



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Subject **Sorafenib (Nexavar®)**

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INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA covers sorafenib (Nexavar®) as medically necessary for treatment of ANY of the following indications:

- advanced renal cell carcinoma (RCC)
- unresectable hepatocellular carcinoma (HCC)
- thyroid carcinoma
- gastrointestinal stromal tumors (GIST) when there is no longer benefit from imatinib or sunitinib
- angiosarcoma

FDA Approved Indications

Hepatocellular Carcinoma

Nexavar is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

Renal Cell Carcinoma

Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

FDA Recommended Dosing

The recommended daily dose of Nexavar is 400 mg (2 x 200 mg tablets) taken twice daily without food (at least 1 hour before or 2 hours after a meal). Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Nexavar therapy. When dose reduction is necessary, the Nexavar dose may be reduced to 400 mg once daily. If additional dose reduction is required, Nexavar may be reduced to a single 400 mg dose every other day.

General Background

Pharmacology

Sorafenib inhibits several intracellular and cell surface kinases believed to be important in cancer cell proliferation and angiogenesis. Sorafenib reaches peak plasma concentrations three hours after a single oral dose and reaches steady state in less than seven days with multiple dosing. It is approximately 99.5% protein bound. It is primarily metabolized by cytochrome P450 3A4 (CYP3A4) and glucuronidation in the liver. Approximately 77% is excreted in the feces, and approximately 19% is excreted in the urine.

Disease Overview

Sorafenib is an oral multiple kinase inhibitor used to reduce the progression of advanced RCC. Median survival for patients with metastatic RCC is only 13 months. The primary treatment for RCC is excision, most commonly, radical nephrectomy. Medical therapies are usually reserved for locally advanced or metastatic disease. Surgery is the only curative intervention, so the goals of medical therapy are to slow progression of the disease and extend the patient's life. Response rates to medical treatment are low. Chemotherapy alone has only had response rates of about 4% to 6%. Immunomodulatory therapies are the current treatments of choice for advanced RCC. Interferon alfa alone has shown a response rate of about 14%, with a median duration of about six months among responders. Aldesleukin is considered the standard of therapy for advanced RCC. High-dose aldesleukin has a response rate of 21%, with a median duration of 54 months among responders. Sorafenib is the first of two multiple kinase inhibitors available in the United States for the treatment of advanced RCC and treatment of unresectable hepatocellular carcinoma. Sunitinib is the other available agent in this class.

Guidelines

The National Comprehensive Cancer Network (NCCN) recommends Nexavar for the following: HCC - treatment as a single agent for patients (Child-Pugh Class A or B) with unresectable disease or who are inoperable by performance status or comorbidity (local disease only) or with metastatic disease. Not recommended for patients who are candidates for liver transplantation. Caution: There are limited safety data available for Child-Pugh Class B patients. Use with extreme caution in patients with elevated bilirubin levels (grade 1). RCC - subsequent therapy as a single agent for relapsed or medically unresectable stage IV disease in patients with predominant clear cell histology who have progressed on prior first-line therapy (grade 1); first-line therapy as a single agent for relapsed or medically unresectable stage IV disease in selected patients with predominant clear cell histology or non-clear cell histology (grade 2A). Follicular thyroid carcinoma - consider for treatment of clinically progressive or symptomatic metastatic disease in patients with nonradioiodine-avid tumors at sites other than central nervous system (grade 2A); Hürthle cell thyroid carcinoma - consider for treatment of clinically progressive or symptomatic metastatic disease in patients with nonradioiodine-avid tumors at sites other than central nervous system (grade 2A); Medullary thyroid carcinoma - treatment of disseminated symptomatic disease (grade 2A); Papillary thyroid carcinoma - consider for treatment of clinically progressive or symptomatic metastatic disease in patients with nonradioiodine-avid tumors at sites other than central nervous system (grade 2A). Gastrointestinal stromal tumors (GIST) - treatment for progressive disease when patient is no longer receiving benefit from imatinib or sunitinib (grade 2A). Soft tissue sarcoma of the extremity or retroperitoneal/ intra-abdominal - may be useful as a single agent for angiosarcoma (grade 2A).

