-1: 53.5
Inter-2: 9.3
High: 2.3</td><td>N_R=43
<table><tr><th>Response</th><th>25
N=13</th><th>10
N=13</th><th>10/21
N=17</th><th>Total
N=43</th></tr><tr><td>RBC</td><td></td><td></td><td></td><td></td></tr><tr><td>Maj</td><td>6</td><td>6</td><td>9</td><td>21</td></tr><tr><td>Min</td><td>0</td><td>1</td><td>2</td><td>3</td></tr><tr><td>Total</td><td>6</td><td>7</td><td>11</td><td>24</td></tr><tr><td>Weeks to response</td><td>9</td><td>10.5</td><td>11.5</td><td></td></tr></table></td><td>Most common: neutropenia and thrombocytopenia

Severe myelosuppression was dose dependent.

3 deaths thought to be treatment related: cholecystitis with rupture, splenic infarct in patient with splenomegaly, pneumonia with neutropenia

Pruritus in 28% , restricted to scalp

Diarrhea in 21% of patients treated for greater than 3 months</td></tr>
</table>

Citation Design Analysis type Setting	Eligibility Criteria	Interventions	Patient Population Profile	Efficacy Results	Safety Results
	blasts >30% 8. chromosome abnormalities common to AML ie t(8:21), t(15:17), inv(16) 9. nutritional anemias				

N_R, Number randomized. Add abbreviations, other footnotes.