

## The Treatment of Multiple Myeloma and Myelodysplastic Syndromes with Immunomodulatory Agents

a report by

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### Immunomodulatory Drugs

Recently, immunomodulatory drugs (IMiDs) have received attention for their clinical efficacy in the treatment of multiple myeloma (MM) and the myelodysplastic syndromes (MDS). Thalidomide is the parent IMiD and was first used in Europe in the late 1950s as treatment for hyperemesis gravidarum and as a sleep-aid remedy. It quickly became notorious as a potent teratogen by inducing phocomelia (severe malformation of the limbs) in approximately 10,000 children. Later, work on the mechanism of the action of thalidomide led to the discovery of its anti-inflammatory and anti-angiogenic properties and it again found clinical use, beginning with the treatment of leprosy.

The exact mechanism of action of thalidomide is not known. It is postulated that there are multiple targets of action, including reducing pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- $\alpha$ ), raising T cell and natural killer (NK) cell stimulatory signals IL2 and interferon gamma (IFN-g), and inhibiting the secretion of angiogenic compounds such as vascular endothelial growth factor (VEGF).<sup>1</sup> Newer and more potent analogs of thalidomide have since been developed

for clinical use. Lenalidomide (CC-5013, Revlimid®, Celgene Corporation, Summit, New Jersey) is the most commonly used derivative and is 100–50,000 times more potent (depending on the specific mechanism of action that is studied), and has also been shown to be directly cytotoxic to malignant cells.<sup>2</sup>

In clinical practice, thalidomide has side effects of somnolence, constipation, a slowed pattern of thinking that many patients refer to as a ‘brain fog,’ and the potential to cause an irreversible peripheral sensory neuropathy if not discontinued in a timely manner. Thalidomide has also been shown to increase the risk for venous thrombosis when used in combination with corticosteroids.<sup>3</sup> While lenalidomide is structurally similar to its parent chemical, the major side effect is bone marrow suppression. This toxicity is related to the clearance of this drug by the kidney and a study has shown that the rate of myelosuppression is greatly decreased in patients with a creatinine clearance of greater than 40cc/min.<sup>4</sup> Like thalidomide, lenalidomide may also be prothrombotic when used in combination with corticosteroids.<sup>3</sup>

Thalidomide and lenalidomide have revolutionized the current standard of practice for hematologists treating MM and MDS, and have offered new hope for patients suffering from these diseases. Patients who were once refractory to treatment with standard chemotherapeutics could obtain responses to IMiDs and enjoy longer periods of remission. The clinical observations and trials leading to the approval of IMiD use in MM and MDS are outlined below.



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### Multiple Myeloma

MM is the second most common type of hematological malignancy after non-Hodgkin's lymphoma, with nearly 20,000 new cases and 11,000 deaths every year in the US alone.<sup>5</sup> MM is characterized by the malignant clonal growth of plasma cells in the bone marrow with associated monoclonal immunoglobulin production that is detectable as a monoclonal (M)-spike on serum protein electrophoresis. Currently, MM is an incurable malignancy that has been historically treated with conventional cytotoxic chemotherapies such as the alkylating agent melphalan in combination with corticosteroids, with expected response rates in the 30–50% range as up-front therapy and 15–25% in the relapsed setting.<sup>6</sup> High-dose chemotherapy followed by an autologous stem cell transplant has been shown to extend overall survival in patients healthy enough to tolerate the procedure; however, patients ultimately relapse.

While the transforming event in MM is not currently known, the survival of the malignant plasma cells in MM is highly dependent on its association

with the bone marrow milieu, in which cytokine signals for growth and survival, such as IL-6 and VEGF, are received. The adhesion between malignant plasma cells and the marrow stromal cells themselves have also been shown to be important in the continuing survival of MM.<sup>7</sup> The IMiDs target many of these essential molecular pathways and are powerful new agents in clinical practice.