Clinical Efficacy

RCC

Two randomized controlled clinical trials established the safety and efficacy of sorafenib in patients with advanced RCC. Currently, these trials are only available as abstracts. Patients treated with sorafenib had significantly longer median progression-free survival (PFS) rates (23 to 24 weeks) than placebo (six to 12 weeks). Although no head-to-head trials have been published, clinical data based on PFS can be compared. Patients treated with a combination of subcutaneous interferon alfa-2a, subcutaneous aldesleukin, intravenous fluorouracil, and oral 13-cis-retinoic acid have a median PFS of seven months. Patients treated with a combination of subcutaneous interferon alfa-2a, subcutaneous aldesleukin, and intravenous fluorouracil have a median PFS of six months. Patients treated with a combination of subcutaneous interferon alfa-2a and intravenous vinblastine have a median PFS of five months. Patients treated with a combination of subcutaneous interferon alfa-2a and oral 13-cis-retinoic acid have a median PFS of 5.1 months. Patients treated with subcutaneous interferon alfa-2a alone have a median PFS of 3.2 months.

HCC

An international, randomized, Phase III placebo-controlled study [Sorafenib hepatocellular carcinoma (HCC) Assessment Randomized Protocol (SHARP)] evaluated sorafenib in 602 patients with inoperable HCC. Treatment and placebo group were comparable with regard to age, gender, race, the stage and other characteristics of their cancer, and the types of cancer treatment they had received before entering the clinical trial. The trial was stopped after a planned interim analysis showed a statistically significant advantage in overall survival for the patients treated with sorafenib compared to placebo. This study demonstrated that sorafenib improved overall survival by 44% in patients with HCC ($p=0.0006$) versus placebo. In the study, median overall survival was 10.7 months in sorafenib-treated patients compared to 7.9 months for those taking placebo. No indication of imbalance was observed in serious adverse events between the sorafenib and placebo-treated groups, with the most commonly observed adverse events in patients receiving sorafenib being diarrhea and hand-foot skin reaction. A separate analysis showed that tumors progressed more slowly in patients who received Nexavar compared to patients who had received placebo.

Clinical Efficacy of Off-Label Indications

Thyroid Carcinoma

Given the molecular pathophysiology of thyroid cancer and the spectrum of kinases inhibited by sorafenib, including Raf kinase, vascular endothelial growth factor receptors, platelet-derived growth factor receptor, and RET tyrosine kinases, an open-label phase II trial was conducted to determine the efficacy of sorafenib in patients with advanced thyroid carcinoma. Eligible patients with metastatic, iodine-refractory thyroid carcinoma received sorafenib 400 mg orally twice daily. Responses were measured radiographically every 2 to 3 months. The study end points included response rate, progression-free survival (PFS), and best response by Response Evaluation Criteria in Solid Tumors. Thirty patients were entered onto the study and treated for a minimum of 16 weeks. Seven patients (23%; 95% CI, 0.10 to 0.42) had a partial response lasting 18+ to 84 weeks. Sixteen patients (53%; 95% CI, 0.34 to 0.72) had stable disease lasting 14 to 89+ weeks. Seventeen (95%) of 19 patients for whom serial thyroglobulin levels were available showed a marked and rapid response in thyroglobulin levels with a mean decrease of 70%. The median PFS was 79 weeks. Toxicity was consistent with other sorafenib trials, although a single patient died of liver failure that was likely treatment related. Sorafenib has clinically relevant antitumor activity in patients with metastatic, iodine-refractory thyroid carcinoma, with an overall clinical benefit rate (partial response + stable disease) of 77%, median PFS of 79 weeks, and an overall acceptable safety profile. These results represent a significant advance over chemotherapy in both response rate and PFS and support further investigation of this agent in these patients.

