

U.S. Food and Drug Administration Approval: Carfilzomib for the Treatment of Multiple Myeloma

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Abstract

The U.S. Food and Drug Administration (FDA) review leading to accelerated approval of carfilzomib is described. A single-arm trial enrolled 266 patients with multiple myeloma refractory to the most recent therapy who had received prior treatment with bortezomib and an immunomodulatory agent (IMiD). Patients received carfilzomib by intravenous infusion over 2 to 10 minutes at a dose of 20 mg/m² on days 1, 2, 8, 9, 15, and 16 of the 28 days of cycle 1, and at a dose of 27 mg/m² on the same schedule in cycle 2 and subsequent cycles. The primary efficacy endpoint was overall response rate (ORR) as determined by an independent review committee using International Myeloma Working Group Uniform Response Criteria. The safety of carfilzomib was evaluated in 526 patients with multiple myeloma treated with various dosing regimens. The ORR was 23%. The median duration of response was 7.8 months. The most common adverse reactions associated with carfilzomib infusion were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and fever. The most common serious adverse events were pneumonia, acute renal failure, fever, and congestive heart failure. Infusion reactions to carfilzomib could be reduced by pretreatment with dexamethasone and intravenous fluids. On July 20, 2012, the FDA granted accelerated approval of carfilzomib for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an IMiD and who have shown disease progression while on therapy or within 60 days of completion of the last therapy. *Clin Cancer Res*; 19(17); 4559–63. ©2013 AACR.

Introduction

Multiple myeloma is characterized by the accumulation of malignant clones of plasma cells in the bone marrow and of monoclonal proteins in the blood and/or urine, osteolysis resulting in bone pain and pathologic fractures, hypercalcemia, frequent infections, anemia, and renal failure. There were 21,700 estimated new cases of multiple myeloma in 2012 with 10,710 estimated deaths (1). Multiple myeloma is a disease of older individuals with the median age at diagnosis being 66 years (2). Multiple myeloma is, in general, an incurable disease with the median overall survival of patients with multiple myeloma estimated at 5 to 7 years (3).

Current treatment focuses on therapies that decrease the clonal plasma cell population and result in an improvement in the signs and symptoms of the disease. Treatment choices are based on age and presence of comorbidities. High-dose chemotherapy with autologous hematopoietic stem cell transplantation has become a standard treatment for patients under the age of 65 years. For patients over age 65 and for those with significant pretreatment comorbidities, initial treatment might include an alkylating agent such as melphalan and prednisone with or without a proteasome inhibitor or an immunomodulatory agent (IMiD) such as thalidomide or lenalidomide (4). When patients relapse, they may be retreated either with the same combination therapy, if previously successful, or with combination regimens including agents not previously administered.

The first proteasome inhibitor, bortezomib, was approved in 2003 and rapidly became a mainstay in the treatment of relapsed or refractory and, subsequently, of previously untreated multiple myeloma. Bortezomib inhibits the ubiquitin-proteasome pathway, the major proteolytic mechanism in eukaryotic cells (5, 6). The major protease activity in this pathway is the 26S proteasome, an ATP-dependent proteolytic complex, which is formed by the 20S catalytic core particle, also known as the 20S proteasome, complexed with two 19S regulatory subunits (7, 8). The 20S proteasome

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is responsible for the degradation of key proteins involved in apoptosis, DNA repair, endocytosis, and cell-cycle control, as well as of proteins with abnormal conformation (8–10). Bortezomib inhibits this pathway by binding to the active site of the 20S proteasome. The binding is reversible.

Carfilzomib binds to the $\beta 5$ subunit of the 20S constitutively expressed proteasome and the alternately assembled immunoproteasome expressed in hematopoietic cells (11). This binding is by an irreversible covalent bond, resulting in inhibition of the chymotrypsin-like activity, subsequent accumulation of protein substrates within the cell, and induction of apoptosis. At higher concentrations, carfilzomib also inhibits trypsin-like and peptidyl-glutamyl peptide-hydrolyzing (PGPH)-like activities via inhibition of all three catalytic subunits, $\beta 1$, $\beta 2$, and $\beta 5$.

In July 2012, the U.S. Food and Drug Administration (FDA) approved carfilzomib under the accelerated approval pathway for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an IMiD and who have shown disease progression on or within 60 days of completion of the last therapy. In this report, we describe the review process leading to the FDA approval of carfilzomib.

Chemistry

Carfilzomib is a proteasome inhibitor consisting of an epoxyketone pharmacophore attached to a tetrapeptide backbone (Fig. 1). The chemical name of carfilzomib is (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$, and the molecular weight is 719.91. The commercial name for this product is Kyprolis (Onyx Pharmaceuticals) for injection. It is supplied in single-use vials containing 60 mg of carfilzomib as lyophilized powder.