### Clinical Trials of Immunomodulatory Drugs in Relapsed or Refractory Multiple Myeloma

Thalidomide was first reported in 1999 to show clinical activity as monotherapy for MM.<sup>8</sup> Eighty-four patients with relapsed or refractory MM (76 who underwent prior autologous stem cell transplant) were treated with thalidomide at escalating doses ranging from 200 to 800mg daily. Thalidomide produced a clinical response, measured by an M-protein decrease in 32% of patients, with two patients achieving complete remission. The responses seen were consistent, with approximately 60% of the patients surviving at the end of one year of follow-up. However, treatment with thalidomide was toxic, with many patients experiencing constipation and somnolence (~40%) and neuropathy (~20%).

Subsequently, in 2001 Palumbo et al. reported a phase II study showing that the combination of low-dose thalidomide (100mg daily) plus dexamethasone was an even more potent salvage therapy for relapsed/refractory MM, with a total 41% response rate and an additional 25% of patients maintaining stable disease.<sup>9</sup> The side effect of neuropathy was significant in 17% of the patients, prompting either dose reduction or discontinuation of therapy. A phase II trial conducted at our institution with the combination of clarithromycin (Biaxin®), low-dose thalidomide, and dexamethasone (BLT-D) in patients with previously treated MM or Waldenstrom's macroglobulinemia (or newly diagnosed patients unable to tolerate standard initial myelosuppressive therapy) showed a high rate of response of 93% in the evaluable patients, including 13% complete remissions, 40% near-complete responses, 13% major responses, and 27% partial responses.<sup>10</sup> However, neurotoxicity was limiting as 18% of the patients developed grade 3 or higher neuropathy from BLT-D treatment.

Next, lenalidomide was tested in clinical trials with the hope that the side effect profile would be more favorable while maintaining the efficacy of thalidomide. Initial phase I studies of lenalidomide in patients with relapsed or refractory MM found that the maximal tolerated dose was 25mg daily, limited by myelosuppression.<sup>11</sup> A reduction of at least 25% in the M-spike (defined as minor response or better) was seen in 71% of the study participants. Moreover, 11 of 16 patients who had a history of prior thalidomide use responded to thalidomide. From this study, it appeared that lenalidomide could be used as a powerful agent in MM, had tolerable side effects, and was not cross-resistant to thalidomide.

A large multicenter phase II trial published in 2006 evaluated lenalidomide monotherapy in 102 patients with relapsed or refractory multiple myeloma.<sup>12</sup> Patients were initially randomized to one of two dosing schedules of lenalidomide: 15mg twice daily or 30mg once daily for 21 days of a 28-day cycle. Later interim analysis showed increased grade 3/4 myelosuppression in the twice-daily arm (41 versus 13%), and the subsequently enrolled patients were eventually assigned to the once-

daily group. The study was designed so that if a patient did not respond after two cycles of lenalidomide monotherapy, dexamethasone was added at a dose of 40mg daily for four days every two weeks. Lenalidomide monotherapy was found to induce a minor response or better in 25% of patients. The addition of dexamethasone produced a response in another 29% of patients who did not have M-spike reduction with lenalidomide alone, giving an overall response rate of 54% in all study participants. Importantly, prior thalidomide or bortezomib therapy significantly influenced the efficacy of lenalidomide, thus confirming the earlier phase I data.

Two multicenter phase III studies, one conducted in North America by Weber et al. (the MM-090 study) and the other internationally by Dimopoulos et al. (the MM-010 study), were recently published and confirmed that lenalidomide in combination with dexamethasone was a more effective treatment than high-dose dexamethasone alone for previously treated MM.<sup>13,14</sup> In both trials the response rate to lenalidomide plus dexamethasone was nearly 60% versus approximately 20% with dexamethasone alone. The median time to progression for combination therapy was longer with dexamethasone alone (~12 months versus ~5 months), and overall survival was increased with lenalidomide in both studies.

