Clinical Policy Bulletin:
Eribulin Mesylate (Halaven)

Number: 0831

Policy

Aetna considers eribulin mesylate (Halaven) medically necessary for the following indications:

- Treatment of recurrent or human epidermal growth factor receptor (HER2) negative metastatic breast cancer that meets any of the following criteria: with symptomatic visceral disease or visceral crisis; or that is hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory; or

- Use as single agent palliative therapy for the following soft tissue sarcomas: angiosarcoma; or unresectable of progressive retroperitoneal/intraabdominal soft tissue sarcoma; or pleomorphic rhabdomyosarcoma; or synchronous stage IV or recurrent soft tissue sarcoma of the extremity/superficial trunk with disseminated metastases.

Aetna considers eribulin mesylate experimental and investigational for all other indications including the following because its effectiveness for these indications has not been established (not an all-inclusive list):

- Brain metastases (e.g., leptomeningeal carcinomatosis) from other solid tumors, and from breast cancer in persons who do not meet above listed criteria
- Fallopian tube cancer
- Head and neck cancer
- Non-small-cell lung cancer
- Ovarian cancer
- Pancreatic cancer
- Peritoneal cancer
- Prostate cancer
- Urothelial (bladder) cancer
Eribulin mesylate, a non-taxane microtubule dynamics inhibitor, is isolated from the sea sponge Halichondria okadai. Although the exact mechanism is unknown, it is believed that eribulin's anti-mitotic activity works via inhibition of the growth phase of microtubule dynamics, without affecting the shortening phase, thus sequestering tubulin into non-productive aggregates. Eribulin mesylate is used in the treatment of patients with locally advanced or metastatic breast cancer who have previously been treated with at least 2 chemotherapeutic regimens, including an anthracycline and a taxane. In in-vitro studies, eribulin displayed anti-proliferative activity against human breast cancer cell lines. Regression and elimination of breast tumors were observed in human tumor xenograft models. In the randomized, open-label, multi-national, phase III EMBRACE trial in patients with locally recurrent or metastatic breast cancer, median overall survival (OS) was significantly longer in patients who received intravenous (i.v.) eribulin \( (n = 508) \) \[13.1 \text{ months}\] compared with that in patients who received a treatment of physician's choice \( (n = 254) \) \[10.6 \text{ months}; \text{hazard ratio} \ 0.81; \ 95 \% \text{ confidence interval} \ [0.66, 0.99]; \ p = 0.041\]. Prior to enrolment, subjects had received between 2 and 5 chemotherapeutic regimens, including an anthracycline and a taxane. Consistent with the findings of earlier phase I and II clinical trials, eribulin was reported to have a manageable tolerability profile in the EMBRACE trial. Peripheral neuropathy (incidence 5 \%) was the most common adverse event resulting in the discontinuation of eribulin treatment. The most common grade 3/4 adverse events in the eribulin group were neutropenia, leukopenia and asthenia or fatigue (Perry, 2011).

In a single-arm, multi-center open-label, phase II trial, Aogi et al (2011) evaluated the effectiveness and tolerability of eribulin in Japanese patients with heavily pre-treated metastatic breast cancer (MBC). Patients pre-treated with an anthracycline and a taxane received 1.4 mg/m\( ^2 \) eribulin mesylate (2- to 5-min i.v. infusion on days 1 and 8 of a 21-day cycle). The primary efficacy end point was overall response rate (ORR) by independent review. Patients \( (n = 80) \) had received a median of 3 prior chemotherapeutic regimens (range of 1 to 5). ORR was 21.3 \% \ (95 \% \text{ CI}: 12.9 to 31.8; all partial responses (PRs)), stable disease (SD) occurred in 30 patients (37.5 \%) and the clinical benefit rate (complete response + PR + SD greater than or equal to 6 months) was 27.5 \% \ (95 \% \text{ CI}: 18.1 to 38.6). Median duration of response was 3.9 months (95 \% \text{ CI}: 2.8 to 4.9), progression-free survival (PFS) was 3.7 months \ (95 \% \text{ CI}: 2.0 to 4.4) and OS was 11.1 months \ (95 \% \text{ CI}: 7.9 to 15.8). The most frequent treatment-related grade 3/4 adverse events were neutropenia (95.1 \%), leukopenia (74.1 \%) and febrile neutropenia (13.6 \%). Grade 3 peripheral neuropathy occurred in 3.7 \% of patients (no grade 4). The authors concluded that eribulin exhibited effectiveness and tolerability in Japanese patients with heavily pre-treated MBC.