Nonclinical Pharmacology and Toxicology

In rats, carfilzomib was quickly metabolized via peptidase cleavage and epoxide hydrolysis, resulting in a short half-life of less than 20 minutes. Approximately 31% of the

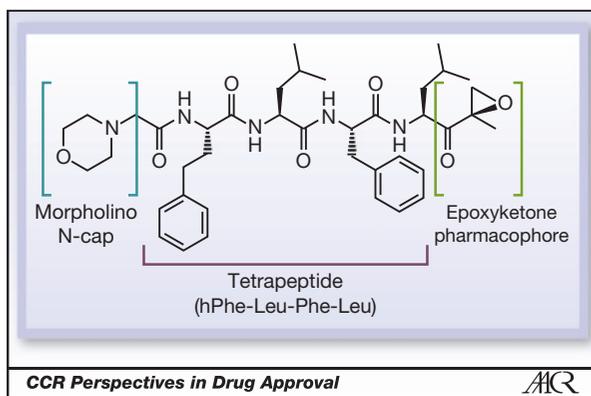


Figure 1. Structure of carfilzomib [excerpt from the Kyprolis U.S. Package Insert (07/2012)]. With permission from Onyx Pharmaceuticals.

administered drug undergoes hepatic degradation, whereas approximately 26% is excreted by the kidneys.

Adverse effects in rats and/or monkeys included cardiovascular (decreased blood pressure, increased heart rate, increased troponin-I, cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), pulmonary (hemorrhage/inflammation), hepatic (changes in serum transaminases), and hematopoietic toxicities. Some toxicities observed following administration of carfilzomib may be related to the C_{max} , as they were reduced when carfilzomib was administered as a 10- or 30-minute infusion rather than as a bolus injection.

Carfilzomib caused embryofetal toxicity in rats and rabbits but was not teratogenic. Pregnancy Category D was assigned to Kyprolis, as the potential benefit in pregnant women in the indicated patient population may outweigh the potential risk to the developing fetus.

Clinical Pharmacology

In vitro studies showed carfilzomib is metabolized in plasma via protein peptidase and epoxide hydrolysis. In addition, various P450 enzyme inhibitors did not influence the *in vitro* biotransformation rate of carfilzomib. An *in vitro* study showed carfilzomib to be a moderate CYP3A4 inhibitor. However, a pharmacokinetic study in patients with cancer showed that the C_{max} and AUC of the CYP3A4 substrate midazolam were similar in the absence and presence of carfilzomib, indicating that carfilzomib as tested does not alter the pharmacokinetics of CYP3A4 substrates.

In a renal impairment study, the pharmacokinetics and safety of carfilzomib were evaluated in patients with normal renal function and those with mild, moderate, and severe renal impairment as well as in patients on chronic dialysis, treated with carfilzomib doses of 15 mg/m² during cycle 1, 20 mg/m² during cycle 2, and 27 mg/m² for cycles 3 and beyond. Pharmacokinetics data were available for the 15- and 20-mg/m² dose levels. The C_{max} and AUC of carfilzomib were similar across all renal function categories following carfilzomib doses of 15 and 20 mg/m². The overall safety profile of carfilzomib was similar in patients in all renal function categories during mean treatment duration of 5.5 months. However, a recent publication of the renal impairment data described here points out that 6 patients with baseline renal impairment had further renal function deterioration during the study period (12).

Clinical Trials

The primary efficacy trial submitted for FDA review was a single-arm, multicenter trial of carfilzomib in patients with relapsed and refractory multiple myeloma who had previously received bortezomib and at least one of the two currently available IMiDs. Carfilzomib was administered by intravenous infusion over a period of 2 to 10 minutes at 20 mg/m² on days 1, 2, 8, 9, 15, and 16 of the 28 days of cycle 1, and at 27 mg/m² on the same schedule in cycle 2 and subsequent cycles.

Table 1. Baseline demographic and disease characteristics of the patients enrolled in the primary trial

Feature	Patients (N = 266)
Median age, years (range)	63 (37–87)
Age group, <65/≥65	146 (55%)/120 (45%)
Gender (female/male)	111 (42%)/155 (58%)
Race (white/black/Asian/other)	190 (71%)/53 (20%)/ 6 (2%)/17 (6%)
Number of prior regimens, median (range)	5 (1–20)
Prior transplant	198 (74%)
Refractory to most recent therapy ^a	252 (95%)
Years since diagnosis, median (range)	5 (1–22)

^a"Refractory" is defined as progression during or within 60 days of completion of most recent therapy or ≤25% response to treatment.

The phase II dosing schedule was based on the nonclinical and phase I clinical studies. Carfilzomib was better tolerated when given twice weekly for 3 out of 4 weeks, instead of over 5 consecutive days each week. Carfilzomib was also better tolerated when administered at a lower dose (20 mg/m²) in cycle 1 before higher doses in subsequent cycles. The maximum tolerated dose in patients with multiple myeloma was 36 mg/m². Pretreatment steroids reduced the severity of infusion reactions associated with carfilzomib administration.