These trials provided the basis for US Food and Drug Administration (FDA) approval of the combination of lenalidomide and dexamethasone in patients with MM who had received at least one prior therapy. Venous thrombosis and thromboembolism were more frequent in the lenalidomide/dexamethasone group versus dexamethasone alone (11.4 versus 4.6% in the MM-010 study, 14.7 versus 3.4% in MM-090). Prophylactic anticoagulation is generally recommended, but is not strictly defined in terms of which agent to use. Prior observations by our group show that low-dose aspirin (81mg daily) can effectively diminish the risk of thrombosis and thromboembolism in combination with IMiD/corticosteroid therapy.<sup>3</sup>

The standard practice of care for newly diagnosed symptomatic multiple myeloma is induction therapy to reduce the disease burden followed by high-dose chemotherapy with stem cell rescue.

### Clinical Trials of Immunomodulatory Drugs as Front-line Therapy in Multiple Myeloma

The standard practice of care for newly diagnosed symptomatic MM is induction therapy to reduce the disease burden followed by high-dose chemotherapy with stem cell rescue in an effort to improve long-term disease survival. The encouraging results of the use of IMiDs in relapsed or refractory myeloma prompted trials of this drug class as first-line induction therapy, looking specifically at disease response as well as the ability to harvest adequate numbers of stem cells for later use in autologous stem cell transplantation. A phase II study of thalidomide plus dexamethasone in treatment-naïve MM was published in 2002 with encouraging results.<sup>15</sup>

In this trial, 50 patients with newly diagnosed MM were treated with 200mg of thalidomide daily in combination with 40mg of dexamethasone given in four-day on/off pulses. Overall, 62% of patients objectively responded to therapy and there was no impairment in the ability to harvest stem cells for transplant. Four patients (8%) had progression of their myeloma while on study. Significant adverse effects were seen in 32% patients, including venous thrombosis (12%) and constipation (8%).

In 2003, Weber et al. published a comparison of thalidomide monotherapy versus thalidomide plus dexamethasone therapy in a phase II trial of 28 patients.<sup>16</sup> This study showed that the effects of thalidomide and dexamethasone were cumulative, with thalidomide yielding an objective response in 36 versus 72% of patients in the combination group. The rate of neuropathy was comparable at 20% for both groups, but there was an increased risk of venous thrombosis in the combination group (15%) versus the thalidomide alone (4%).

In 2006, the results of a phase III trial comparing thalidomide plus dexamethasone versus dexamethasone alone were published and led to FDA approval of the combination for front-line treatment of MM.<sup>17</sup> Two hundred and seven patients with treatment-naïve MM were randomly assigned to four months of treatment with either 200mg thalidomide daily in combination with pulse dexamethasone or dexamethasone therapy alone. The overall response rates were 72 versus 50%, respectively, for combination versus dexamethasone monotherapy. Complete remission was seen in 4% of the patients in the thalidomide/dexamethasone arm, while none were seen with dexamethasone alone. Furthermore, fewer disease progressions were seen with combined therapy (2 versus 5%). Grade 3 or higher toxicity was twice as likely with the use of thalidomide/dexamethasone (45 versus 21%), notably with more venous thrombosis (17 versus 3%) and grade 3/4 neuropathy (7 versus 4%).

A phase II trial of lenalidomide plus dexamethasone in newly diagnosed patients with MM in 2005 yielded even more impressive results than the thalidomide/dexamethasone combination.<sup>18</sup> Thirty-four patients with newly diagnosed MM were treated with lenalidomide 25mg daily on days one to 21 and dexamethasone pulse therapy. Thirty-one patients (91%) had achieved a greater than 50% reduction in their M-protein, and of the three remaining patients two had minimal responses with M-protein reductions between 25 and 50% and one had stable disease. No patient progressed while on therapy and the median time to response was one month. Stem cell harvest was successfully performed in all attempts.

