CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-068

CROSS DISCIPLINE TEAM LEADER REVIEW

Date	October 24, 2007
From	Ramzi Dagher, MD
Subject	Cross-Discipline Team Leader Review
NDA #	22068
Proprietary / Established (USAN) names	Tasigna (nilotinib)
Dosage forms / strength	capsules /
Proposed Indication	Tasigna (nilotinib) is indicated for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (CML) in adult patients resistant or intolerant to prior therapy that included imatinib
Recommendation	Approval

1. Background and Introduction to Review

Nilotinib, a synthetic aminopyrimidine, is an inhibitor of the kinase activity of the Bcr-Abl oncoprotein. This protein is the product of the BCR-ABL fusion gene, which results from a reciprocal chromosomal translocation in a bone marrow hematopoietic stem cell. Nilotinib is an inhibitor of the Abl tyrosine kinase activity of the Bcr-Abl oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia cells. The drug binds tightly to the inactive conformation of the kinase domain in such a manner that it is an inhibitor of wild-type Bcr-Abl and maintains activity against 32/33 imatinib-resistant mutant forms of Bcr-Abl.

Nilotinib is pharmacologically related to imatinib mesylate (Gleevec®) and dasatinib (Sprycel®), both of which are inhibitors of Bcr-Abl tyrosine kinase.

Imatinib mesylate (Gleevec®) was approved in 2001 for the treatment of CML in three clinical settings: CML-BC, CML-AP and CML-CP. The most frequently reported drug related adverse events were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (cutaneous toxicity). A variety of adverse events represented local or general fluid retention including pleural effusion, ascites, pulmonary edema and

rapid weight gain with or without superficial edema. Cytopenias included neutropenia and thrombocytopenia. Severe hepatotoxicity including elevations of transaminases or bilirubin lead to liver failure or death. Post marketing safety reports included cardiotoxicity including severe congestive heart failure in ten patients, hypophosphatemia, with associated changes in bone and mineral metabolism and fatal hepatitis

Dasatinib was approved in 2006 for the treatment of adult patients with imatinib resistant/intolerant CML-CP, CML-AP and Ph + ALL. The most common severe toxicities associated with dasatinib were hematologic, including neutropenia thrombocytopenia and anemia. Others included neutropenic fever, bleeding events, pyrexia, dyspnea, pleural effusion, and diarrhea. Other significant less commonly occurring adverse reactions included cardiac failure, QTc prolongation and CNS hemorrhages, most of which were fatal.

2. Clinical Pharmacology/Biopharmaceutics

The clinical pharamacology review was completed by Qi Liu, Ph.D., Roshni Ramchandani, Ph.D. and Brian Booth, Ph.D. as team leader. Roshni Ramchandani, Ph.D., Rajnikanth Madabushi, Ph.D. and Christine Garnett, Ph.D. served as QT reviewers.

The reviewers concluded that the proposed dosing regimen of 400 mg orally twice daily is reasonable. The reviewers recommended the following post-marketing commitments :

"To submit the completed study report and datasets for the hepatic impairment study

To submit the completed study report and datasets for the absolute bioavailability study

To conduct clinical studies to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C9 substrate. If significant interaction was demonstrated, additional clinical studies to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C8 substrate and/or a sensitive CYP3A4 substrate may be needed.

To conduct a clinical study to evaluate if H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib. "

3. Clinical/Statistical

A joint clinical/statistical review was completed by Dr Maitreyee Hazarika and Dr Xiaoping Jiang. Drs Dagher and Sridhara served as medical and statistical team leaders, respectively. The following is a summary of their findings.

Evidence of nilotinib efficacy is based on the results of a single Phase 2 study with two populations studied, CML-CP and CML-AP. The primary efficacy endpoint in the CML-CP population was major cytogenetic response rate (MCyR), defined as elimination or diminution to less than 35% of Ph+ hematopoietic cells. According to the protocol, the primary efficacy endpoint in CML-AP was overall hematologic response rate which included complete hematologic response (CHR) or no evidence of leukemia (NEL) and return to chronic phase (RTC). The reviewers consider CHR and NEL (a major hematologic response) as surrogates reasonably likely to predict clinical effectiveness for accelerated approval for the CML-CP indication. However, the reviewers do not consider RTC as a surrogate reasonably likely to predict clinical benefit. Therefore, FDA reviewers recommend presentation of the hematologic response data for the CML-AP population based on CHR and NEL only.

CML-CP: A total of 92 of 232 (40%) evaluable patients achieved an unconfirmed MCyR (95% CI: 33, 46). This included a 28% complete cytogenetic response rate and a 12% partial response rate. Fifty-nine percent of CML-CP patients with a major cytogenetic response had a duration of response of at least 6 months.

CML-AP: The major hematologic response (MHR) which included complete hematologic response and no evidence of leukemia/marrow response rate (CHR + NEL) was 26% (27 / 105) with a (95% CI: 18, 35). Sixty-three percent of CML-AP patients with a confirmed hematologic response had a duration of response of at least 6 months.

Four hundred and thirty eight patients comprised the safety population including 318 patients with CML-CP and 120 patients with CML-AP. All patients were treated with a starting dose of 400 mg orally twice daily.