The primary endpoint of the primary efficacy trial was overall response rate (ORR), consisting of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) to carfilzomib treatment as defined by the International Myeloma Working Group Uniform Response Criteria (13) and as determined by an Independent Review Committee (IRC).

The demographic and baseline characteristics of the 266 patients entered onto the primary efficacy trial are summarized in Table 1. The median age was 63 years (range, 37–87 years). Forty-two percent of patients were female, 71% were white, and 20% were black. The patients had been heavily pretreated, with the median number of prior regimens being 5 (range, 1–20). Seventy-four percent of patients had undergone at least one autologous stem cell transplant following myeloablative therapy, and 95% of patients were considered refractory to their most recent therapy. "Refractory" was defined in the study protocol as having progressed during the most recent therapy or within 60 days after the most recent therapy, or having achieved less than a PR (excludes patients with minimal response or stable disease; ref. 13).

The ORR to carfilzomib, calculated on the basis of all patients entered in the trial (N = 266) and not on an evaluable population, was 23%, including 1 (0.4%) CR,

13 (5%) VGPRs, and 47 (18%) PRs. The median duration of response was 7.8 months [95% confidence interval (CI), 5.6–9.2].

Safety data were evaluated in 526 patients with relapsed and/or refractory multiple myeloma who received carfilzomib as monotherapy in phase II studies. Patients received a median of 4 treatment cycles. Fifty-three percent of these patients received 20 mg/m² for cycle 1 and 27 mg/m² for cycle 2 and beyond, 38% received only 20 mg/m², and 9% received a dose escalation program consisting of 15, followed by 20 and 27 mg/m².

Adverse reaction intensity was determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3 (14). The most common adverse reactions (incidence of 10% or more) are shown in Table 2. Adverse reactions in several organ systems, while not frequent, raise concerns. Cardiac failure events were reported in 7% of patients, and most were of grade 3 to 4 severity. There were several deaths due to cardiac events that occurred within hours or a few days after administration of carfilzomib. Pulmonary arterial hypertension was reported in 2% of patients. Dyspnea (not further characterized) was reported in 35% of patients, with grade 3 in 5%, and 1 death. Anemia and thrombocytopenia were common, occurring in 47% and 36% of patients, respectively. Typically, the platelet count nadir occurred around day 8 of each 28-day cycle with recovery to baseline by the time of the next cycle. Liver function abnormalities were relatively uncommon; however, 2 patients died of liver failure after entering the trial with normal liver function tests. Increases in blood creatinine were mainly grade 1, but in 3% of patients they were grade 3 or 4 and there was 1 death due to renal failure. Peripheral neuropathy occurred in 14% of patients; the severity was mainly grade 1, although it was grade 3 in 1% of patients. Tumor lysis syndrome was reported in 1 patient (<1%) following the institution of prophylactic measures.

To reduce the intensity of infusion-related reactions to carfilzomib, dexamethasone (4 mg orally or intravenously) was administered before each carfilzomib administration in cycle 1 and on the first cycle when the dose was escalated (cycle 2 or subsequent cycle) and, thereafter, at the discretion of the investigator. This pretreatment did not entirely prevent infusion reactions, which were observed in the first cycle as well as in subsequent cycles.

Discussion

The first proteasome inhibitor approved for treatment of patients with multiple myeloma, bortezomib (Velcade; Millennium/Takeda), a modified dipeptidyl boronic acid, has become one of the most effective therapeutic agents (4). The second approved proteasome inhibitor, carfilzomib, a modified tetrapeptidyl epoxide, differs from bortezomib in structure, activity, and irreversibility of its binding to one of the active sites, the β5 subunit of the 20S proteasome. Preclinical studies had shown that carfilzomib was active against bortezomib-resistant multiple myeloma cell lines

Table 2. Incidence of adverse reactions occurring in $\geq 10\%$ of patients with multiple myeloma treated with carfilzomib

