Clinical Policy Bulletin:
Cabazitaxel (Jevtana)

Number: 0806

Policy

Note: **REQUIRES PRECERTIFICATION**

Aetna considers cabazitaxel (Jevtana) in combination with prednisone medically necessary for the treatment of hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen (see Appendix).

Continued use of cabazitaxel is considered not medically necessary for persons whose disease has progressed with cabazitaxel or who have developed intolerance to this drug.

Aetna considers cabazitaxel experimental and investigational for the treatment of other solid tumors (e.g., brain tumors, breast, cervical, colorectal, endometrial and lung cancers; not an all-inclusive list) and all other indications because its effectiveness for these indications has not been established.

Note: * Precertification of cabazitaxel is required of all Aetna participating providers and members in applicable plan designs. For precertification of cabazitaxel, call (866) 503-0857, or fax (866) 267-3277.

See also CPB 0521 - Prostate Cancer Screening, CPB 0698 - Prostate Saturation Biopsy, and CPB 0802 - Prostate Cancer Vaccine.

Background

Prostate cancer, accounting for 33% of all male cancers worldwide, is the second leading cause of cancer-related death among men, exceeded only by lung cancer. The disease is histologically evident in as many as 34% of men during their fifth decade of life and in up to 70% of men aged 80 years old and older. In the United States, prostate cancer represents the most common cancer among men, with an estimated 192,280 new cases diagnosed in 2009. The median survival for men with metastatic castrate-resistant prostate cancer (MCRPC) is 1 to 2 years, with improvements in survival seen primarily with cytotoxic chemotherapy (docetaxel-based chemotherapy). In the field of MCRPC,
systemic therapy options are limited and survival benefit remains to be seen with the new therapies (Lassi and Dawson, 2010).

In a review on immunological strategies for the treatment of prostate cancer, Drake and Antonarakis (2010) stated that along with initial therapy using cryotherapy, radiotherapy, or surgery, hormonal therapy is the mainstay of treatment. For men with metastatic disease, docetaxel-based chemotherapy is Food and Drug Administration (FDA)-approved, and provides a significant survival advantage. This relative paucity of treatment options drives an ongoing quest for additional treatment modalities; among these is immunotherapy. The concept that prostate cancer is a malignancy that can be targeted by the immune system may seem counter-intuitive; certainly kidney cancer and melanoma are more traditionally thought of as immune responsive cancers. However, prostate cancer arises in a relatively unique organ and may express a number of antigens against which an immune response can be generated. Several of these agents have now demonstrated a significant survival benefit in randomized controlled clinical trials. On April 29, 2010, the FDA approved sipuleucel-T (Provenge, Dendreon Corporation, Seattle, WA) for the treatment of asymptomatic or minimally symptomatic prostate cancer that has metastasized and is resistant to standard hormone treatment.

Cabazitaxel, a microtubule inhibitor, is a new chemotherapeutic agent for the treatment of advanced prostate cancer. It is an anti-neoplastic agent that belongs to the taxane class. Cabazitaxel binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to the stabilization of microtubules resulting in the inhibition of mitotic and inter-phase cellular functions. In a review on current and emerging treatment strategies for MCRPC, Di Lorenzo and colleagues (2010) noted that recent results from 2 large phase III clinical trials of sipuleucel-T and cabazitaxel show that these 2 agents significantly prolong overall survival (OS) in patients with MCRPC.

On June 17, 2010, the FDA approved cabazitaxel (Jevtana) for use in combination with prednisone for the treatment of men with prostate cancer. Cabazitaxel is the first treatment for advanced, hormone-refractory, prostate cancer that has worsened during or after treatment with docetaxel. The safety and effectiveness of cabazitaxel was established in a single clinical study (n = 755); all subjects had previously received docetaxel. The study was designed to measure OS (the length of time before death) in men who received cabazitaxel in combination with prednisone compared with those who received the mitoxantrone in combination with prednisone. Patients were randomized to receive either cabazitaxel 25 mg/m2 intravenously every 3 weeks in combination with prednisone 10 mg/day (n = 378), or mitoxantrone 12 mg/m2 intravenously every 3 weeks in combination with prednisone 10 mg/day (n = 377). They were treated until disease progression, death, unacceptable toxicity, or completion of 10 cycles of therapy. This study included patients over 18 years of age with hormone-refractory metastatic prostate cancer either measurable by Response Evaluation Criteria in Solid Tumors (RECIST) criteria or non-measurable disease with rising prostate-specific antigen levels or appearance of new lesions, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. Patients had to have neutrophils greater than 1,500 cells/mm3, platelets greater than 100,000 cells/mm3, hemoglobin greater than 10 g/dL, creatinine less than 1.5 x upper limit of normal (ULN), total bilirubin less than 1 x ULN, aspartate transaminase less than 1.5 x ULN, and alanine transaminase less than 1.5 x ULN. Patients with a history of congestive heart failure, or myocardial infarction within the last 6
months, or patients with uncontrolled cardiac arrhythmias, angina pectoris, and/or hypertension were not included in the study.