The median duration of exposure to nilotinib in CML-CP patients was 245 days. Fifty-two percent were treated for 6 - 12 months, while 19% were treated for less than 3 months and 20% were treated for more than 12 months.

The median duration of exposure to nilotinib in CML-AP patients was 138 days. Thirty-five percent were treated for 6 - 12 months, while 23% were treated for less than 3 months and 11% were treated for more than 12 months.

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.

Treatment-emergent grade 3/4 thrombocytopenia occurred in 28% of CML-CP patients and 37% of CML-AP patients. Grade 3/4 neutropenia occurred in 28% of CML-CP patients and 37% of CML-AP patients. Grade 3/4 anemia occurred in 8% of CML-CP patients and 28% of CML-CP patients.

Other treatment-emergent grade 3/4 laboratory abnormalities occurring in CML patients receiving nilotinib included:

greater than 5% incidence : elevated lipase, hyperglycemia, hypophosphatemia, elevated bilirubin

less than 5% : elevated SGOT or SGPT, hyperkalemia, hyponatremia, hypokalemia, decreased albumin, hypocalcemia, elevated alkaline phosphatase, and elevated creatinine

A relatively high number of patients experienced QTcF prolongations from baseline of > 30 msec (33.0% of CML-CP patients, 40.8% of CML-AP patients). QTcF increases of > 60 msec were reported in 1.9% of CML-CP and 2.5% of CML-AP patients. The incidence of absolute QTcF values > 500 msec was < 1%. There were ten sudden deaths reported. Six sudden deaths occurred in the ongoing phase 1/2 study (an additional death was reported after database lock but appeared to be possibly related to cardiac surgery and other moribidity) ; 4 deaths occurred in the expanded access program or with single patient use.
The following wording is recommended for the black box warning:

WARNING: QT PROLONGATION AND SUDDEN DEATHS

Tasigna prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored. 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 dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

The clinical and statistical reviewers recommend the following post-marketing commitment:

"To submit the complete study report (at least 24 months follow-up in all patients) and data from study 2101, a phase 2 multi-center study of nilotinib in patients with imatinib resistant or intolerant chronic myeloid leukemia."

4. Advisory Committee Meeting

There was no advisory committee meeting held. The following wording is recommended for inclusion in the action letter to explain the rationale for this decision.

"This application was not taken to the Oncologic Drugs Advisory Committee (ODAC) because, for the following reasons, we determined that the application did not warrant ODAC review. The Office of Oncology Drug Products has previously accepted the endpoint of cytogenetic response as an approval endpoint in the setting of chronic phase CML and the endpoint of hematologic response in the setting of accelerated phase CML. The major toxicities can be managed with dose modifications, dose interruption, attention to concomitant medications, and safety monitoring."

There was a CDER regulatory briefing held on August 17, 2007 to discuss the sudden deaths observed and QT prolongation by nilotinib. There was consensus that if and when approval was contemplated, a black box warning regarding QT prolongation and sudden deaths should be included in labeling.

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5. Financial Disclosure

The clinical reviewers did not consider any financial disclosures as likely to influence the study outcomes.

6. Risk Management Plan

The Office of Safety and Epidemiology reviewers were Jeanine Best, Mary Dempsey, Joyce Weaver, and Sam Chan. The reviewers had several suggested modifications to the risk management plan. These were conveyed to the sponsor. The sponsor has committed to providing a revised plan for review as stated in the following post-marketing commitment:

" Submit a supplement containing a revised version of the complete RiskMAP (goals and objectives, tools, implementation plan, evaluation plan and reports to the agency) including all supporting materials. This should incorporate the amendments agreed to in correspondence of October 22, 2007. This should be submitted by November 30, 2007.

OSE reviewers also recommended the following wording to be included in the labeling in order to optimize compliance with reporting requirements :

"We remind you that you must comply with reporting requirements for an approved NDA (21CFR 314.80 and 314.81).

We remind you of your commitment to provide reports regarding medication errors involving dosing outside of the Tasigna (nilotinib) labeled recommendations. The reports and their contents are listed below:

[redacted] **15 days** [redacted]

1. [redacted]
2. Medication Errors should include, but is not limited to:
   - dosing with food
   - dosing outside of the recommended 12 hour frequency
   - taking more tablets than prescribed or recommended by the sponsor
   - or administration with other drug products potentially affecting the absorption or metabolism of nilotinib (e.g. CYP3A4 inhibitor)
3. [redacted] reports of QTc prolongation should include information and follow-up as to whether the adverse event was the result of a medication error (e.g., dosing with food, dosing outside of the 12 hr frequency, etc). "

7. Conclusions and Recommendations

The medical team leader/CDTL recommends approval of nilotinib for the following indication :

"Tasigna (nilotinib) is indicated for the treatment of chronic phase and accelerated phase 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."

The risks associated with nilotinib use are acceptable given the benefits demonstrated in CML-AP and CML-CP patients who are intolerant or resistant to prior therapy including imatinib.

I agree with the proposed post-marketing commitments as described above.

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/s/

Ramzi Dagher
10/24/2007 09:45:46 AM
MEDICAL OFFICER