Another phase II trial conducted by our institution explored the combination of clarithromycin with clarithromycin and dexamethasone in newly diagnosed patients in MM.<sup>19</sup> Use of this combination of therapy in 72 patients yielded objective responses in 90.3% with a 38.9% complete remission rate, which is unprecedented for any myeloma induction regimen. This regimen did not interfere with stem cell harvest in patients who were mobilized with the combination of cyclophosphamide and granulocyte-colony stimulating factor (G-CSF), and the major toxicities seen were thromboembolic events, cytopenias, and corticosteroid-related morbidity.

The accrual of more experience with the use of lenalidomide in clinical practice has revealed that this drug has a significant impact on the ability

to collect adequate CD34+ stem cells for use in later autologous stem cell transplant.<sup>20,21</sup> Kumar et al. showed that patients with newly diagnosed MM who were treated with lenalidomide mobilized significantly fewer CD34+ cells in response to G-CSF therapy alone and had a concomitant increase in the required number of days of apheresis. The duration of prior lenalidomide therapy and patient age were also both significant factors for the number of stem cells that were collected. Our group has corroborated these results and has found that that combination cyclophosphamide/G-CSF as a mobilization regimen effectively abrogates the negative impact of lenalidomide therapy, regardless of the length of prior treatment.<sup>22</sup>

As for front-line therapy for MM patients who are not candidates for autologous stem cell transplant, encouraging results have also been seen with the use of IMiDs in combination with the standard therapy of melphalan plus prednisone. A randomized controlled trial of thalidomide 100mg with melphalan and prednisone (MPT) versus melphalan and prednisone (MP) alone in patients over 65 years of age yielded an impressive response rate in favor of the MPT arm (76 versus 48%).<sup>23</sup> Intriguingly, there was a trend toward improved overall survival at three years of follow-up in the MPT group (80 versus 64%) that did not achieve statistical significance. The high response rates in this study for MPT came at the cost of a doubling of the grade 3 or 4 toxicity rate (48 versus 25%), including a thromboembolism rate of 20% prior to the introduction of enoxaparin prophylaxis for all MPT patients. These results were confirmed and extended in a later study comparing MPT versus standard MP versus tandem reduced-intensity autologous stem cell transplantation (using a 100mg/m<sup>2</sup> dose of intravenous melphalan, half the usual dose) in previously untreated elderly patients with MM.<sup>24</sup> The primary end-point of the study was overall survival. The median survival was 51.6 months for the MPT-treated patients versus 33.2 months for MP versus 38.3 months for low-intensity transplant. This study redefined the standard of care of the elderly myeloma patient by illustrating the additional contribution of the immunomodulatory therapy on survival.

The same investigator group that developed MPT next tested the combination of melphalan plus prednisone and low-dose lenalidomide (5–10mg daily for 21 days of a 28-day cycle) (RMP) in newly diagnosed elderly MM patients.<sup>25</sup> Eighty-one percent had an objective response rate to RMP, with a 24% complete response rate. The major toxicities were hematological and manageable and aspirin provided effective thrombosis prophylaxis, showing that similar rates of response with lower rates of toxicity could be achieved when using RMP versus MPT.

Randomized trials evaluating the efficacy of lenalidomide and dexamethasone at both low dose and high dose versus dexamethasone alone for newly diagnosed MM are currently under way to confirm the activity of this drug in the front-line setting.

### The Myelodysplastic Syndromes

MDS are malignancies of the hematopoietic progenitor cells in the bone marrow that result in ineffective blood cell production. Patients with MDS often suffer from fatigue, bleeding, or increased susceptibility to infections due to underlying combinations of anemia, thrombocytopenia, and/or leucopenia. MDS is a clinically heterogeneous disease and is subclassified by the World Health Organization (WHO) on the basis of

bone marrow histological criteria as well as genetic markers, with a range of disease types from the slightly altered bone marrow findings (e.g. refractory anemia) to incipient acute leukemia (e.g. refractory anemia with excess blasts, type 2).<sup>26</sup>

