

The following is a message from the FDA's Office of Oncology Drug Products Director, Dr. Richard Pazdur:

On November 16, 2007, the U.S. Food and Drug Administration approved sorafenib (NEXAVAR®, Bayer Pharmaceuticals Corporation and Onyx Pharmaceuticals, Inc.), an orally administered kinase inhibitor, for the treatment of patients with unresectable hepatocellular carcinoma (HCC). Sorafenib was originally approved in December 20, 2005 for the treatment of patients with advanced renal cell carcinoma.

The current approval was based on the results of an international, multicenter, randomized, double-blind, placebo-controlled trial in patients with unresectable, biopsy-proven hepatocellular carcinoma. Overall survival was the primary efficacy endpoint. A total of 602 patients were randomized; 299 to sorafenib 400 mg twice daily and 303 to matching placebo. Demographics and baseline disease characteristics were similar between the sorafenib and placebo groups.

Prior treatments included surgical resections (20%), locoregional therapies (including radiofrequency ablation, percutaneous ethanol injection and transarterial chemoembolization in 40%), radiotherapy (5%), and systemic therapy (4%). The trial was stopped following a pre-specified second interim analysis for survival disclosing a statistically significant advantage for sorafenib [median 10.7 vs. 7.9 months; HR: 0.69 (95% CI: 0.55, 0.87), p= 0.00058]. The final analysis of time-to-tumor progression (TTP) by independent radiologic review was based on data from an earlier time point and demonstrated a statistically significant improvement in TTP in the sorafenib arm [median 5.5 vs. 2.8 months; HR: 0.58 (95% CI: 0.45, 0.74), p=0.000007]. The most common adverse reactions (≥20%) considered related to sorafenib were fatigue, weight loss, rash/ desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain. Diarrhea was reported in 55% of sorafenib patients (grade 3 in 10%). Hand-foot syndrome (21% overall; grade 3 in 8%) and rash (19% overall; grade 3 in 1%) were the most common dermatologic adverse reactions to sorafenib.

Cardiac ischemia or infarction was reported in 2.7% of sorafenib patients (1.3% placebo). Treatment-emergent hypertension was reported in 9% of sorafenib patients (4% placebo). Grade 3 hypertension was reported in 4% of sorafenib patients (1% placebo). Elevated serum lipase occurred in 40% of sorafenib patients (37% placebo), and hypophosphatemia occurred in 35% of sorafenib patients (11% placebo). 2

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at
<http://www.fda.gov/cder/foi/label/2007/021923s007lbl.pdf>.