The median OS time was 15.1 months (95 % confidence interval [CI]: 14.1 to 16.3 months) for patients who received the cabazitaxel regimen compared with 12.7 months (95 % CI: 11.6 to 13.7 months; hazard ratio, 0.7 (95 % CI: 0.59 to 0.83; p < 0.0001) for those who received the mitoxantrone regimen. Additionally, investigator-assessed tumor response of 14.4 % (95 % CI: 9.6 to 19.3) was higher for patients in the cabazitaxel regimen group compared to 4.4 % (95 % CI: 1.6 to 7.2) for patients in the mitoxantrone regimen group (p = 0.0005). No complete responses were observed on either arm.

The National Comprehensive Cancer Network’s guidelines for prostate cancer (NCCN, 2010) have been updated to include cabazitaxel with steroids as an option under systemic salvage therapy of MCRPC (category 1 designation).

The individual dosage of cabazitaxel is based on calculation of the body surface area and is 25 mg/m² administered as a 1-hour intravenous infusion every 3 weeks in combination with oral prednisone 10 mg administered daily throughout cabazitaxel treatment. Side effects associated with the use of cabazitaxel included anemia, asthenia, constipation, diarrhea, fatigue, leukopenia, nausea, neutropenia, renal failure, thrombocytopenia, and vomiting. Cabazitaxel is contraindicated in patients with neutrophil counts of less than or equal to 1,500/mm³, and in those who have a history of severe hypersensitivity reactions to cabazitaxel or to other drugs formulated with polysorbate 80.

Cabazitaxel is also being investigated in the treatment of other malignancies. There are ongoing clinical trials that examine the combinations of cabazitaxel with cisplatin (completion date: September 2011) as well as cabazitaxel with gemcitabine (completion date: March 2012) for the treatment of advanced solid malignancies (Worldwide Clinical Trials Listings, 2010).

In a phase I/II clinical trial, Villanueva et al (2011) evaluated the maximum tolerated dose (MTD), safety profile, pharmacokinetics, and activity of cabazitaxel plus capecitabine in patients with metastatic breast cancer (MBC) who had been previously treated with taxanes and anthracyclines. In part I, these investigators used a 3+3 dose-escalation scheme to assess the MTD of intravenous cabazitaxel (day 1) with oral capecitabine twice-daily (days 1 to 14) every 3 weeks. In part II, they assessed the objective response rate (ORR) at the MTD. A total of 33 patients were enrolled and treated (15 in part I; 18 in part II). Cabazitaxel 20mg/m² plus capecitabine 1000 mg/m² was the MTD. Pharmacokinetic analysis showed no apparent drug-drug interaction. In all patients, the main grade 3 to 4 toxicities were asthenia (n = 5), hand-foot syndrome (n = 5), neutropenia (n = 21), neutropenic infection (n = 1), and neutropenic colitis (n = 1). One patient had febrile neutropenia. Anti-tumor activity was observed at all dose-levels with 2 complete responses, 5 partial responses (PRs), and 20 disease stabilizations (7 unconfirmed PR). At the MTD, 21 patients were evaluable for efficacy. The ORR was 23.8 % (95 % CI: 8.2 to 47.2 %). The median response duration was 3.1 months (95 % CI: 2.1 to 8.4 months), with 4 of 5 lasting for more than 3 months. Median time to progression was 4.9 months. The authors concluded that cabazitaxel combined with capecitabine is active, has a safety profile consistent with a taxane plus capecitabine combination and warrants further investigation in patients with MBC.

Dieras and colleagues (2013) noted that although the taxanes paclitaxel and docetaxel are among the most active agents for the treatment of a wide range of cancers, tumors
often develop resistance to these treatments. Cabazitaxel is a novel taxane active in both pre-clinical models of chemotherapy-sensitive and -resistant human tumors and patients with advanced prostate cancer that progressed following docetaxel treatment. In a phase I clinical study, these researchers aimed to establish the MTD and dose-limiting toxicities (DLTs) of cabazitaxel. Cabazitaxel was administered every 3 weeks to patients with advanced solid tumors. The design allowed intra-patient dose escalation. The primary objective was to determine the MTD. Secondary objectives were to describe the safety profile, establish an appropriate dose, determine the pharmacokinetic (PK) profile of cabazitaxel, and assess anti-tumor activity. A total of 21 patients were recruited. The MTD was reached at 30 mg/m$^2$, at which 3 of 5 patients experienced hematologic DLTs during the first cycle; DLTs during subsequent cycles were mainly hematologic and reported at 25 and 30 mg/m$^2$ dosing levels. Nail disorders and severe alopecia were not reported, and neurotoxicity, fluid retention and hypersensitivity were mild and infrequent. Cabazitaxel demonstrated linear PK, a tri-phasic elimination profile, with a long half-life and high clearance. Of the 19 patients evaluable for response, 1 unconfirmed partial response and 6 occurrences of stable disease were reported. The authors concluded that the 25 mg/m$^2$ dose of cabazitaxel was recommended for use in future clinical studies. In this study, cabazitaxel had an acceptable tolerability profile and activity in cervical, colorectal, endometrial and lung cancers.

Girard and colleagues (2014) stated that there is an unmet need in the treatment of pediatric brain tumors for chemotherapy that is efficacious, avoids damage to the developing brain, and crosses the blood-brain barrier. These researchers evaluated the effectiveness of cabazitaxel in mouse models of pediatric brain tumors. The anti-tumor activity of cabazitaxel and docetaxel were compared in flank and orthotopic xenograft models of patient-derived atypical teratoid rhabdoid tumor (ATRT), medulloblastoma, and central nervous system primitive neuroectodermal tumor (CNS-PNET). Effectiveness of cabazitaxel and docetaxel were also assessed in the Smo/Smo spontaneous mouse medulloblastoma tumor model. This study observed significant tumor growth inhibition in pediatric patient-derived flank xenograft tumor models of ATRT, medulloblastoma, and CNS-PNET after treatment with either cabazitaxel or docetaxel. Cabazitaxel, but not docetaxel, treatment resulted in sustained tumor growth inhibition in the ATRT and medulloblastoma flank xenograft models. Patient-derived orthotopic xenograft models of ATRT, medulloblastoma, and CNS-PNET showed significantly improved survival with treatment of cabazitaxel. The authors concluded that these data support further testing of cabazitaxel as a therapy for treating human pediatric brain tumors.

Appendix

Selection Criteria: Cabazitaxel (Jevtana) is considered medically necessary for members who meet the following criteria:

1. Adult men (18 years of age or older) with histologically confirmed adenocarcinoma of the prostate with radiologic evidence of metastases to soft tissue, lymph nodes or bone; and
2. Treatment with surgical (bilateral orchiectomy) castration or 3 or more months of chemical castration (luteinizing hormone releasing hormone (LHRH) agonists or antagonists$^*$); for members treated with chemical castration, serum testosterone concentration (current or at initiation of chemical castration) must be less than 50 ng/dL to document adequacy of castration; and
3. Evidence of progressive disease after surgical or chemical castration (known as castrate-resistant, hormone-refractory, or androgen-independent prostate cancer), adapted from PSA Consensus Criteria (Bubley et al, 1999), showing progressive measurable disease, worsening disease on bone scan, or an increasing prostate-specific antigen (PSA), as defined below:

1. **Progressive measurable disease**, as evidenced by changes in size of lymph nodes or parenchymal masses on physical examination or radiographic studies; or

2. **Bone scan progression**, as evidenced by 1 or more new lesions or increase in size of lesions (not including "flare" that occurs at commencement of hormonal therapy or chemotherapy); or

3. **PSA progression**: An increase in PSA over a previous reference value, where the PSA value is a measured a minimum of 1 week from the reference value, and the PSA measurement is a minimum of 25 % greater than the reference value, and an absolute-value increase in PSA of at least 5 ng/ml over the reference value, and this PSA increase is confirmed by a second value; and

4. Evidence of previous treatment with docetaxel-containing treatment regimen.

* LHRH agonists (analogs) include leuprolide (Lupron, Viadur, Eligard), goserelin (Zoladex), triptorelin (Trelstar), and histrelin (Vantas). Degarelix (Firmagon) is an LHRH antagonist that is thought to work like LHRH agonists. See CPB 0501 - Gonadotropin-Releasing Hormone Analogs and Antagonists.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**Other CPT codes related to the CPB:**

96401 - 96417

**HCPCS codes covered if selection criteria are met:**

J9043  Injection, cabazitaxel, 1 mg

**Other HCPCS codes related to the CPB:**

J7506  Prednisone, oral, per 5 mg

J7509  Methylprednisolone, oral, per 4 mg

J7510  Prednisolone, oral, per 5 mg

J9171  Docetaxel, 1 mg IV [treatment regimen prior to carbazitaxel]

**ICD-9 codes covered if selection criteria are met:**

185  Malignant neoplasm of prostate
ICD-9 codes not covered for indications listed in the CPB (not an all inclusive list):

140.0 - 184.9. Neoplasms [except malignant neoplasm of prostate]
186.0 -239.9

Other ICD-9 codes related to the CPB:

995.27 Other drug allergy [intolerance to cabazitaxel]
E933.1 Adverse effect of antineoplastic and immunosuppressive drugs [intolerance to cabazitaxel]
V58.11 Encounter for antineoplastic chemotherapy

The above policy is based on the following references:


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