MDS have a high risk of progressing from a smoldering disease to acute leukemia, which loosely follows the WHO classification. This risk can be estimated using the International Prognostic Scoring System (IPSS), which takes into account variables to determine the probability of progression to acute leukemia, such as the percentage of bone marrow blasts, the presence of karyotype abnormalities, and the number of concurrent cytopenias present.<sup>27</sup> The most common karyotype abnormality seen in MDS is chromosome 5q31 interstitial deletion, which can be either isolated or associated with more complex karyotypes. MDS with isolated del(5q) has its own WHO classification. This is considered a more indolent MDS, characterized by hypoplastic anemia, dysplastic megakaryocytes, and a generally more favorable prognosis and lower IPSS scores than MDS with other cytogenetic abnormalities.

Thus far, the underlying pathophysiological abnormality in MDS has not been found, but there appear to be a number of factors involved. These include the increased replication of bone marrow stem cells with both disordered maturation and an increased rate of apoptosis, altered bone marrow stromal cell signaling activity characterized by overproduction of inflammatory and neovascular cytokines such as TNF $\alpha$ , IL-6, and VEGF, and a blunted response of bone marrow cells to physiological stimuli such as erythropoietin. There is also evidence that suggests an aberrant immune response is the cause of MDS in a subset of younger patients, as there have been responses to antithymocyte globulin therapy in this particular group.

### Clinical Trials of Immunomodulatory Drugs in Myelodysplastic Syndromes

The pro-inflammatory cytokine milieu, i.e. enhanced neo-angiogenesis and disordered immune response that characterize MDS, were postulated to be potential targets for immunomodulatory drugs. Thalidomide was the first IMiD used for the treatment of MDS and showed activity in about 30–50% of patients who took the drug for 12–16 weeks.<sup>28,29</sup> Patients who responded tended to have a lower IPSS score and were manifested by a decrease in transfusion dependence, as well as in the percentage of blasts in the bone marrow. There was no association with any particular karyotype abnormality with the degree of response. The data appeared to be promising; however, virtually all study participants experienced side effects with the thalidomide therapy, which had to be given in the relatively large dose of 400mg daily. In the end, many patients, especially with higher-grade MDS by WHO classification, dropped out of the clinical trials due to excessive fatigue, constipation, and peripheral neuropathy.

Lenalidomide was the next agent tested for use in MDS, with the first reported trial in 2005. In this study, lenalidomide was prescribed to 53 MDS patients with low to intermediate IPSS scores with symptomatic or transfusion-dependent anemia.<sup>30</sup> Prior to enrollment, these patients were shown to be either refractory to erythropoietin (EPO) therapy or already had high circulating EPO levels and were thus not felt to benefit from further EPO supplementation. The results of the study showed a marked response to lenalidomide therapy after 16 weeks of therapy in 24 patients (56%),

with 20 (47%) achieving complete sustained independence from transfusion up to 81 weeks of follow-up, three (7%) with a 50% reduction in transfusion requirement, and one (2%) with an increase in hemoglobin by 2g/dl but continued need for transfusions. Three different lenalidomide dosing schedules were used in the study and, interestingly, while the expected side effects of bone marrow suppression occurred at the higher doses, the efficacy of the drug was not different at the lowest dose of lenalidomide (10mg daily for 21 days out of a 28-day-cycle), which is the dosing currently used in clinical practice.

The severity of the MDS by the IPSS and WHO classifications and prior thalidomide therapy did not statistically influence the likelihood of response to lenalidomide. In fact, the only characteristic of the MDS that did predict the likelihood of response to lenalidomide therapy was karyotype. Patients with the deletion of the 5q31.1 region had a high major erythroid response rate of 83%. While nearly all of the patients had isolated del(5q), one patient with del(5q) who responded had concurrent trisomy.<sup>21</sup> All patients with del(5q)31.1 who had a major erythroid response had complete cytogenetic remission and resolution of megakaryocyte dysplasia on follow-up bone marrow samples. While many patients found clinical benefit with lenalidomide in this study, the dramatic response observed in the patients with the del(5q) was particularly encouraging and warranted further investigation.