Events	Patients [N = 526 (%)]		
	All grades ^a	Grade 3	Grade 4
Fatigue	292 (56)	38 (7)	2 (<1)
Anemia	246 (47)	111 (21)	7 (1)
Nausea	236 (45)	7 (1)	0 (0)
Thrombocytopenia	191 (36)	69 (13)	54 (10)
Dyspnea	182 (35)	25 (5)	1 (<1)
Diarrhea	172 (33)	4 (<1)	1 (<1)
Pyrexia	160 (30)	7 (1)	2 (<1)
Upper respiratory tract infection	149 (28)	17 (3)	0 (0)
Headache	145 (28)	7 (1)	0 (0)
Cough	137 (26)	1 (<1)	0 (0)
Blood creatinine increased	127 (24)	13 (3)	1 (<1)
Lymphopenia	126 (24)	84 (16)	11 (2)
Edema peripheral	126 (24)	3 (<1)	0 (0)
Vomiting	117 (22)	5 (1)	0 (0)
Constipation	110 (21)	1 (<1)	0 (0)
Neutropenia	109 (21)	50 (10)	4 (<1)
Back pain	106 (20)	15 (3)	0 (0)
Insomnia	94 (18)	0 (0)	0 (0)
Chills	84 (16)	1 (<1)	0 (0)
Arthralgia	83 (16)	7 (1)	0 (0)
Muscle spasms	76 (14)	2 (<1)	0 (0)
Hypertension	75 (14)	15 (3)	2 (<1)
Asthenia	73 (14)	12 (2)	1 (<1)
Hypokalemia	72 (14)	14 (3)	3 (<1)
Hypomagnesemia	71 (14)	2 (<1)	0 (0)
Leukopenia	71 (14)	27 (5)	1 (<1)
Pain in extremity	70 (13)	7 (1)	0 (0)
Pneumonia	67 (13)	52 (10)	3 (<1)
AST increased	66 (13)	15 (3)	1 (<1)
Dizziness	66 (13)	5 (1)	1 (<1)
Hypoesthesia	64 (12)	3 (<1)	0 (0)
Anorexia	63 (12)	1 (<1)	0 (0)
Pain	63 (12)	12 (2)	1 (<1)
Hyperglycemia	62 (12)	16 (3)	3 (<1)
Chest wall pain	60 (11)	3 (<1)	0 (0)
Hypercalcemia	58 (11)	13 (3)	8 (2)
Hypophosphatemia	55 (11)	24 (5)	3 (<1)
Hyponatremia	54 (10)	31 (6)	3 (<1)

Abbreviation: AST, aspartate aminotransferase.

^aThe intensity of adverse reactions was determined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.

(11), and the pivotal trial described above showed its activity in patients with bortezomib-resistant multiple myeloma. Thus, approval of carfilzomib may prove to be another milestone in the treatment of this disease.

Bortezomib was initially approved under the accelerated approval pathway (15). The approval was based on the results of a single-arm trial of 202 patients with relapsed multiple myeloma who had received a median of 6 prior therapies. The ORR was 28%, and the median duration of response was 12 months. Subsequent randomized trials in previously treated patients (bortezomib vs. high-dose dexamethasone; refs. 16, 17) and in previously untreated patients (melphalan and prednisone with or without added bortezomib; ref. 18) showed that the addition of bortezomib resulted in clinical benefit, as shown by significantly longer time to progression, progression-free survival, and overall survival. In consideration of these results, bortezomib received regular approval.

The sponsor of carfilzomib is pursuing a similar path of development. Carfilzomib received accelerated approval on the basis of the results of a single-arm trial in a highly pretreated population of patients. A large, randomized phase III trial was ongoing at the time of FDA approval, in which patients with relapsed or refractory multiple myeloma are treated with carfilzomib plus lenalidomide with low-dose dexamethasone or lenalidomide and low-dose dexamethasone, with progression-free survival as the primary endpoint. The results of this trial may verify clinical benefit and lead to regular approval.

The safety profile of carfilzomib at the time of approval is derived from clinical trials without comparator arms. There were cardiovascular, pulmonary, and hepatic adverse reactions that may have been due to carfilzomib toxicity or to comorbidities and prior treatments. The cardiac and pulmonary safety signals of carfilzomib will be studied prospectively in an ongoing trial comparing the effect of carfilzomib and dexamethasone with that of bortezomib and dexamethasone in patients with relapsed multiple myeloma. The trial will evaluate the effects of carfilzomib on cardiac and pulmonary functions and will allow for the comparison of other adverse events such as treatment-related neuropathy between carfilzomib and bortezomib. In addition, to clarify whether the renal toxicity signals observed during the review process were related to infusion rate, dose, or the pharmacologic target, an additional prospective pharmacokinetics and safety trial in patients with baseline renal impairment is ongoing.

The benefit-risk assessment for carfilzomib is favorable for the treatment of patients with multiple myeloma whose disease has relapsed after they received established and approved treatments such as bortezomib, lenalidomide, thalidomide, melphalan, and other alkylating agents. Cardiac adverse events, pulmonary adverse events, and hepatobiliary system events require further characterization. Because these safety signals were identified using data from a single-arm study, it is not possible to ascertain their relationship to carfilzomib, multiple myeloma, or the prior therapy of the heavily pretreated patients enrolled in these studies. The benefit of the ORR of 23% with a mean duration of response of 7.8 months observed in the primary efficacy study in a population of patients, 89% of whom were resistant to bortezomib, may outweigh the adverse

events that occurred at low frequency in a heavily pretreated population of patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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