AETNA BETTER HEALTH®
Clinical Policy Bulletin:
Carfilzomib (Kyprolis)

Number: 0845

Policy

Aetna considers carfilzomib injection (Kyprolis) medically necessary for the following indications:

- for previously treated multiple myeloma for disease relapse or for progressive or refractory disease
- or for transplant candidates with progressive solitary plasmacytoma or smoldering myeloma (asymptomatic) that has progressed to active (symptomatic) myeloma;
- or for individuals with Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma, either as primary therapy or for relapse.

Aetna considers carfilzomib injection experimental and investigational and therefore not medically necessary for the treatment of the following:

- Use not approved by the FDA; AND
- The use is unapproved and not supported by the literature or evidence as an accepted off-label use."

See also CPB 0675 - Bortezomib (Velcade).

Background

The proteasome, a multi-catalytic protease present in all eukaryotic cells, plays an important role in the regulation of cell cycle, neoplastic growth, and metastasis. Proteasome inhibitors (PIs) specifically induce apoptosis in cancer cells. Bortezomib as first-in-class PI has proven to be highly effective in some hematological
malignancies, overcomes conventional chemoresistance, directly induces cell cycle arrest and apoptosis, and also targets the tumor microenvironment. It has been approved by the Food and Drug administration (FDA) for relapsed multiple myeloma (MM), and recently for relapsed mantle cell lymphoma. Combination chemotherapy regimens have been developed providing high remission rates and remission quality in frontline treatment or in the relapsed setting in MM. The combination of proteasome inhibition with novel targeted therapies is an emerging field in oncology. Moreover, novel PIs such as carfilzomib (a selective PI that binds irreversibly to its target) have been developed (Sterz et al, 2008).

Vij et al (2012) stated that in phase 1 studies, carfilzomib elicited promising responses and an acceptable toxicity profile in patients with relapsed and/or refractory MM (R/R MM). In the present phase 2, multi-center, open-label study, 129 bortezomib-naive patients with R/R MM (median of 2 prior therapies) were separated into cohort 1, scheduled to receive intravenous carfilzomib 20 mg/m(2) for all treatment cycles, and cohort 2, scheduled to receive 20 mg/m(2) for cycle 1 and then 27 mg/m(2) for all subsequent cycles. The primary end point was an overall response rate [ORR] (greater than or equal to partial response) of 42.4 % in cohort 1 and 52.2 % in cohort 2. The clinical benefit response (ORR + minimal response) was 59.3 % and 64.2 % in cohorts 1 and 2, respectively. Median duration of response was 13.1 months and not reached, and median time to progression was 8.3 months and not reached, respectively. The most common treatment-emergent adverse events (AEs) were fatigue (62.0 %) and nausea (48.8 %). Single-agent carfilzomib elicited a low incidence of peripheral neuropathy (PN) --17.1 % overall (1 grade 3; no grade 4) -- in these pretreated bortezomib-naive patients. The authors concluded that the findings of the present study support the use of carfilzomib in R/R MM patients.

In an open-label, single-arm phase 2 study, Siegel et al (2012) examined the effects of carfilzomib in patients with relapsed and refractory MM. Participants received carfilzomib 20 mg/m(2) intravenously twice-weekly for 3 of 4 weeks in cycle 1, then 27 mg/m(2) for less than or equal to 12 cycles. The primary endpoint was ORR (greater than or equal to partial response). Secondary endpoints included clinical benefit response rate (greater than or equal to minimal response), duration of response, progression-free survival, overall survival, and safety. A total of 266 patients were evaluable for safety, 257 for efficacy; 95 % were refractory to their last therapy; 80 % were refractory or intolerant to both bortezomib and lenalidomide. Patients had median of 5 prior lines of therapy, including bortezomib, lenalidomide, and thalidomide. Overall response rate was 23.7 % with median duration of response of 7.8 months. Median overall survival was 15.6 months. Adverse events were manageable without cumulative toxicities. Common AEs were fatigue (49 %), anemia (46 %), nausea (45 %), and thrombocytopenia (39 %); 33 patients (12.4 %) experienced PN, primarily grades 1 or 2; and 33 patients (12.4 %) withdrew because of an AE. Durable responses and an acceptable tolerability profile in this heavily pretreated population demonstrated the potential of carfilzomib to offer meaningful clinical benefit.

