CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July- August

BRAND NAME
Revlimid®

GENERIC NAME
lenalidomide

MANUFACTURER
Celgene Corporation

DATE OF APPROVAL
February 22, 2017

PRODUCT LAUNCH DATE
January 5, 2006

REVIEW TYPE

☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)[1]
Current Indication(s):
- For the treatment of multiple myeloma, in combination with dexamethasone
- For the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities

- For the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade)

New Indication(s):

- For the treatment of patients with multiple myeloma (MM) as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT)

OFF-LABEL USES[2]

Systemic Light Chain Amyloidosis (NCCN 2A recommendation in combination with dexamethasone)

CLINICAL EFFICACY

The use of Revlimid as maintenance therapy following auto-HSCT in patients with MM was evaluated in two phase 3, multicenter, randomized, double-blind, placebo-controlled studies: CALGB 100104 (Study 1) and IFM 2005-02 (Study 2).

Study 1 included patients with MM and were 18 to 70 years old, Eastern Cooperative Oncology Group performance status of 0 or 1, and received any induction regimen of 2 to 12 months duration (at most, two induction regimens excluding dexamethasone alone could have been received) followed by auto-HSTC. Within 90-100 days after auto-HSCT, patients with at least a stable disease response were randomized 1:1 to receive either Revlimid (N = 231) or placebo maintenance (N = 229).[3]

Study 2 included patients younger than 65 years of age with multiple myeloma that had not progressed in the interval between first-line autologous stem-cell transplantation (either one or two procedures), performed within the previous 6 months, and randomization. Following transplantation, all patients received two consolidation treatment cycles with Revlimid. After consolidation was complete, patients were randomized 1:1 to receive either Revlimid (N = 307) or placebo maintenance (N = 307).[4]

In both studies, the Revlimid maintenance dose was 10 mg once daily on days 1-28 of repeated 28-day cycles, could be increased to 15 mg once daily after 3 months in the absence of dose-limiting toxicity, and treatment was to be continued until disease progression or patient withdrawal for another reason. A dose increase to 15 mg once daily occurred in 135 patients (58%) in Study 1, and in 185 patients (60%) in Study 2.

The primary endpoint in both studies was progression-free survival (PFS) defined from randomization to the date of progression or death, whichever occurred first. Overall survival was included as a secondary outcome. Both studies were unblinded upon the recommendations of their respective data monitoring committees and after surpassing the respective thresholds for preplanned interim analyses of PFS. Study 1 allowed patients in the placebo arm to cross over to

receive Revlimid ((76 patients [33%] crossed over to REVLIMID). The results at unblinding and an updated analysis as of March 2015 are summarized in the following table.

	Maintenance Study 1		Maintenance Study 2	
	REVLIMID N = 231	**Placebo N = 229**	**REVLIMID N = 307**	**Placebo N = 307**
PFS at Unblinding				
PFS Events n (%)	46 (20)	98 (43)	103 (34)	160 (52)
Median in months [95% CI]	33.9 [NE, NE]	19.0 [16.2, 25.6]	41.2 [38.3, NE]	23.0 [21.2, 28.0]
Hazard Ratio [95% CI]	0.38 [0.27, 0.54]		0.50 [0.39, 0.64]	
Log-rank Test p-value	<0.001		<0.001	
PFS at Updated Analysis 1 March 2015 (Studies 1 and 2)				
PFS Events n (%)	97 (42)	116 (51)	191 (62)	248 (81)
Median in months [95% CI]	68.6 [52.8, NE]	22.5 [18.8, 30.0]	46.3 [40.1, 56.6]	23.8 [21.0, 27.3]
Hazard Ratio [95% CI]	0.38 [0.28, 0.50]		0.53 [0.44, 0.64]	
OS at Updated Analysis 1 Feb 2016 (Studies 1 and 2)				
OS Events n (%)	82 (35)	114 (50)	143 (47)	160 (52)
Median in months [95% CI]	111.0 [101.8, NE]	84.2 [71.0, 102.7]	105.9 [88.8, NE]	88.1 [80.7, 108.4]
Hazard Ratio [95% CI]	0.59 [0.44, 0.78]		0.90 [0.72, 1.13]	

Date of Unblinding in Maintenance Study 1 and 2 = 17 December 2009 and 7 July 2010, respectively
Auto-HSCT = autologous hematopoietic stem cell transplantation; CI = confidence interval;
ITT = intent to treat; NE = not estimable; PFS = progression-free survival
PFS at time of unblinding for Maintenance Study 2 was based on assessment by an Independent Review Committee. All other PFS analyses were based on assessment by investigator.
Note: The median is based on Kaplan-Meier estimate, with 95% CIs about the median overall PFS time. Hazard ratio is based on a proportional hazards model stratified by stratification factors comparing the hazard functions associated with treatment arms (lenalidomide:placebo).