In a phase III open-label, randomized trial, Cortes et al (2011) compared OS of heavily pre-treated patients receiving eribulin versus currently available treatments. Women with locally recurrent or MBC were randomly allocated (2:1) to eribulin mesylate \ (1.4 mg/m\( ^2 \)) administered intravenously during 2 to 5 mins on days 1 and 8 of a 21-day cycle) or treatment of physician's choice (TPC). Patients had received between 2 and 5 previous chemotherapeutic regimens (2 or more for advanced disease), including an anthracycline and a taxane, unless contraindicated. Randomization was stratified by geographical region, previous capecitabine treatment, and human epidermal growth factor receptor 2 status. Patients and investigators were not masked to treatment allocation. The primary endpoint was OS in the intention-to-treat population. A total of 762 women were randomly allocated to treatment groups \ (eribulin, \ n = 508; \ TPC, \ n = 254)\). Overall survival
was significantly improved in women assigned to eribulin (median 13.1 months, 95 % CI: 11.8 to 14.3) compared with TPC (10.6 months, 9.3 to 12.5; hazard ratio 0.81, 95 % CI: 0.66 to 0.99; p = 0.041). The most common adverse events in both groups were asthenia or fatigue (270 [54 %] of 503 patients on eribulin and 98 [40 %] of 247 patients on TPC at all grades) and neutropenia (260 [52 %] patients receiving eribulin and 73 [30 %] of those on TPC at all grades). Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin, occurring in 24 (5 %) of 503 patients. The authors concluded that eribulin showed a significant and clinically meaningful improvement in OS compared with TPC in women with heavily pre-treated MBC.

On November 15, 2010, the Food and Drug Administration (FDA) approved eribulin mesylate (Halaven) for the treatment of patients with MBC who have received at least 2 prior chemotherapeutic regimens for late-stage disease. Before receiving Halaven, patients should have received prior anthracycline- and taxane-based chemotherapy for early- or late-stage breast cancer. The most common side effects reported by women treated with Halaven include alopecia (hair loss), anemia, asthenia (weakness), constipation, fatigue, leukopenia (a decrease in the number of white blood cells), nausea, neutropenia (a decrease in infection-fighting white blood cells), and peripheral neuropathy (nerve damage). The recommended dose of Halaven is 1.4 mg/m2 administered intravenously over 2 to 5 mins on days 1 and 8 of a 21-day cycle.

The National Comprehensive Cancer Network's Drugs and Biologic Compendium (2015) lists eribulin as a preferred single agent for recurrent or metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer:

- with symptomatic visceral disease or visceral crisis; or
- that is hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory.

In a non-randomized multi-center phase II clinical study, Schoffski et al (2011) evaluated the activity and safety of eribulin in 4 strata of patients with different types of soft-tissue sarcoma. Patients were included if they had progressive or high-grade soft-tissue sarcoma and had received no more than 1 previous combination chemotherapy or up to 2 single drugs for advanced disease. They were stratified by the type of soft-tissue sarcoma they had. Eribulin was given intravenously at a concentration of 1.4 mg/m(2) over 2 to 5 mins at days 1 and 8 every 3 weeks to primarily assess PFS at 12 weeks (RECIST 1.0), which these researchers evaluated in all patients who started treatment. Safety analyses were done in all patients who started treatment. Of 128 patients included, 37 had adipocytic sarcoma, 40 had leiomyosarcoma, 19 had synovial sarcoma, and 32 had other sarcomas; 12 (31.6 %) of 38 patients with leiomyosarcoma evaluable for the primary endpoint, 15 (46.9 %) of 32 patients with adipocytic sarcoma, 4 (21.1 %) of 19 with synovial sarcoma, and 5 (19.2 %) of 26 in other sarcomas were progression-free at 12 weeks. The most common grade 3 to 4 adverse events were neutropenia (66 [52 %] of 127 patients evaluable for safety), leucopenia (44 [35 %]), anemia (9 [7 %]), fatigue (9 [7 %]), febrile neutropenia (8 [6 %]), abnormal alanine aminotransferase concentrations (6 [5 %]), mucositis (4 [3 %]), and sensory neuropathy (4 [3 %]). The authors concluded that eribulin deserves further study in this setting, based on PFS at 12 weeks in leiomyosarcoma and adipocytic sarcoma.

Matsuoka et al (2013) described the case of a 57-year old Japanese woman who was diagnosed with stage IV breast cancer that metastasized to multiple organs including liver and lung. After receiving 3 regimens, the patient showed evidence of brain metastases, and whole brain radiation therapy was performed. Lapatinib and capecitabine was then administered as 4th-line chemotherapy, but the patient was hospitalized due to the exacerbation of interstitial pneumonitis and progression of brain and liver metastases. To
control the systemic disease, eribulin was commenced as 5th-line chemotherapy. One month later, a significant response of brain metastases had been achieved, and this response persisted for the last 4 months. These researchers noted anti-tumor effect of eribulin against brain metastases from breast cancer. They stated that this case was the first report that indicated potential treatment of brain metastases using this medication. The authors concluded that the findings of this report suggested that eribulin treatment may be beneficial for breast cancer patients with brain metastases progressing after whole brain radiation therapy. However, they stated that further clinical studies are needed to determine the clinical effect of eribulin in brain metastases.

Salgia et al (2014) presented a patient with leptomeningeal carcinomatosis from breast cancer treated with intrathecal topotecan and intravenous eribulin. The regimen was well-tolerated and provided clinical stability in a patient with progression on a prior intrathecal chemotherapy regimen. The findings of this case study need to be validated by well-designed studies.

Eribulin mesylate is also being investigated in the treatment of other solid tumors including head and neck cancer, non-small-cell lung cancer, ovarian cancer, pancreatic cancer, and prostate cancer. Its use for these malignancies is undergoing various phases of clinical trial.

In a 2-cohort phase II clinical study, Hensley et al (2012) assessed the effectiveness of eribulin in platinum-resistant and platinum-sensitive recurrent ovarian cancer. Patients with recurrent, measurable epithelial ovarian cancer who had received less than or equal to 2 prior cytotoxic regimens and who had adequate organ function were enrolled into 2 separate cohorts: (i) platinum-resistant patients (who had a progression-free interval less than 6 months after their last platinum-based therapy), and (ii) platinum-sensitive patients (who had a progression-free interval greater than or equal to 6 months after their last platinum-based therapy). Eribulin 1.4 mg/m^2 was administered over 15 mins intravenously on days 1 and 8 every 21 days. Effectiveness was determined by objective response on computed tomography studies. In the platinum-resistant cohort, 37 patients enrolled, and 36 patients were evaluable for response and toxicity. Two patients achieved a PR (5.5 %), and 16 patients (44 %) had SD as their best response. The median PFS was 1.8 months (95 % CI: 1.4 to 2.8 months). In the platinum-sensitive cohort, 37 patients enrolled, and all were evaluable for response. Seven patients achieved a PR (19 %). The median PFS was 4.1 months (95 % CI, 2.8 to 5.8 months). The major toxicity was grade 3 or 4 neutropenia (42 % of platinum-resistant patients; 54 % of platinum-sensitive patients). The authors concluded that eribulin produced an objective response in 5.5 % of women with platinum-resistant, recurrent ovarian cancer and in 19 % of women with platinum-sensitive disease. The median PFS was 1.8 months in the platinum-resistant group and 4.1 months in the platinum-sensitive group.

In an open-label, single-arm phase II trial, de Bono et al (2012) evaluated eribulin mesylate in patients with metastatic castration-resistant prostate cancer (CRPC) with or without previous taxane exposure. Men with histologically proven CRPC, with or without prior taxane exposure, were enrolled in this study. Patients received eribulin mesylate 1.4 mg/m^2 as a 2- to 5-min i.v. bolus infusion on days 1 and 8 of a 21-day cycle. The primary efficacy end point was prostate-specific antigen (PSA) response rate. A total of 108 patients were assessable for safety (50 were taxane-pretreated) and 105 for efficacy in the per-protocol population. The median age of patients was 71 years and median number of cycles was 4. PSA decreases of greater than or equal to 50 % were achieved in 22.4 % and 8.5 % of taxane-naive and taxane-pretreated patients, respectively. The most common grade 3/4 adverse event was neutropenia, seen in 22.4 % of chemo-naive and 40 % of taxane-pretreated men. Grade 3 peripheral neuropathy occurred in none of the taxane-naive patients and 6.0 % of taxane-pretreated patients. The authors
concluded that eribulin mesylate demonstrated activity and a relatively favorable toxicity profile in metastatic CRPC.

Scarpace (2012) reviewed eribulin's medication profile, including pharmacology, pharmacokinetic properties, efficacy, and tolerability. PubMed, the Cochrane Central Register of Controlled Trials, and Clinical Trials.gov were searched from the beginning of each database through January 3, 2012, for relevant articles on human studies published in English. Search terms included eribulin, eribulin mesylate, and Halaven. Clinical trials, case reports, comparative studies, meta-analyses, evaluation studies, controlled clinical trials, and randomized controlled trials were included as search limits. The references from selected articles were also reviewed to identify additional publications. Eisai, the manufacturer of eribulin mesylate, was also contacted for information regarding trials listed in Clinicaltrials.gov but not yet published. One phase III trial was identified that evaluated eribulin for use in patients with MBC. Four phase II trials were identified that studied eribulin in patients with head and neck, pancreatic, and non-small-cell lung cancers. The median OS among previously treated MBC patients treated with eribulin was 13.1 months compared with 10.6 months (p = 0.041) with other active chemotherapy for this setting. In non-small-cell lung cancer, median OS in eribulin-treated patients has been reported as 9.4 months in an unselected population and varies according to taxane sensitivity: 12.6 months in taxane-sensitive disease versus 8.9 months in taxane-resistant disease. Patients with head and neck or pancreatic cancers did not experience improvements in response rates or survival outcomes when treated with eribulin in clinical trials. The authors noted that eribulin is approved by the FDA for patients with previously treated MBC and has demonstrated a survival benefit compared with standard treatment options in this setting. Non-small-cell lung cancer patients had improved response rates when treated with eribulin in open-label, non-randomized, phase II trials reported in abstract form. Eribulin was not effective in the treatment of head and neck, or pancreatic cancer in phase II trials.

Preston and Trivedi (2012) reviewed the chemistry, pharmacology, pharmacokinetics, safety, and efficacy of eribulin (Halaven). A literature search (up to December 2011) using the terms eribulin, Halaven, ER-086526, and E7389 was performed with PubMed, Google Scholar, selected Ovid bibliography searches, and the abstract search tool from the American Society of Clinical Oncology Annual Meetings and the San Antonio Breast Cancer Symposia. Additional references from the bibliographies of these articles were also assessed. English-language pre-clinical and clinical studies on the chemistry, pharmacology, pharmacokinetics, safety, and efficacy of eribulin were reviewed. Eribulin is a novel microtubule inhibitor with a unique mechanism of action, which involves interaction with a distinct binding site on β-tubulin leading to G(2)/M phase cell-cycle arrest and apoptosis. Eribulin has been approved by the FDA for the treatment of metastatic breast cancer in patients who have been previously treated with an anthracycline and a taxane. In a pivotal phase III study conducted in patients with metastatic breast cancer, eribulin 1.4 mg/m(2), administered over 2 to 5 mins as an intravenous infusion on days 1 and 8 of 21-day cycles, was associated with a significantly increased median OS of 13.1 months compared to the median OS of 10.6 months in the therapy of physician's choice. Eribulin has also shown activity in phase II studies in other types of cancers (e.g., non-small cell lung cancer, prostate cancer, soft tissue sarcomas, urothelial cancer, as well as platinum-susceptible ovarian, fallopian tube, or peritoneal cancers). The most severe (grade 3/4) adverse effects associated with eribulin include neutropenia, leukopenia, and peripheral neuropathy. Common toxicities include fatigue, neutropenia, alopecia, anemia, and peripheral neuropathy. The authors concluded that eribulin is a promising new cytotoxic chemotherapy agent due to its ability to treat cancers that are refractory or resistant to other drugs as well as its manageable toxicity profile.
Shetty and Gupta (2014) stated that eribulin is an anti-cancer drug approved for treatment of metastatic breast cancer. This drug is a synthetic derivative from Japanese marine sponge Halichondria okadai. It acts by interfering with the microtubular growth ultimately leading to apoptosis after prolonged mitotic blockage. In patients with metastatic breast cancer refractory to anthracyclines and taxanes, eribulin is one of the life-saving options. Neutropenia, neuropathy and QT prolongation are the most frequent adverse events associated with this drug. The authors also noted that phase I/II trials are also underway in refractory lung, ovarian, pancreatic, bladder, and soft tissue tumors; and larger prospective studies are needed to define the role of this drug in a wide variety of tumors.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96409  Chemotherapy administration; intravenous, push technique, single or initial substance/drug

HCPCS codes covered if selection criteria are met:

J9179  Injection, eribulin mesylate, 0.1

ICD-9 codes covered if selection criteria are met:

174.0 - 175.9  Malignant neoplasm of breast [for individuals with recurrent or metastatic breast cancer]

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

140.0 - 173.99, 176.0 - 239.9  Malignant neoplasm [except recurrent or metastatic breast cancer]

The above policy is based on the following references:


