

Off-label uses included in the table represent only those uses that have been submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI).

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
Transfusion-dependent low-risk or intermediate-1 risk myelodysplastic syndrome without the del 5q chromosomal abnormality	Lenalidomide 10 mg orally once daily; continued until disease progression, treatment failure, or toxicity occurred. <sup>1</sup>	Moderate quality; Hematologic improvement-erythroid (HI-E) response	Not fully established	No conflicts of interest were disclosed during this review.	January 2009

### ***Clinical Trial Summary:***

Use of lenalidomide in transfusion-dependent myelodysplastic syndrome patients without the deletion 5q (del 5q) cytogenetic abnormality

#### **MDS-002 Study<sup>1</sup>**

- MDS-002 was a phase 2 study (n=214) evaluating the safety and efficacy of lenalidomide in transfusion-dependent (i.e., requiring 2 or more units of packed red blood cells [RBC] within 8 weeks) patients with low or intermediate-1 risk myelodysplastic syndrome (MDS) patients (as classified according to the International Prognostic Scoring System [IPSS]) who did not have the deletion 5q (del 5q) cytogenetic abnormality.<sup>1</sup>
- Initially, patients were treated with lenalidomide 10 mg orally once daily, administered for 21 days of each 28-day schedule with a 1-week rest period.<sup>1</sup> The protocol was subsequently amended to use a continuous dosing schedule of 10 mg once daily.<sup>1</sup> Treatment was interrupted and subsequent dosages were modified if grade 3 toxicity or greater occurred.<sup>1</sup> For patients experiencing grade 4 neutropenia or thrombocytopenia, lenalidomide was omitted for the remainder of the cycle and then restarted at a dosage of 5 mg daily for subsequent cycles after the toxicity had resolved.<sup>1</sup>
- A hematologic improvement-erythroid (HI-E) response, using the International Working Group (IWG) 2000 response criteria, was defined as transfusion independence with an increase in hemoglobin concentration of 1 g/dL or greater; minor erythroid response was defined as a 50% or greater reduction in the number of transfusions compared with baseline.<sup>1</sup> Newer IWG response criteria (proposed in 2006, IWG 2006) also were used to assess only clinically important or major erythroid responses, defined as either a 4-unit reduction in RBC transfusion requirements during any 8-week period (initiated in response to a hemoglobin value of 9 g/dL or lower among transfusion-dependent patients) or a rise in hemoglobin concentrations of 1.5 g/dL or greater in non-transfusion dependent patients.<sup>1</sup> Using both criteria, a sustained effect lasting for at least 8 weeks was required to be considered a response to the drug.<sup>1</sup>
  - In transfusion-dependent patients (approximately two-thirds of the study cohort), 43% of the patients had an HI-E response characterized by a reduction in transfusion requirements according to IWG 2000 criteria; 26% of the patients experienced transfusion independence and

an increase in hemoglobin concentration of 1 g/dL or more.<sup>1</sup> The median interval to the beginning of transfusion independence was 4.8 weeks; most patients (90%) who achieved transfusion independence did so by 16.9 weeks.<sup>1</sup> The median duration of transfusion independence in responding patients was 41 weeks (approximately 10 months).<sup>1</sup> Transfusion independence lasting at least 6 months was reported in 63% of responding patients, with 36% of those patients remaining transfusion free beyond 1 year.<sup>1</sup> Using IWG 2006 criteria, 33% of the patients experienced an HI-E response; 17% were characterized as transfusion independent.<sup>1</sup>

- Transfusion independence was more common in patients with a lower baseline transfusion requirement (i.e., less than 4 units of RBC per 8 weeks) compared with those requiring 4 units or more during the same time frame (44 and 17%, respectively).<sup>1</sup> In the subset of patients with a clonal cytogenetic abnormality (22%), only 19% experienced a cytogenetic response.<sup>1</sup>
- Grade 3–4 neutropenia and thrombocytopenia were reported in 30 and 25% of patients, respectively, and represented the most common reasons for dosage modification.<sup>1</sup>