In both studies, the primary analysis of PFS at unblinding was significantly longer with Revlimid compared to placebo: Study 1 HR 0.38 (95% CI: 0.27-0.54 p <0.001; median follow-up of 18 months) and Study 2 HR 0.50 (95% CI: 0.39-0.64 p <0.001). The results were consistent at the updated analysis performed in March 2015 with a median follow-up period of 72.4 and 86 months for Study 1 and 2 respectively. For the secondary endpoint of overall survival (OS) after a median follow-up time of 81.6 and 96.7 months, the median OS for patients that received

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Revlimid was 111.0 and 105.9 months compared to placebo of 84.2 and 88.1 months respectively for Study 1 and 2. The individual studies were not adequately powered for the overall survival endpoint. In Study 1, 22% (51/31) of Revlimid treated patients discontinued therapy due to progressive disease. The number of patients who withdrew from the study due to lack of efficacy was not available for Study 2.

CONTRAINDICATIONS
Pregnancy

BLACK BOX WARNINGS[1]

- Embryo-fetal toxicity: Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.
- Hematologic toxicity: Revlimid can cause significant neutropenia and thrombocytopenia. For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.
- Venous and arterial thromboembolism: Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma receiving Revlimid with dexamethasone. Anti-thrombotic prophylaxis is recommended.

DRUG INTERACTIONS[1]

- Digoxin: Periodic monitoring of digoxin plasma levels is recommended due to increased C_{max} and AUC with concomitant Revlimid therapy.
- Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thrombosis.

ADVERSE REACTIONS[1]

- The most frequently reported adverse reactions (more than 20%) were neutropenia, thrombocytopenia, leukopenia, anemia, upper respiratory tract infection, bronchitis, nasopharyngitis, cough, gastroenteritis, diarrhea, rash, fatigue, asthenia, muscle spasm and pyrexia.
- The most frequently reported Grade 3 or 4 reactions (more than 20%) included neutropenia, thrombocytopenia, and leukopenia.

DOSAGE AND ADMINISTRATION[1]

- 10 mg PO QD continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity.
- After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.

- Revlimid maintenance therapy following auto-HSCT should be initiated after adequate hematologic recovery (ANC ≥ 1000/mcL and/or platelet counts ≥75,000/mcL).

PRODUCT AVAILABILITY[1]
Capsules: 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
bortezomib (Velcade)	**Multiple Myeloma (maintenance therapy following auto-HSTC):** 1.3 mg/m^2 SC/IV every 2 weeks	2A recommendation per NCCN

Boldface indicates generic availability

Utilization Management Recommendation
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): (1) To prevent inappropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes. (2) NCCN recommends Revlimid be used in combination with dexamethasone for newly diagnosed or previously treated multiple myeloma. Single agent Revlimid therapy is only recommended for maintenance therapy following autologous hematopoietic stem cell transplantation. ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison[5]
• It would not be clinically appropriate to require a trial of Velcade (NCCN category 2A recommendation) prior to initiation of Revlimid (NCCN category 1 recommendation) for maintenance therapy following autologous hematopoietic stem cell transplantation.

REFERENCES

[1] Revlimid [Prescribing Information]. Summit, NJ: Celgene Corporation; February 2017.
[2] Lenalidomide: NCCN Drugs & Biologics Compendium. Available at: https://www.nccn.org/professionals/drug_compendium/content/contents.asp. Accessed March 6, 2017.
[3] Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma. N Engl J Med 2012; 366: 1782-1791.
[4] McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366: 1770-1781.
[5] Multiple Myeloma: NCCN Guidelines Version 3.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed March 6, 2017.