The robust response of MDS with the interstitial deletions of chromosome 5q deletion to lenalidomide treatment was confirmed in the MDS-003 study in 2006.<sup>31</sup> In this multicenter international trial, 148 patients with the chromosome 5q31 deletion (both isolated and as part of a more complex karyotype abnormality) were treated with lenalidomide. All participants had transfusion-dependent anemia and 120 (81%) had low to intermediate-1 IPSS score prior to entry. Among these patients, 76% had a reduced transfusion requirement with treatment, with 67% becoming transfusion-free. The mean hemoglobin rise in responders was 5.6g/dl and the effect was sustained over 104 weeks of follow-up. In 86 patients with serial bone marrow cytogenetic studies, 73% had cytogenetic improvement and 45% had a complete cytogenetic remission. There was no statistically significant association between the karyotype complexity and anemia improvement, cytogenetic response, or overall survival. This finding is of particular importance, since patients with additional karyotype abnormalities in conjunction with del(5q) historically have traditionally higher-risk MDS.

These data suggest that lenalidomide treatment may have a disease-altering effect for patients with high-risk karyotypes that contain the del(5q). The side effects of grade 3 or 4 neutropenia and thrombocytopenia were seen in 55 and 44% of patients, respectively, with a lower rate in those patients who took lenalidomide at 10mg daily for 21 days of a 28-day cycle compared with 10mg daily continuously. The dose was not statistically associated with the quality of response. This trial demonstrated the clinical efficacy of lenalidomide suppression of the 5q-clone and led to FDA approval for lenalidomide in the treatment of MDS associated with del(5q).

A second multicenter phase II trial, MDS-002, studied the effect of lenalidomide treatment in MDS, specifically excluding patients with interstitial deletions of chromosome 5q.<sup>32</sup> The study used the same entry criteria as the

MDS-003, targeting patients with low to intermediate-1 MDS who were transfusion-dependent; however, all participants lacked deletion 5q. Overall, 43% of the 214 patients had hematological improvement, with 26% achieving transfusion independence. The patients who responded to therapy achieved a median hemoglobin rise of 3.2g/dl and median duration of transfusion independence was 41 weeks. Neutropenia and thrombocytopenia were the major adverse effects, affecting 30 and 25% of patients, respectively. The lower rates of myelosuppression in these patients may reflect a different mechanism of action of lenalidomide in the non-del(5q) state. In summary, while the erythroid responses seen in these patients were not as profound or as durable as those with the del(5q), there is a clinical utility for lenalidomide in patients with transfusion-dependent low-risk MDS without this karyotype abnormality.

Further clinical trials are under way or in planning to test the efficacy of lower doses of lenalidomide for MDS and also the use of lenalidomide in combination with erythropoietin.

## Conclusion

Immunomodulatory drugs have been shown to provide strong, durable responses for a high proportion of patients with MM and MDS, and in the case of MM have been shown to increase overall survival. The side effects of myelosuppression can be managed with growth factors such as G-CSF, and the risk of venous thrombosis is greatly reduced with the use of prophylactic aspirin or other anticoagulation.

The main question of whether lenalidomide or thalidomide could be used in place of autologous stem cell transplant for MM remains to be determined with clinical trials. However, patients who cannot tolerate this procedure can be treated with excellent results with combinations of low-dose lenalidomide or thalidomide with standard agents such as melphalan plus prednisone.

There is no doubt that lenalidomide is a powerful agent for use in MDS with interstitial deletion of the long arm of chromosome 5, whether it is isolated or in conjunction with more complex karyotypes. The robust response rate and durable freedom transfusions have made this drug a first choice for treatment of this condition. Lenalidomide has also shown activity, to a lesser extent, in non-del(5q)-containing MDS as well, and potentially works through a different mechanism of action. One caveat is that the trials of lenalidomide in MDS have all been performed mostly in patients with prognostically favorable (low to intermediate-1) IPSS scores, and caution should be used if treating patients with higher-grade MDS.

