AETNA BETTER HEALTH®
Clinical Policy Bulletin:
Ixabepilone (Ixempra)

Number: 0869

Policy

Aetna considers ixabepilone (Ixempra) medically necessary for members with locally advanced, recurrent or metastatic invasive breast cancer.

Aetna considers ixabepilone experimental and investigational for all other indications including the following (not an all-inclusive list):

- Gastric cancer
- Non-small-cell lung cancer
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Renal cell carcinoma
- Triple-negative breast cancer
- Uterine leiomyosarcoma

Background

Ixabepilone was approved by the Food and Drug Administration (FDA) in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated. The FDA labeling indicates Ixabepilone as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

Guidelines on breast cancer from the National Comprehensive Cancer Network (2013) indicate Ixempra as a single agent for recurrent or metastatic disease that is:
Hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis
HER2-negative and either hormone receptor-negative, or hormone receptor-positive and endocrine therapy refractory
Progressive with no clinical benefit after three consecutive endocrine therapy regimens or with symptomatic visceral disease.

In a phase II study, Kim et al (2012) examined the effects of ixabepilone in patients with advanced gastric cancer previously treated with fluoropyrimidine-based chemotherapy. Asian patients with unresectable or metastatic gastric adenocarcinoma who had failed fluoropyrimidine-based chemotherapy received ixabepilone 40 mg/m(2) by 3-hour intravenous infusion every 3 weeks. The primary end-point was objective response rate (ORR). A total of 52 patients were treated (65.4 % men; median age of 56.5 years). The ORR was 15.4 % (95 % confidence interval [CI]: 6.9 to 28.1); 8 patients achieved partial responses (PR) for a median duration of 3.1 months (95 % CI: 2.6 to 4.1 months) and 26 patients (50.0 %) had stable disease (SD). Median progression-free survival (PFS) was 2.8 months (95 % CI: 2.1 to 3.5 months). The most common grade 3 non-hematological toxicities were fatigue (9.6 %), decreased appetite (7.7 %), sensory neuropathy (5.8 %), and diarrhea (5.8 %). Grade 3/4 neutropenia occurred in 46.2 % of patients. The authors concluded that ixabepilone is active in Asian patients with advanced gastric cancer and shows a toxicity profile similar to those previously reported in other tumor types. These findings need to be validated in phase III clinical trials.

Vishnu et al (2012) evaluated anti-tumor activity of the combination of ixabepilone and sunitinib in pre-clinical models of chemotherapy naïve and refractory epithelial ovarian tumors, and investigated the mechanism of synergy of such drug combination. HOVTAX2 cell line was derived from a metastatic serous papillary epithelial ovarian tumor (EOC) and a paclitaxel-resistant derivative was established. Dose response curves for ixabepilone and sunitinib were generated and synergy was determined using combination indexes. The molecular mechanism of anti-tumor synergy was examined using shRNA silencing. The combination of ixabepilone and sunitinib demonstrated robust anti-tumor synergy in naïve and paclitaxel-resistant HOVTAX2 cell lines due to increased apoptosis. The GTPase, RhoB, was synergistically up-regulated in cells treated with ixabepilone and sunitinib. Using shRNA, RhoB was demonstrated to mediate anti-tumor synergy. These results were validated in 2 other EOC cell lines. The authors concluded that ixabepilone plus sunitinib demonstrated anti-tumor synergy via RhoB in naïve and paclitaxel-resistant cells resulting in apoptosis. This study demonstrated a novel mechanism of action leading to anti-tumor synergy and provided “proof-of-principle” for combining molecular targeted agents with cytotoxic chemotherapy to improve anti-tumor efficacy. They stated that RhoB could be envisioned as an early biomarker of response to therapy in a planned phase II clinical trial to assess the efficacy of ixabepilone combined with a receptor tyrosine kinase inhibitor such as sunitinib. To the best of the authors’ knowledge, this was the first demonstration of anti-tumor synergy between these 2 classes of drugs in EOC and the pivotal role of RhoB in this synergy.
In a phase II clinical trial, Liu et al (2012) evaluated the activity of a weekly ixabepilone in men with metastatic castrate-resistant prostate cancer (CRPC) to minimize hematologic toxicity. These investigators reported the activity and toxicity of ixabepilone, administered by using a weekly schedule, in men with metastatic CRPC. Patients with metastatic CRPC received ixabepilone at 20 mg/m\(^2\) intravenous weekly × 3, in 4-week cycles. This non-comparative study stratified patients to either a chemotherapy naive (CN), prior taxane (Tax) only, or 2 prior cytotoxic (TCx) chemotherapy arm. The primary end-point was prostate-specific antigen response by using PCWG (Prostate Cancer Working Group) 1 criteria. Secondary end-points included radiographic response when using RECIST (Response Evaluation Criteria In Solid Tumors). A total of 124 patients were enrolled, of whom, 109 were eligible (35 CN, 42 Tax, and 32 TCx) for the primary response determination in this study. Prostate-specific antigen responses were seen in 12 (34.3 %) of 35, 12 (28.6 %) of 42, and 7 (21.9 %) of 32 patients with the partial objective response in 5 (22.7 %) of 22, 2 (8.0 %) of 25, and 0 (0.0 %) of 24 patients for the CN, Tax, and TCx arms, respectively. Significant (grade 3/4) neutropenia was seen in 6 (15.4 %), 7 (14.6 %), and 9 (25.0 %); and grade 3/4 sensory neuropathy was seen in 8 (20.5 %), 12 (25.0 %), and 12 (33.3 %) for CN, Tax, and TCx, respectively. Grade 3/4 thrombocytopenia was infrequent and seen in only 1 patient on the CN and the TCx arm. The authors concluded that ixabepilone was found to have an acceptable toxicity profile when administered by using a weekly schedule with less myelosuppression compared with prior studies when using the every 3-week schedule. Single-agent activity was observed and met pre-specified activity levels for the Tax-treated arm. These findings need to be validated in phase III clinical trials.

In a phase II clinical trial, Edelman et al (2013) evaluated ixabepilone-based chemotherapy in stage IIIb/IV non-small-cell lung cancer (NSCLC), compared with paclitaxel-based chemotherapy. Tumor specimens were prospectively evaluated for β3T expression. Patients were stratified by β3T status (positive versus negative) and randomly assigned at a ratio of 1:1 to receive ixabepilone (32 mg/m\(^2\)) and carboplatin (area under concentration-time curve [AUC], 6) or paclitaxel (200 mg/m\(^2\)) and carboplatin (AUC, 6) for up to 6 cycles. The primary end-point was PFS in the β3T-positive subgroup. A total of 95 patients (β3T positive, 52; β3T negative, 43) received ixabepilone plus carboplatin; 96 patients (β3T positive, 49; β3T negative, 47) received paclitaxel plus carboplatin. No significant differences in median PFS were observed between arms for either subgroup (β3T positive, 4.3 months in both arms; β3T negative, 5.8 versus 5.3 months). Ixabepilone did not significantly improve overall survival (OS) for the β3T-positive subset or the overall population. Adverse events were similar between the 2 arms and comparable with those in previous studies. The authors concluded that there was no predictive value of β3T in differentiating clinical activity of ixabepilone- or paclitaxel-containing regimens. Ixabepilone did not improve PFS or OS in patients with β3T-positive tumors. β3T-positive patients had worse PFS relative to β3T-negative patients, regardless of treatment; hence, β3T expression seems to be a negative prognostic factor, but not a predictive factor, in advanced NSCLC treated with either ixabepilone or paclitaxel platinum-based doublets.

von Roemeling et al (2013) noted that metastatic renal cell carcinoma (mRCC) is more resistant to conventional cytotoxic chemotherapeutic agents than other solid
tumors. Although significant progress has been made over the last decade with several novel therapeutics, these agents invariably go on to fail, largely due to either intrinsic or acquired resistance. To help overcome, or at least delay resistance, combinatorial therapies utilizing agents with disparate, and ideally complementary, mechanisms of actions are needed. In this report, these researchers assessed the novel combination of the mTOR inhibitor, temsirolimus, with ixabepilone in RCC. The authors concluded that the results demonstrated synergy in multiple cell lines of RCC and further evaluation of this combination is warranted in the clinical setting.

Smaglo et al (2014) stated that the management of metastatic pancreatic adenocarcinoma is a challenge for medical oncologists because of both the aggressive nature of the disease and the relative paucity of effective systemic treatments with activity against this type of tumor. In the effort to discover new agents and combinations that may augment the therapeutic arsenal available for the management of this cancer, early phase clinical trials have been performed using ixabepilone with promising results. Targeting the microtubule system with certain taxanes in the management of pancreatic adenocarcinoma has been validated; ixabepilone also targets the microtubule system, interfering with it in an alternate manner from the taxane mechanism. Ixabepilone has demonstrated activity in cancers that have become taxane-resistant as well as those that never had any demonstrable taxane susceptibility. The available data for the use of ixabepilone in the management of pancreatic adenocarcinoma are limited but promising. Single-arm studies have demonstrated both clinical efficacy and tolerable toxicity for the use of ixabepilone as monotherapy. The trial data available for ixabepilone used as a part of combination therapy are similar: it has been paired with chemotherapy (carboplatin, irinotecan) and biologic therapy (dasatinib, sunitinib) at the phase I level to treat solid tumors in general, again with tolerable side effects and a suggestion of benefit. A single phase II study has evaluated combination therapy with ixabepilone in the management of patients with pancreatic cancer, pairing it with cetuximab with clinical benefit. The authors concluded that although these trials are promising with regard to addition of ixabepilone to the slim armamentarium for management of pancreatic cancer, further work still needs to be done.

