

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

On October 29, 2007, the U. S. Food and Drug Administration granted accelerated approval to nilotinib (TASIGNA® Capsules, Novartis Pharmaceuticals Corporation) for use in the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib.

The effectiveness of Tasigna® is based on hematologic and cytogenetic response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. Submission of further follow-up data from an ongoing study is required to convert this accelerated approval to regular approval.

Efficacy was demonstrated in one ongoing non-randomized multi-center study. Patients were treated with nilotinib at a starting dose of 400 mg twice daily. At the time of data cut-off, 232 CML-CP patients and 105 CML-AP patients were considered evaluable for efficacy. Prior treatment included imatinib (100%), hydroxyurea (85%), interferon (62%) and bone marrow transplantation (8%). Imatinib was discontinued in 73% of patients because of resistance; 27% discontinued imatinib because of drug intolerance. The highest prior maximum imatinib dose was > 600 mg/day in 77% of patients.

The efficacy endpoint for CML-CP was unconfirmed major cytogenetic response, defined as elimination or substantial diminution (by at least 65%) of Ph⁺ metaphases in the bone marrow. The major cytogenetic response rate in CP patients was 40% (95% CI: 33%, 46%). The efficacy endpoint for CML-AP was hematologic responses. Hematologic response was defined as either a complete hematologic response or no evidence of leukemia. The hematologic response rate in AP patients was 26% (95% CI: 18%, 35%). The median duration of response has not been reached for CML-CP and CML-AP. At the time of data cutoff, 59% of CML-CP patients and 63% of CML-AP patients had a response duration of at least 6 months.

The safety population included 318 patients with CML-CP and 120 patients with CML-AP. In CML-CP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritis, nausea, fatigue, headache, constipation, diarrhea and vomiting. The common serious drug-related adverse reactions were thrombocytopenia and neutropenia. In CML-AP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritus and constipation. The common serious drug-related adverse reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Nilotinib prolongs the QT interval and sudden deaths have been reported; this risk is described in a Boxed Warning in the labeling. Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking a dose. ECG's should be obtained to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, as well as following dose adjustments.

Full prescribing information, including clinical trial information, safety, dosing, drug-drug interactions and contraindications is available at
<http://www.fda.gov/cder/foi/label/2007/022068lbl.pdf>.