As more clinical studies are conducted with lenalidomide and other IMiDs for MM and the MDS, we should expect that these drugs will become an important part of the therapeutic armamentarium of the hematologist treating malignant diseases. The pleiotropic action of IMiDs provides a basis for understanding the complex pathophysiology underpinning MM and MDS, and hopefully will help elucidate the main transforming events for these diseases in the future. ■

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For patients who have received at least 1 prior therapy

# LEADING THE CHARGE™ IN MULTIPLE MYELOMA AND MANTLE CELL LYMPHOMA\*



**VELCADE®**  
(bortezomib) FOR INJECTION

\*VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy. VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol. VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

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**Please see Brief Summary of  
full Prescribing Information  
on adjacent page.**



## Important Safety Information

Contraindications, warnings, and precautions are derived from an integrated analysis evaluating single-agent VELCADE® (bortezomib) for Injection dosed at 1.3 mg/m<sup>2</sup> at the same schedule in multiple myeloma and mantle cell lymphoma clinical trials. This integrated analysis does not include the phase 3, VELCADE plus DOXIL® (doxorubicin HCl liposome injection) study.

**INDICATIONS:** VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with multiple myeloma who have received at least 1 prior therapy. VELCADE® (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

**CONTRAINDICATIONS:** VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol.

### WARNINGS AND PRECAUTIONS:

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE. **Pregnancy Category D:** Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m<sup>2</sup> in the rat and 0.05 mg/kg; 0.6 mg/m<sup>2</sup> in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area. Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05 mg/kg (0.6 mg/m<sup>2</sup>) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m<sup>2</sup> based on body surface area. There are no adequate and well-controlled studies in pregnant women. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. **Peripheral Neuropathy:** VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE. Following dose adjustments, improvement in or resolution of peripheral neuropathy was reported in 51% of patients with ≥Grade 2 peripheral neuropathy in the phase 3 multiple myeloma study. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma. **Hypotension:** The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 13%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics. **Cardiac Disorders:** Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or existing heart disease should be closely monitored. In the phase 3 multiple myeloma study, the incidence of any treatment-emergent cardiac disorder was 15% and 13% in the VELCADE and dexamethasone groups, respectively. The incidence of heart failure events (acute pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock, pulmonary edema) was similar in the VELCADE and dexamethasone groups, 5% and 4%, respectively. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established. **Pulmonary Disorders:** There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal. A higher proportion of these events have been reported in Japan. In a clinical trial, the first two patients given high-dose cytarabine (2 g/m<sup>2</sup> per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy. There have been rare reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease. In the event of new or worsening cardiopulmonary symptoms, a prompt comprehensive diagnostic evaluation should be conducted. **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** There have been rare reports of RPLS in patients receiving VELCADE. RPLS is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing RPLS, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing RPLS is not known. **Gastrointestinal Adverse Events:** VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetic and antidiarrheal medications. Fluid and electrolyte replacement should be administered to prevent dehydration. **Thrombocytopenia/Neutropenia:** VELCADE is associated with thrombocytopenia and neutropenia. Platelets and neutrophils were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent over the 8 cycles of twice weekly dosing, and there was no evidence of cumulative thrombocytopenia or neutropenia. The mean platelet count nadir measured was approximately 40% of baseline. A baseline platelet count of 50,000/μL was required for study eligibility. The severity of thrombocytopenia was related to pretreatment platelet count. In the phase 3 multiple myeloma study, the incidence of significant bleeding events (≥Grade 3) was similar on both the VELCADE (4%) and dexamethasone (5%) arms. Platelet counts should be monitored prior to each dose of VELCADE. VELCADE therapy should be held when the platelet count is <25,000/μL and reinitiated at a reduced dose. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may be considered. The incidence of febrile neutropenia was <1%. **Tumor Lysis Syndrome:** Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells, the complications of tumor lysis syndrome may occur. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken. **Hepatic Events:** Rare cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic events include increases in liver enzymes, hyperbilirubinemia, and hepatitis. Such changes may be reversible upon discontinuation of VELCADE. There is limited re-challenge information in these patients. **Patients with Hepatic Impairment:** Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in patients with hepatic impairment. These patients should be closely monitored for toxicities when treated with VELCADE. **Drug/Laboratory Test Interactions:** None known.