Buac et al (2012) noted that bortezomib is the first FDA-approved PI used as a frontline treatment for newly diagnosed MM, relapsed/refractory MM and mantle cell lymphoma. Though successful in improving clinical outcomes for patients with hematological malignancies, relapse often occurs in those who initially responded to bortezomib. Thus, the acquisition of bortezomib resistance is a major issue with its therapy. Furthermore, some neuro-toxicities have been associated with bortezomib treatment and its efficacy in solid tumors is lacking. These observations have
encouraged researchers to pursue the next generation of PIs, which would ideally overcome bortezomib resistance, have reduced toxicities and a broader range of anti-cancer activity. The authors described recent advances in the field, including, and most notably, the most recent FDA approval of carfilzomib a second generation PI.

Thompson (2013) reviewed and summarized data on carfilzomib, which was approved by the FDA in July 2012 for the treatment of patients with relapsed and refractory MM who received prior bortezomib and thalidomide or lenalidomide. A literature search through PubMed was conducted through October 2012 using the terms carfilzomib, PR-171, proteasome inhibitor (PI), and MM. Data were also obtained through the American Society of Clinical Oncology and American Society of Hematology abstracts and FDA briefing documents. The literature search was limited to human studies published in English. Priority was placed on trials of carfilzomib in relapsed and refractory MM. Carfilzomib is a new PI that differs in pharmacology and pharmacokinetics from bortezomib, the first-in-class PI. The FDA approval was based on efficacy data from a phase 2 study of carfilzomib in patients with relapsed and refractory MM (n = 266). All patients had received prior bortezomib and 80% were refractory or intolerant to both bortezomib and lenalidomide.

On July 20, 2012, the Food and Drug Administration approved carfilzomib injection (Kyprolis, Onyx Pharmaceuticals), for the treatment of patients with multiple myeloma who have received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (e.g., thalidomide or lenalidomide), and have demonstrated disease progression on or within 60 days of the completion of the last therapy. The approval was based on the results of a single-arm, multi-center clinical trial enrolling 266 patients with relapsed MM who had received at least 2 prior therapies, including bortezomib and an immunomodulatory agent (thalidomide or lenalidomide). To reduce the incidence and severity of infusion reactions associated with carfilzomib administration, dexamethasone (4 mg orally or intravenously) was administered prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose-escalation (27 mg/m²) cycle. Dexamethasone pre-medication was re-instated if these symptoms re-appeared during subsequent cycles. The primary efficacy endpoint was ORR, determined by Independent Review Committee assessment using International Myeloma Working Group criteria. The ORR was 22.9% (95% CI: 18.0 to 28.5), consisting of 1 complete response, 13 very good partial responses and 47 partial responses. The median response duration was 7.8 months (95% CI: 5.6 to 9.2). Safety data was evaluated in 526 patients with relapsed MM who received carfilzomib as monotherapy. Patients received a median of 4 treatment cycles with a median cumulative carfilzomib dose of 993.4 mg. The most common AEs (incidence of 30% or greater) observed in clinical trials of patients with MM were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. Serious adverse reactions were reported in 45% of patients. The most common serious AEs were pneumonia, acute renal failure, pyrexia, and congestive heart failure. There were 37/526 (7%) deaths on study. The most common causes of death, other than underlying disease, were cardiac (5 patients), end-organ failure (4 patients), and infection (4 patients). As a condition of accelerated approval, Onyx will submit the complete analysis of an ongoing randomized phase 3 trial comparing lenalidomide plus low-dose dexamethasone to lenalidomide plus carfilzomib. The primary endpoint of this trial is progression-free survival, with enrollment of patients with relapsed or refractory MM after 1 to 3 prior therapies.

Carfilzomib should be administered intravenously over 2 to 10 mins, on 2 consecutive days weekly (for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12 day rest period.
(days 17 to 28). Recommended cycle one dose is 20 mg/m²/day, and, if tolerated, the recommended dose for the second and succeeding cycles is 27 mg/m²/day.

The National Comprehensive Cancer Network (NCCN, 2015) recommends the use of carfilzomib for the following indications in multiple myeloma:

- Used in combination with lenalidomide and dexamethasone for transplant candidates with progressive solitary plasmacytoma or smoldering myeloma (asymptomatic) that has progressed to active (symptomatic) myeloma as primary chemotherapy.
- therapy on or off clinical trials for disease relapse after 6 months following primary chemotherapy with the same regimen.
- Preferred therapy for previously treated myeloma on or off clinical trials for disease relapse or for progressive or refractory disease in combination with lenalidomide and dexamethasone as a single agent.