GIST

GISTs are rare mesenchymal tumors usually caused by mutations in the KIT or PDGFRA gene. Advanced disease generally cannot be cured by surgery nor by tyrosine kinase inhibitors (TKI), but TKIs have considerably improved outcome for patients (pts) with advanced GIST. Patients failing TKI treatment with imatinib (IM), sunitinib (SU) or nilotinib (NI) have a poor prognosis. Sorafenib is a multi kinase inhibitor that blocks not only receptor tyrosine kinases such as KIT, VEGFR and PDGFR but also

serine/threonine kinases along the RAS/RAF/MEK/ERK pathway. Recently, clinical activity of sorafenib in third-line treatment in patients with GIST after IM and SU failure has been shown. Preliminary data of 32 pts treated with sorafenib in nine European centers has been reported. Centers were selected based on their previous and known experience in GIST and reported all pts treated. Pts received sorafenib after failure of IM, SU and NI in fourth-line treatment. Baseline characteristics and treatment details have been retrieved via questionnaire. Primary tumor site was gastric or small intestine in 25% and 41% of pts, respectively. All pts had failed IM, SU, NI. 19 % of pts achieved partial remission and 44% disease stabilization. Approximately half of the pts had an improvement of symptoms and/or performance. Half of the pts were on treatment longer than 4 months (actuarial data) and 41% of pts continue to receive sorafenib. Median progression-free survival is 20 weeks and median overall survival 42 weeks (Kaplan-Meier), at a median follow-up of 22 weeks (range 3-54). This is the largest series assessing efficacy of sorafenib fourth-line treatment for IM, SU and NI refractory GIST reported yet. Sorafenib displays significant clinical activity in this heavily pretreated group of patients.

Sarcoma

A multicenter phase II study of daily oral sorafenib in patients with recurrent or metastatic sarcoma was performed. A multiarm study design, each representing a sarcoma subtype with its own Simon optimal two-stage design was used. In each arm, 12 patients who received 0 to 1 prior lines of therapy were treated (0 to 3 for angiosarcoma and malignant peripheral-nerve sheath tumor). If at least one Response Evaluation Criteria in Solid Tumors (RECIST) was observed, 25 further patients with that sarcoma subtype were accrued. Between October 2005 and November 2007, 145 patients were treated; 144 were eligible for toxicity and 122 for response. The median number of cycles was 3. Five of 37 patients with angiosarcoma had a partial response (response rate, 14%). This was the only arm to meet the RECIST response rate primary end point. Median progression-free survival was 3.2 months; median overall survival was 14.3 months. Adverse events (typically dermatological) necessitated dose reduction for 61% of patients. Statistical modeling in this limited patient cohort indicated sorafenib toxicity was correlated inversely to patient height. There was no correlation between phosphorylated extracellular signal regulated kinase expression and response in six patients with angiosarcoma with paired pre- and post-therapy biopsies. As a single agent, sorafenib has activity against angiosarcoma and minimal activity against other sarcomas. Further evaluation of sorafenib in these and possibly other sarcoma subtypes appears warranted, presumably in combination with cytotoxic or kinase-specific agents.

Adverse Reactions/Warnings

Sorafenib significantly increases the time patients remain progression-free. Skin toxicities, including rash and hand-foot skin reactions, are common dose-limiting side effects of sorafenib. Other common adverse events include diarrhea, rash, fatigue, alopecia, nausea, pruritus, hypertension, hemorrhage, and neuropathies. Common lab abnormalities include hypophosphatemia, elevated lipase, elevated amylase, lymphopenia, neutropenia, and thrombocytopenia. Cardiac ischemia/infarction is higher in patients using sorafenib compared to those taking placebo. The discontinuation rate for sorafenib is 10%. This rate is similar to placebo.

Sorafenib inhibits the metabolism of drugs which go through the glucuronidation pathway UGT1A1, such as irinotecan. When used with CYP3A4 inducers, concentrations of sorafenib are expected to decrease. Sorafenib is a competitive inhibitor of CYP2C9. When used at the same time as warfarin, frequent monitoring of the prothrombin time-international normalized ratio (PT-INR) is recommended.

Coding/Billing Information

Note: This section not in use

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	12/15/2007	6109	Sorafenib (Nexavar [®])
Great-West Healthcare	8/2007	P06.101.1	Nexavar

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.