



Therapeutic Class ReviewSM

lenalidomide (Revlimid[®])

April 2006

New Product for Review:

Lenalidomide (Revlimid[®]) [Celgene]

Dossier Provided by Manufacturer: No

Dossier Evaluation: not applicable

- 1- dossier w/missing components
- 2- all components present, except pharmacoeconomic model
- 3- all components present (comprehensive)

Available Therapeutic Alternatives for Treatment of Myelodysplastic Syndrome:

Preferred/Formulary	Non-preferred/non-formulary
COVERED UNDER PHARMACY BENEFIT	
	thalidomide (Thalomid [®]) [Celgene]
COVERED UNDER MEDICAL BENEFIT	
azacitidine (Vidaza [®]) [Pharmion]	
antithymocyte globulin (Atgam [®]) [Pharmacia & Upjohn]	

Reason for Review

- Determine formulary status for lenalidomide (Revlimid), a new immunomodulatory drug (IMiD[®]) indicated for use in patients with myelodysplastic syndrome (MDS) who are transfusion-dependent.

Executive Summary

- Lenalidomide (Revlimid), an analogue of thalidomide, is an immunomodulatory drug (IMiD).
- Lenalidomide (Revlimid) was approved for use in MDS in December 2005 and is currently undergoing review for use in the treatment of Multiple Myeloma (MM).
- Myelodysplastic syndrome (MDS) is an incurable, progressive disease characterized by hemopoietic insufficiency (low red blood cell, platelet, and/or white blood cell counts).
 - There are 15,000 to 20,000 new cases in the U.S. each year.
 - MDS may lead to potentially serious morbidity, and mortality.
 - Risk is categorized as Low, Intermediate-1, Intermediate-2, or High and describes the survival outlook and potential for evolution to acute myelocytic anemia (AML).

- Lenalidomide (Revlimid) has only shown potential benefit in patients with one particular subtype of MDS (Low- to Intermediate-1-risk MDS associated with a specific chromosome (5q) deletion).
- Potential treatment alternatives for MDS may include: erythropoetin alfa (Procrit[®]), azacitidine (Vidaza), thalidomide (Thalomid) and antithymocyte globulin (Atgam).
- Allogeneic bone marrow transplant is the only hope for a cure for MDS, however not all patients are candidates for this procedure due to age limitations (< 65 years).
- Safety concerns with lenalidomide (Revlimid) include potential for birth defects, severe neutropenia/thrombocytopenia, and increased risk of pulmonary embolism and deep venous thrombosis.
- There are ongoing trials that study lenalidomide (Revlimid) in a host of other conditions, which puts it at high risk for off-label use.

Evidence

MDS

- There is no useful evidence supporting the use of lenalidomide (Revlimid) in the treatment of transfusion-dependent anemia resulting from MDS.
 - Trials were all of open-label design with no placebo- or active- control.
- Harms data is not reliable for the purposes of evaluating long-term benefit versus risks of lenalidomide (Revlimid).
- There is no evidence that lenalidomide (Revlimid) is safer or better tolerated than other treatment options.
- The evidence for other MDS treatment options is also not useful.

Multiple myeloma

- There is no useful evidence supporting the use of lenalidomide (Revlimid) in the treatment of multiple myeloma.
 - No details of the trials are available (unpublished).
 - Study endpoints include tumor response and time to progression (no survival data).

Other conditions

- There is no useful evidence supporting the use of lenalidomide (Revlimid) in other off-label conditions.

Considerations in subpopulations:

- *Pediatrics:* There is no useful evidence to establish the safety and efficacy in pediatric patients (< 18 years of age).
- *Geriatrics:* There is no useful evidence to establish differences in efficacy between older (> 65 years of age) and younger patients.

Elderly patients may be more prone to adverse effects from lenalidomide (Revlimid):

- Serious adverse events occurred with greater frequency in patients > 65 years of age.
- A greater proportion of patients > 65 years of age discontinued treatment due to adverse events.

- *Race, ethnicity, and/or gender:* Current clinical experience has not identified differences in safety or efficacy based on race, ethnicity or gender.

Conclusion

- Lenalidomide (Revlimid) is non-preferred/non-formulary because:
 - There is no good evidence to support its overall benefit in the treatment of MDS.
 - There is high potential of overuse for off-label indications for which there is no good evidence.
 - There are safety concerns with its use.

Products used in treatment of MDS:

Drug Products	FDA approval	FDA approved indications	Usual Dose/Route	Cost ^a	Potential Off-label Uses ^b
azacitidine (Vidaza) ¹	05/2004	Refractory anemia resulting from MDS; chronic myelomonocytic leukemia.	75 to 100 mg/m ² subcutaneously daily x 7 days; repeat q 4 weeks.	\$7,875 ^e	acute myeloid leukemia (AML); beta Thalassemia; chronic myeloid leukemia (CML); malignant mesothelioma; sickle cell anemia.
antithymocyte globulin (equine) (Atgam) ²	12/1996	Acute rejection in renal transplant in conjunction with concomitant immunosuppression; aplastic anemia.	40 mg/kg x 4 days ^c	\$17,100 ^f (single 4-day treatment)	anemia with MDS; bone marrow transplant; graft vs. host; thrombocytopenic purpura; pure red cell aplasia.
lenalidomide (Revlimid) ³	12/2005	Transfusion-dependent anemia due to Low- to Intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality.	Initial: 10 mg orally daily; decrease or hold dose based on blood counts	\$7,900	Multiple myeloma; chronic lymphocytic leukemia; glioma; renal cell cancer; myelofibrosis; melanoma; solid tumors.
thalidomide (Thalomid) ⁴	7/1998	Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL); maintenance therapy for prevention and suppression of cutaneous manifestations of ENL recurrence.	ENL: 100 to 400 mg per day MDS: 100 to 400 mg per day ^d	\$3,100 to \$6,100	Multiple myeloma; MDS; chronic lymphocytic leukemia; glioma; renal cell cancer; myelofibrosis; melanoma; solid tumors.

^a Cost estimate based on AWP (average wholesale price) listed in First Data Bank as of February 2006 for 28 days of therapy.

^b As listed in © 1974 - 2005 Thomson MICROMEDEX database or as referenced.

^c Greenberg PL, et al. 2002.

^d Raza A, et al. 2001.

^e Based on a dose of 75 to 100mg/m² administered for 7 days per 28-day cycle for a patient with a BSA of 1.7m² and rounded to two, 100-mg vials due to short expiration of reconstituted drug.

^f Based on 70 kg adult patient.

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