



Therapeutic Class ReviewSM

Immunomodulators: lenalidomide (Revlimid[®])

Update: February 2008

New Product for Review:

Lenalidomide (Revlimid[®]) [Celgene]

Dossier Provided by Manufacturer: Yes

Dossier Evaluation: 1

1- Dossier missing significant clinical trials

2- Mfg provided all relevant trials; missing pharmacoeconomic model

3- Mfg provided all relevant trials and information

Executive Summary

- Lenalidomide (Revlimid), an analogue of thalidomide, is an immunomodulatory drug (IMiD).
- Lenalidomide (Revlimid) was approved by the FDA for use in Myelodysplastic Syndrome (MDS) in December 2005 and for use in Multiple Myeloma (MM) in June 2006.
- 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).
- 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).
- Lenalidomide (Revlimid) is among several alternatives used in the treatment of advanced or relapsed multiple myeloma.
 - Alternative therapies may include melphalan/prednisone, bortezomib, dexamethasone, thalidomide, cyclophosphamide, and conventional chemotherapy (cisplatin, doxorubicin, etoposide, vincristine), and combinations thereof.
- Several Black Box Warnings describe serious safety concerns with lenalidomide (Revlimid) which include the potential for birth defects, severe neutropenia and thrombocytopenia, and increased risk of pulmonary embolism and deep venous thrombosis.
- There are ongoing trials that study lenalidomide (Revlimid) in several other conditions, which may increase the potential for off-label use.

Evidence

Myelodysplastic Syndrome (MDS)

- There is uncertain evidence supporting the use of lenalidomide (Revlimid) in the treatment of transfusion-dependent anemia resulting from MDS. Trials:
 - Were all of open-label design.
 - Lacked a comparative placebo- or active- control arm.
- There is no evidence that lenalidomide (Revlimid) is safer or better tolerated than other treatment options.
- It is unknown if lenalidomide (Revlimid) slows transformation of MDS to acute myeloid leukemia (AML) or improves survival in this population.
- Evidence for other treatment options is also not helpful in establishing clinical or long-term benefits in MDS.

Multiple myeloma (MM)

- There is no useful or possibly useful evidence supporting the use of lenalidomide (Revlimid) in the treatment of MM.
- There is no evidence that lenalidomide (Revlimid) is superior to other options in the treatment of advanced or relapsed MM.
- It is unknown whether time to progression (the primary endpoint in the two pivotal MM studies) correlates to improved survival in patients with MM.

Other conditions

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

Safety

- There is no evidence that lenalidomide (Revlimid) is safer or better tolerated than other options for the treatment of either MDS or MM.
- Dose-dependent hematologic adverse effects (neutropenia and thrombocytopenia) were the most commonly reported adverse events in patients receiving lenalidomide (Revlimid).
- Other common adverse events included diarrhea, pruritus, rash, and fatigue.
- Serious adverse events reported with a greater incidence with lenalidomide (Revlimid) than placebo included neutropenia, thrombocytopenia, anemia, and vascular events such as deep venous thrombosis and pulmonary embolism.

Decision

Lenalidomide (Revlimid) is preferred/formulary not based on evidence, which is not reliable, but based on the need for treatment options and recommendations in current national guidelines.

Products used in treatment of MDS and MM:

Drug Products	FDA approval ^a	Patent Expiration(s) ^b	FDA approved indications	Usual Dose/Route	Potential Off-label Uses ^c
azacitidine (Vidaza™) ¹	05/2004	05/2011	<ul style="list-style-type: none"> Refractory anemia resulting from MDS. Chronic myelomonocytic leukemia. 	75 to 100 mg/m ² subcutaneously daily x 7 days; repeat q 4 weeks.	Acute myeloid leukemia (AML); beta Thalassemia; chronic myeloid leukemia (CML); malignant mesothelioma; sickle cell anemia.
antithymocyte globulin (equine) (Atgam®) ²	12/1996	not available	<ul style="list-style-type: none"> Acute rejection in renal transplant along with concomitant immuno-suppression. Aplastic anemia. 	40mg/kg x 4 days ^e	Anemia with MDS; bone marrow transplant; graft vs. host; thrombocytopenic purpura; pure red cell aplasia.
bortezomib (Velcade®) ²³	5/2003	12/2009 05/2017	<ul style="list-style-type: none"> Treatment of patients with MM who have had at least one prior therapy. Treatment of patients with mantle cell lymphoma who have received at least one prior therapy. 	<i>Initial:</i> 1.3mg/m ² /dose IV twice weekly x 2 weeks, then 10 days off. <i>Maintenance:</i> weekly x 4 weeks, then off x 13 days.	Newly diagnosed MM in combination with other medications.
decitabine (Dacogen™) ²⁴	5/2006	05/2013	<ul style="list-style-type: none"> Myelodysplastic syndrome Chronic myelomonocytic leukemia. 	15 mg/m ² IV over 3 hours Q8H x 3 days; repeat cycle every 3 weeks; min. of 4 cycles.	Acute lymphoid leukemia (ALL), AML, CML, malignant melanoma, various solid tumors (e.g., prostate, lung, testicular).
dexamethasone (generics) ²⁵	10/1958	expired	<ul style="list-style-type: none"> Glucocorticoid: many uses include treatment of cancers, and inflammatory conditions. 	<i>MM, varies:</i> e.g., 40mg/day x 4 days 2-3x per cycle.	Vast array of inflammatory conditions and neoplasms.
lenalidomide (Revlimid®) ³	12/2005	07/2016 04/2023	<ul style="list-style-type: none"> Transfusion-dependent anemia due to Low- to Intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality. Multiple myeloma (MM) with dexamethasone in patients who have had at least one prior therapy. 	<i>Initial (MDS):</i> 10 mg orally daily; decrease or hold dose based on blood counts <i>Initial (MM):</i> 25 mg orally daily x 21 days out of each 28-day cycle	chronic lymphocytic leukemia (CLL); glioma; renal cell cancer; myelofibrosis; melanoma; solid tumors.
thalidomide (Thalomid®) ⁴	7/1998	05/2013 05/2014	<ul style="list-style-type: none"> Acute and maintenance treatment of moderate to severe erythema nodosum leprosum (ENL). Newly diagnosed MM in combination with dexamethasone. 	<i>ENL:</i> 100 to 400 mg per day <i>MDS:</i> 100 to 400 mg per day ^f	MDS; chronic lymphocytic leukemia; glioma; renal cell cancer; myelofibrosis; melanoma; solid tumors.

^a Date applies to approval date for the original brand name medication where there are now generics available.

^b Based on patents listed in the Orange Book as of January 2008.

^c As listed in ©1974-2008 Thomson MICROMEDEX database or as referenced.

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