### DRUG INTERACTIONS:

No formal drug interaction studies have been conducted with VELCADE. Patients who are concomitantly receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy. Bortezomib is a poor inhibitor of human liver cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC<sub>50</sub> values of >30 μM (>11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC<sub>50</sub> = 18 μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

### USE IN SPECIAL POPULATIONS:

**Nursing Mothers:** It is not known whether bortezomib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VELCADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and effectiveness of VELCADE in children has not been established. **Geriatric Use:** Of the 669 patients enrolled in the phase 3 multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on dexamethasone arm. Median time to progression and median duration of response for patients ≥65 were longer on VELCADE compared to dexamethasone [5.5 mo versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥65 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients ≤50, 51-64 and ≥65 years old, respectively. No overall differences in safety or effectiveness were observed between patients ≥65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out. **Patients with Renal Impairment:** The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, the drug should be administered after the dialysis procedure. **Patients with Hepatic Impairment:** No pharmacokinetic studies were conducted with bortezomib in patients with hepatic impairment. **Patients with Diabetes:** During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication.

### NONCLINICAL TOXICOLOGY:

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies have not been conducted with bortezomib. Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the in vitro chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the in vitro mutagenicity assay (Ames test) and in vivo micronucleus assay in mice. Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat toxicity study, degenerative effects in the ovary were observed at doses ≥0.3 mg/m<sup>2</sup> (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m<sup>2</sup>. VELCADE could have a potential effect on either male or female fertility. **Animal Toxicology: Cardiovascular Toxicity:** Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours post dose. Doses ≥1.2 mg/m<sup>2</sup> induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed. **Chronic Administration:** In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for 2 weeks followed by 1-week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

### PATIENT COUNSELING INFORMATION:

Physicians are advised to discuss the patient information section with patients prior to treatment with VELCADE. **Ability to Drive or Operate Machinery or Impairment of Mental Ability:** VELCADE may cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Patients should be advised not to drive or operate machinery if they experience these symptoms. **Dehydration/Hypotension:** Since patients receiving VELCADE therapy may experience vomiting and/or diarrhea, patients should be advised regarding appropriate measures to avoid dehydration. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells.

### INTEGRATED SAFETY DATA:

Safety data from phase 2 and 3 studies of single-agent VELCADE 1.3 mg/m<sup>2</sup>/dose twice weekly for 2 weeks followed by a 10-day rest period in 1163 patients with previously treated multiple myeloma (N=1008) and previously treated mantle cell lymphoma (N=155) were integrated and tabulated. In these studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma. In the integrated analysis, the most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation (41%), peripheral neuropathy NEC (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia) (each 36%), pyrexia (34%), vomiting (33%), and anemia (29%). Twenty percent (20%) of patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (5%) and neutropenia (3%). A total of 50% of patients experienced serious adverse events (SAEs) during the studies. The most commonly reported SAEs included pneumonia (7%), pyrexia (6%), diarrhea (5%), vomiting (4%), and nausea, dehydration, dyspnea and thrombocytopenia (each 3%). Adverse events thought by the investigator to be drug-related and leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (8%), asthenic conditions (3%) and thrombocytopenia and diarrhea (each 2%). In total, 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug: including reports of cardiac arrest, congestive heart failure, respiratory failure, renal failure, pneumonia and sepsis. This integrated analysis does not include the phase 3, VELCADE plus DOXIL study.



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