Wang, et al. (2013) previously reported a phase 1b dose-escalation study of carfilzomib, lenalidomide, and low-dose dexamethasone (CRd) in relapsed or progressive multiple myeloma where the maximum planned dose (MPD) was carfilzomib 20 mg/m² days 1 and 2 of cycle 1 and 27 mg/m² days 8, 9, 15, 16, and thereafter; lenalidomide 25 mg days 1 to 21; and dexamethasone 40 mg once weekly on 28-day cycles. Wang, et al. (2013) presented the results from the phase 2 dose expansion at the MPD, focusing on the 52 patients enrolled in the MPD cohort. Median follow-up was 24.4 months. In the MPD cohort, overall response rate (ORR) was 76.9% with median time to response of 0.95 month (range, 0.5-4.6) and duration of response (DOR) of 22.1 months. Median progression-free survival was 15.4 months. ORR was 69.2% in bortezomib-refractory patients and 69.6% in lenalidomide-refractory patients with median DOR of 22.1 and 10.8 months, respectively. A median of 9.5 (range, 1-45) carfilzomib cycles were started with 7.7% of patients requiring carfilzomib dose reductions and 19.2% discontinuing CRd due to adverse events (AEs). Grade 3/4 AEs included lymphopenia (48.1%), neutropenia (32.7%), thrombocytopenia (19.2%), and anemia (19.2%). The investigators reported that CRd at the MPD was well tolerated with robust, rapid, and durable responses.

The National Comprehensive Cancer Network (NCCN, 2015) recommends carfilzomib as a component of CaRD (carfilzomib, rituximab, and dexamethasone) regimen in Waldenstrom's macroglobulinemia/lymphoplasmacytic lymphoma as primary therapy, or for relapse ≥12 months if used as primary therapy.

Issa et al (2011) stated that based on the understanding of the complex interaction between Waldenstrom macroglobulinemia (WM) tumor cells and the bone marrow microenvironment, and the signaling pathways that are deregulated in WM pathogenesis, a number of novel therapeutic agents are now available and have demonstrated significant efficacy in WM. The range of the ORR for these novel agents is between 25 and 96 %. Ongoing and planned future clinical trials include those using protein kinase C inhibitors such as enzastaurin, new PIs such as carfilzomib, histone deacetylase inhibitors such as LBH589, humanized CD20 antibodies such as ofatumumab and additional alkylating agents such as bendamustine. These agents, when compared with traditional chemotherapeutic agents, may lead in the future to higher responses, longer remissions and better quality of life for patients with WM.
Treon, et al. (2014) found that carfilzomib, rituximab and dexamethasone (CaRD) offers a neuropathy sparing approach for proteasome inhibitor based therapy for Waldenström's macroglobulinemia. Bortezomib frequently produces severe treatment-related peripheral neuropathy (PN) in Waldenström's macroglobulinemia (WM). Carfilzomib is a neuropathy-sparing proteasome inhibitor. Treon, et al. (2014) examined carfilzomib, rituximab, and dexamethasone (CaRD) in symptomatic WM patients naïve to bortezomib and rituximab. Protocol therapy consisted of intravenous carfilzomib, 20 mg/m2 (cycle 1) and 36 mg/m(2) (cycles 2-6), with intravenous dexamethasone, 20 mg, on days 1, 2, 8, and 9, and rituximab, 375 mg/m(2), on days 2 and 9 every 21 days. Maintenance therapy followed 8 weeks later with intravenous carfilzomib, 36 mg/m(2), and intravenous dexamethasone, 20 mg, on days 1 and 2, and rituximab, 375 mg/m(2), on day 2 every 8 weeks for 8 cycles. Overall response rate was 87.1% (1 complete response, 10 very good partial responses, 10 partial responses, and 6 minimal responses) and was not impacted by MYD88(L265P) or CXCR4(WHIM) mutation status. With a median follow-up of 15.4 months, 20 patients remained progression free. Grade ≥2 toxicities included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), and cardiomyopathy in 1 patient (3.2%) with multiple risk factors, and PN in 1 patient (3.2%) which was grade 2. The investigators noted that declines in serum IgA and IgG were common.