### ***Discussion:***

The transfusion independence rate with lenalidomide in low-risk MDS patients without the deletion 5q (del 5q) cytogenetic abnormality was lower than the 67% transfusion independence rate reported with the same regimen in transfusion-dependent patients with the deletion 5q abnormality in the MDS-003 study.<sup>1,2</sup> The median duration of transfusion independence of 10 months in patients without the deletion 5q abnormality was shorter than the duration of at least 2 years reported in deletion 5q patients.<sup>1,2,3</sup> However, important differences in the use of prior treatment (i.e., untreated versus prior exposure to an erythropoietic stimulating agent [ESA] with or without filgrastim), the use of different response criteria (IWG 2000 versus IWG 2006), and the potential differences in sensitivity between 5q and non-5q clones limit a full cross-study comparison between the MDS populations with and without the deletion 5q abnormality.<sup>4</sup>

A post-hoc analysis of both the MDS-002 and 003 studies revealed a correlation between development of a clinically important treatment-related cytopenia or neutropenia and the likelihood of achieving transfusion independence in patients with a deletion 5q abnormality; however, a correlation was not apparent for the patients without the deletion 5q abnormality.<sup>2</sup> The incidence of grade 3 or 4 treatment-related neutropenia and thrombocytopenia in patients without the deletion 5q abnormality was approximately half of the reported incidence in deletion 5q patients.<sup>1,2</sup> Low-risk MDS patients without the deletion 5q abnormality achieved transfusion independence 2.5 times less frequently than patients with the deletion 5q karyotype.<sup>2</sup> Further analysis suggests that the achievement of cytogenetic response may correlate with the likelihood of transfusion independence.<sup>2</sup> In patients without the deletion 5q abnormality, 19% achieved an overall cytogenetic response in the MDS-002 study compared with a 73% overall cytogenetic response rate in patients with the deletion 5q abnormality in the MDS-003 study.<sup>1,5</sup>

Data from the pilot MDS-001 lenalidomide study, which reflected a heterogeneous population of low-risk myelodysplastic patients with and without the deletion 5q abnormality revealed a higher response rate of 80% (based on IWG 2000 criteria) in a small number of patients with no prior exposure to erythropoietic therapy compared with a lower erythroid response rate of 48% in patients who had received prior erythropoietin.<sup>6</sup> Some experts have recommended considering the use of lenalidomide in MDS patients without the deletion 5q abnormality who have transfusion-dependent anemia and are not responding to ESA therapy or in patients with an elevated (e.g., greater than 500 mU/mL) endogenous erythropoietin level.<sup>3</sup> However, a correlation between erythroid response and exposure or response to previous exogenous erythropoietin has not been fully established based on the data from the MDS-002 study; additionally, no correlation has been reported for responses based on endogenous erythropoietin concentrations.<sup>1,4</sup> Major responses in other hematopoietic lineages (e.g., neutrophils, platelets) have only been reported in a small number of MDS patients with such preexisting cytopenias receiving lenalidomide.<sup>1,6</sup> Because of the restrictive response in the erythroid lineage, the use of lenalidomide may have limited benefit in MDS patients with substantial neutropenia and/or thrombocytopenia.<sup>3</sup>

**Summary:**

Lenalidomide has activity in low- to intermediate-1 risk, transfusion-dependent, myelodysplastic syndrome patients without the deletion 5q (del 5q) cytogenetic abnormality, with possibly a greater benefit in patients with a low transfusion burden.<sup>4</sup> Additional data are needed to define the patient population that may derive benefit from lenalidomide when used as either first-line (i.e., in patients with a high endogenous erythropoietin level) or as second-line therapy (i.e., progression to transfusion dependence following treatment with either an ESA or a hypomethylating agent).<sup>4</sup> Treatment goals for transfusion-dependent myelodysplastic patients, especially in the relapsed setting, may be considered palliative; therefore, the risk of myelosuppression and the impact on quality of life measures associated with lenalidomide therapy must be weighed against the modest reduction in transfusion requirements in this patient population.<sup>4</sup> Additional data from ongoing trials may help to define the optimal dosage of lenalidomide and possibly the benefit of using a lenalidomide-erythropoietin/darbepoetin combination to increase the hematologic improvement response rate and subsequently to improve the quality of life in these patients.<sup>4</sup> However, based on current evidence, use of lenalidomide for the treatment of low-to intermediate-1 risk, transfusion-dependent MDS patients without the deletion 5q abnormality currently is not fully established because of an unclear risk/benefit in such patients.<sup>4</sup>

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