Yadav et al (2014) noted that triple-negative breast cancer (TNBC) is defined by the lack of immunohistochemical expression of the estrogen and progesterone receptors and human epidermal growth factor receptor 2 (EGFR2). Most TNBC has a basal-like molecular phenotype by gene expression profiling and shares clinical and pathological features with hereditary BRCA1 related breast cancers. These investigators evaluated the activity of available chemotherapy and targeted agents in TNBC. A systematic review of PubMed and conference databases was carried out to identify randomized clinical trials (RCTs) reporting outcomes in women with TNBC treated with chemotherapy and targeted agents. They identified TNBC studies of chemotherapy and targeted agents with different mechanisms of action, including induction of synthetic lethality and inhibition of angiogenesis, growth and survival pathways. Triple-negative breast cancer is sensitive to taxanes and anthracyclins. Platinum agents are effective in TNBC patients with BRCA1 mutation, either alone or in combination with poly adenosine diphosphate polymerase 1 inhibitors. Combinations of ixabepilone and capecitabine have added to PFS without survival benefit in metastatic TNBC. Anti
-angiogenic agents, tyrosine kinase inhibitors and EGFR inhibitors in combination with chemotherapy produced only modest gains in PFS and had little impact on survival. Triple-negative breast cancer subgroups responded differentially to specific targeted agents. The authors concluded that in the future, the treatment needs to be tailored for a specific patient, depending on the molecular characteristics of their malignancy. Moreover, they noted that TNBC, being a chemo-sensitive entity, combination with targeted agents have not produced substantial improvements in outcomes. Appropriate patient selection with rationale combinations of targeted agents is needed for success.

Tredan et al (2014) stated that despite high initial sensitivity to chemotherapy, TNBC is associated with a poor prognosis, highlighting the need for novel therapeutic strategies. In a multi-center, randomized, open-label phase II clinical trial, these researchers evaluated the effectiveness of ixabepilone as monotherapy, and the combination of ixabepilone with cetuximab, as first-line treatment in patients with triple-negative locally advanced non-resectable and/or metastatic breast cancer. Women were randomly assigned to receive either ixabepilone (40 mg/m2) every 21 days (n = 40), or ixabepilone (40 mg/m2) every 21 days with cetuximab (400 mg/m2 loading dose, followed by 250 mg/m2) once-weekly (n = 39). The primary end-point of the trial was to estimate the response rates of ixabepilone monotherapy and ixabepilone with cetuximab combination therapy. Of 79 randomized patients, 77 were treated. Based on an intent-to-treat analysis, an objective response rate of 30 % (95 % CI: 16.6 to 46.5) was observed in the monotherapy arm, and 35.9 % (95 % CI: 21.2 to 52.8) in the combination arm. Median PFS was 4.1 months in both treatment groups. Safety findings were consistent with the known individual toxicity profiles of ixabepilone and cetuximab.

Skin and subcutaneous tissue disorders were more common with combination therapy, as were discontinuations because of adverse events. The authors concluded that ixabepilone monotherapy and the ixabepilone and cetuximab combination demonstrated similar levels of clinical activity in first-line treatment of advanced TNBC, with a predictable safety profile. They stated that further investigation of novel therapies for TNBC is needed to improve patient outcomes.

In a phase II clinical trial, Duska et al (2014) determined the activity of ixabepilone as a single-agent as second-line treatment for patients with metastatic uterine leiomyosarcoma who had received taxane based therapy. Eligible women with unresectable uterine leiomyosarcoma progressing after prior cytotoxic therapy containing a taxane were treated with ixabepilone 40 mg/m2 on day one of a 21-day cycle. Patients with prior pelvic radiation were treated without dose reduction. Response Evaluation Criteria in Solid Tumors response was assessed by computed tomography (CT). Twenty-three of 26 women were evaluable (2 wrong histology, 1 never treated) with 2 of 23 receiving 1 cycle of therapy. There were no complete responses (CR) or PR. Stable disease was seen in 4 patients (17.4 %, median of 3.4 months). Seventeen patients (73.9 %) had increasing disease (PD) and 2 patients were inevaluable per RECIST. One patient had SD over 6 cycles of treatment. Median PFS for all 23 patients was 1.4 months and OS was 7.0 months. The predominant grade 3 or 4 toxicity was uncomplicated myelosuppression: neutropenia grade 3 (13 %), grade 4 (17 %), and anemia grade 3 (22 %). The authors concluded that ixabepilone as a single agent is not an active second-line therapy for uterine leiomyosarcoma previously treated with a taxane.
Appendix

Continued use beyond 3 months (12 weeks) is considered medically necessary for persons with stable disease (tumor size within 25 % of baseline). Continued use is considered not medically necessary when there is evidence of disease progression or unacceptable toxicity occurs.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

96413
+96415

HCPCS codes covered if selection criteria are met:

J9207  Injection, ixabepilone, 1 mg

ICD-9 codes covered if selection criteria are met:

174.0 - 175.9  Malignant neoplasm of breast
198.81  Secondary malignant neoplasm of breast

The above policy is based on the following references:


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