In pre-clinical in-vitro and in-vivo models, carfilzomib is being investigation in the treatment of various diseases/malignancies including diffuse large B-cell lymphoma, head and neck cancer, mantle cell lymphoma, non-Hodgkin's lymphoma, and systemic lupus erythematosus.

Dasmahapatra et al (2011) noted that carfilzomib/vorinostat co-administration resulted in a pronounced reduction in tumor growth compared with single agent treatment in a mantle cell lymphoma xenograft model associated with enhanced apoptosis, λH2A.X formation, and JNK activation. The authors concluded that these findings suggested that regimens of carfilzomib/histone deacetylase inhibitors warrant attention in mantle cell lymphoma.

Dasmahapatra et al (2012) reported that in-vivo administration of carfilzomib and obatoclax to mice inoculated with SUDHL4 cells substantially suppressed tumor growth, activated JNK, inactivated AKT, and increased survival compared with the effects of single-agent treatment. Together, these findings argued that a strategy combining carfilzomib and obatoclax warrants attention in diffuse large B-cell lymphoma.

Mato et al (2012) stated that bortezomib is approved for the treatment of relapsed or refractory mantle cell lymphoma. The mechanisms of proteasome inhibition are very complex by nature and not fully understood. However, mechanisms of action shared by bortezomib and PIs such as carfilzomib are distinct from those of other non-Hodgkin's lymphoma (NHL) treatments, making them attractive options for combination therapy. Pre-clinical evidence suggested that the PIs have additive and/or synergistic activity with a large number of agents both in-vitro and in-vivo, from cytotoxics to new biologicals, supporting a growing number of combination studies currently underway in NHL patients. The authors concluded that the results of these studies will help the understanding about how to best integrate proteasome inhibition in the management of NHL and continue to improve patient outcomes.
In a lupus-prone mice model, Ichikawa et al (2012) investigated the hypothesis that proteasome inhibition may have potential in the treatment of systemic lupus erythematosus, by targeting plasmacytoid dendritic cells (PDCs) and plasma cells, both of which are critical in disease pathogenesis. The authors concluded that inhibition of the immunoproteasome is equally efficacious as dual targeting agents in preventing lupus disease progression by targeting 2 critical pathways in disease pathogenesis, type I IFN activation and autoantibody production by plasma cells.

Zang et al (2012) stated that ONX 0912 (oprozomib) is an orally bioavailable derivative of carfilzomib. The activities of carfilzomib and ONX 0912 against solid tumor malignancies are less well understood. These researchers investigated the impact and mechanisms of action of carfilzomib and ONX 0912 in pre-clinical models of head and neck squamous cell carcinoma (HNSCC). The authors concluded that carfilzomib and ONX 0912 are potently active against HNSCC cells, and the activities of these agents can be enhanced via suppression of Mcl-1 or inhibition of autophagy. They stated that oral ONX 0912 exhibits in-vivo activity against HNSCC tumors and may represent a useful therapeutic agent for this malignancy.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96365 - 96368 Intravenous infusion
96379 Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion
96409 Chemotherapy administration; intravenous, push technique, single or initial substance/drug

HCPCS codes covered if selection criteria are met:

J9047 Injection, carfilzomib, 1 mg

Other HCPCS codes related to the CPB:

J9041 Injection, bortezomib, 0.1 mg

ICD-9 codes covered if selection criteria are met:

200.80 - 200.88 Other named variants of lymphosarcoma and reticulosarcoma and other specified malignant tumors of lymphatic tissue [either as primary therapy or for relapse]

203.00-203.02 Multiple myeloma [including for transplant candidates with smoldering myeloma (asymptomatic) that has progressed to active (symptomatic) myeloma]

203.80 Other immunoproliferative neoplasms, without mention of having achieved remission [for transplant candidates with progressive solitary plasmacytoma]
203.82 Other immunoproliferative neoplasms, in relapse [for transplant candidates with progressive solitary plasmacytoma]

273.3 Macroglobulinemia [Waldenstrom's] [either as primary therapy or for relapse]

ICD-9 codes not covered for indications listed in the CPB (not all inclusive):

- 140.0 - 150.9, Malignant neoplasms of head, face and neck
- 195.0
- 200.40 - 200.48 Mantle cell lymphoma
- 202.80 - 202.88 Other lymphomas [Diffuse Large B cell] [Non-Hodgkins]
- 710.0 Systemic lupus erythematosus

The above policy is based on the following references:


