

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-068

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	October 26, 2007
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # Supp #	22-068
Proprietary / Established (USAN) Names	Tasigna® (nilotinib) Capsules
Dosage Forms / Strength	200 mg hard capsules
Proposed Indication(s)	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.
Action:	<i>Approval</i>

1. Introduction to Review

This new drug application seeks approval of Tasigna 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.

This review will summarize the recommendations of the reviewers and consultants and the resolution of notable issues.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

The efficacy and safety data come from a single, large, open label, multicenter, single-arm study in patients with imatinib-resistant or -intolerant CML. The study included separate cohorts of patients with chronic and accelerated phase disease. The study design and primary endpoints of major cytogenetic response in chronic phase CML and hematologic response in accelerated phase CML were used to support the approval of two other tyrosine kinase inhibitors, imatinib and dasatinib, for the treatment of this disease. The primary safety concerns of QT prolongation and unexplained sudden deaths are discussed further below.

During the review period nilotinib was approved by Switzerland and was given a positive opinion by the EMEA.

3. CMC/Microbiology/Device

The Chemistry Review of 8/30/07 recommended approval. No Phase 4 commitments were recommended. However the review did include a list of comments and deficiencies which were communicated to the applicant. The applicant's responses to these deficiencies were reviewed in the Branch Chief's Memo of 10/10/07 and were found to be adequate. The ONDQA Division Director's Memo of 10/23/07 recommended approval from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation of 8/21/07 stated that the application was approvable pending labeling recommendations. No additional non-clinical studies were requested. The following conclusion from the review summarizes the non-clinical data:

The non-clinical studies of AMN107 (nilotinib) identified the target organs/tissues of toxicity to be liver, bile duct, gall bladder, kidney, heart, lung, spleen, thyroid and pancreas. AMN107 demonstrated potentially pro-arrhythmic, as evidenced by inhibition of hERG current, prolongation of APD, and induction of triangulation and beat-to-beat variability in the in vitro assay systems. It is not mutagenic or clastogenic; but is of teratogenic potential because it induced dose-dependent fetal toxicities in rats. AMN107 is both an inducer and inhibitor of CYP isoenzymes.

The applicant has accepted the pharmacology/toxicology labeling recommendations.

The tertiary review of 10/24/07 agreed with the primary reviewer's conclusions and with the wording of the non-clinical sections of the package insert.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 7/9/07 stated that the NDA is acceptable from a clinical pharmacology perspective but recommended the following Phase 4 commitments:

1. Submit the completed report and datasets for the hepatic impairment study.
2. Submit the completed report and datasets for the absolute bioavailability study.
3. Given the fact that nilotinib is both an inhibitor and an inducer of CYP2C8, CYP2C9 and CYP3A4, and that the currently completed DDI study with midazolam only used a single dose of nilotinib, we recommend a phase 4 commitment for the sponsor to conduct clinical studies to evaluate if multiple dose of nilotinib alter the metabolism of a sensitive CYP2C9 substrate (for

example, S-warfarin). If significant interaction was demonstrated, additional clinical studies to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C8 substrate (for example, repaglinide) and/or a sensitive CYP3A4 substrate (for example, midazolam) may be needed.

4. Given the fact that nilotinib has pH dependent solubility, we recommend a phase 4 commitment for the sponsor to conduct clinical studies to evaluate if antacids and H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib.

The review had the following additional comments to be conveyed to the applicant:

1. Since the in vitro studies suggest that nilotinib is an inhibitor and a substrate for P-glycoprotein, you may wish to consider conducting an in vivo drug interaction study with a P-glycoprotein substrate (for example, digoxin) and an in vivo drug interaction study with a P-glycoprotein inhibitor.
2. Since the in vitro data demonstrated that nilotinib is an inducer of CYP2B6, you may wish to consider conducting clinical studies to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2B6 substrate (for example, efavirenz).

5.1. General Clinical Pharmacology/Biopharmaceutics

The following information is excerpted from the agreed-upon label:

Mechanism of Action: Nilotinib is an inhibitor of the Bcr-Abl kinase. Nilotinib binds to and stabilizes the inactive conformation of the kinase domain of Abl protein. *In vitro*, nilotinib inhibited Bcr-Abl mediated proliferation of murine leukemic cell lines and human cell lines derived from Ph⁺ CML patients. Under the conditions of the assays, nilotinib was able to overcome imatinib resistance resulting from Bcr-Abl kinase mutations, in 32 out of 33 mutations tested. *In vivo*, nilotinib reduced the tumor size in a murine Bcr-Abl xenograft model.

Peak concentrations of nilotinib are reached 3 hours after oral administration. Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily serum exposure to nilotinib of 400 mg twice daily dosing at steady state was 35% higher than with 800 mg once daily dosing. There was no relevant increase in exposure to nilotinib when the dose was increased with 400 mg twice daily to 600 mg twice daily. The bioavailability of nilotinib was increased when given with a meal. Compared to the fasted state, the systemic exposure (AUC) increased by 82% when the dose was given 30 minutes after a high fat meal.

The apparent elimination half-life estimated from the multiple dose pharmacokinetic studies with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib AUC was 32 to 64%. Steady state conditions

were achieved by day 8. An increase in serum exposure to nilotinib between the first dose and steady state was approximately 2-fold for daily dosing and 3.8-fold for twice-daily dosing.

5.2. Drug-drug Interactions

Nilotinib is a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1 in vitro, potentially increasing the concentrations of drugs eliminated by these enzymes. Single-dose administration of Tasigna with midazolam (a CYP3A substrate) to healthy subjects increased midazolam exposure by 30%.

In vitro studies also suggest that nilotinib may induce CYP2B6, CYP2C8 and CYP2C9, and thereby has the potential to decrease the concentrations of drugs which are eliminated by these enzymes.

Nilotinib undergoes metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 can increase or decrease nilotinib concentrations significantly. In healthy subjects receiving ketoconazole, a CYP3A4 inhibitor, at 400 mg once daily for 6 days, systemic exposure (AUC) to nilotinib was increased approximately 3-fold. In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

Nilotinib inhibits human P-glycoprotein. If Tasigna is administered with drugs that are substrates of Pgp, increased concentrations of the substrate drug are likely. Nilotinib is also a substrate of the efflux transporter P-glycoprotein (Pgp, ABCB1). If Tasigna is administered with drugs that inhibit Pgp, increased concentrations of nilotinib are likely.

5.3. Pathway of Elimination

The main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum. None of the metabolites contribute significantly to the pharmacological activity of nilotinib. After a single dose of radiolabeled nilotinib in healthy subjects, more than 90% of the administered dose was eliminated within 7 days mainly in feces (93% of the dose). Parent drug accounted for 69% of the dose. Tasigna has not been studied in patients with impaired renal or hepatic function.

5.4. Demographic Interactions/Special Populations

Age, body weight, gender, or ethnic origin did not significantly affect the pharmacokinetics of nilotinib.

5.5. Thorough QT study or other QT assessment

The results of a dedicated QT study are summarized in the following excerpt from the draft package insert:

In a placebo controlled study in healthy volunteers designed to assess the effects of Tasigna on the QT interval, administration of Tasigna was associated with concentration-dependent QT prolongation; the maximum mean placebo-adjusted QTcF change from baseline was 18 msec (1-sided 95% Upper CI: 26 msec). A positive control was not included in the QT study of healthy volunteers. Peak plasma concentrations in the QT study were 26% lower than those observed in patients enrolled in the single-arm study.

A consultation was requested from the Interdisciplinary Team for QT Studies regarding the dedicated QT study and the reports of unexplained sudden deaths. The 8/16/07 consultation made the following comments:

1. This reviewer was unable to determine the actual total number of patients who have been exposed to nilotinib or the total exposure (i.e., dose x duration). Hence trying to determine a meaningful rate of sudden death is not possible. Sudden death is not unexpected in an older population with serious underlying disease.
2. Novartis has not conducted any controlled studies of nilotinib so contemporary randomized controls for comparison are not available.
3. The actual mode of death is unclear for all of these patients so the question of whether QT prolongation due to nilotinib played a role can not be answered definitively.
4. Nonetheless in three of the cases the timing and circumstances suggest that nilotinib administration may have been related to death. These three are
 - 0303/01001, an older female left ventricular dysfunction and hypokalemia, whose demonstrated prolonged QTc on the second day of nilotinib therapy and then died on day 7, which is approximately the time of Cmax was reached.
 - 0514/00015, an older female with abnormal baseline ECG co-administered fluconazole (a QT prolonger as well as a CYP3A4 inhibitor) who died on day 5, which is approximately the time the new Cmax was attained.
 - PHHO2007DE05370, an older female who was co-administered moxifloxacin (a QT-prolonger), and then died eight days later.

These three cases suggest a concentration dependent relation of nilotinib to sudden death.

5. The causes of sudden death are many and none of these the deaths may be due to prolongation of the QT interval by nilotinib. Therefore, measures taken to minimize or mitigate QT prolongation may not affect the rate of sudden death, if related, after nilotinib administration.

Comment: Because of the unexplained sudden deaths and the potential for QT prolongation with nilotinib, the following boxed warning is included in the package insert:

WARNING: QT PROLONGATION AND SUDDEN DEATHS

Tasigna prolongs the QT interval (5.2). Sudden deaths have been reported in patients receiving nilotinib (5.3). Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome (4). Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored (5.2). Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided (5.7). Patients should avoid food 2 hours before and 1 hour after taking dose (5.8). Use with caution in patients with hepatic impairment (5.9). ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments (5.2, 5.3, 5.6, 5.12).

5.6. Notable Issues

In addition to the boxed warning, an education-based Risk-MAP was proposed (see section 13.3).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical

7.1. General Discussion

The clinical program consists of a single, multicenter, open-label trial as described below. For this reason, the Clinical Review is a joint clinical and statistical review. The study design and efficacy endpoints have been used in the approvals of imatinib and dasatinib for the treatment of CML.

7.2. Efficacy

7.2.1. Dose identification/selection and limitations

The dose of 400 mg b.i.d. is based on the results of a phase 1 trial that identified the MTD as 600 mg b.i.d.

7.2.2. Phase 3/essential clinical studies, including design, analytic features, and results

The design and efficacy results of the essential clinical study are summarized below in the following excerpt from the final agreed-upon draft labeling:

A single open label multicenter study was conducted to evaluate the efficacy and safety of Tasigna in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic and accelerated phase disease. The definition of imatinib resistance included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance was defined as discontinuation of treatment due to toxicity and lack of a major cytogenetic response at time of study entry. At the time of data cut-off, 280 CML-CP patients with a minimum follow-up of 6 months and 105 CML-AP patients with a minimum follow-up of 4 months were enrolled. Of these, 232 CML-CP and all CML-AP patients were evaluable for efficacy. In this study, about 50% of CML-CP and CML-AP patients were males, over 80% were Caucasian, and approximately 30% were age 65 years or older.

Overall, 73% of patients were imatinib resistant while 27% were imatinib-intolerant. The median time of prior imatinib treatment was approximately 31 months. Prior therapy included hydroxyurea in 85% of patients, interferon in 62% and stem cell or bone marrow transplant in 8%. The median highest prior imatinib dose was 600 mg/day for CML-CP patients and 800 mg/day for CML-AP patients, and the highest prior imatinib dose was ≥ 600 mg/day in 77% of all patients with 44% of patients receiving imatinib doses ≥ 800 mg/day.

Median duration of nilotinib treatment was 8.7 months in CML-CP patients and 5.6 months in CML-AP patients.

The efficacy endpoint in chronic phase CML was unconfirmed major cytogenetic response (MCyR) which included complete and partial cytogenetic responses.

The efficacy endpoint in accelerated phase CML was confirmed hematologic response (HR), defined as either a complete hematologic response (CHR) or no evidence of leukemia (NEL). The rates of response for CML-CP and CML-AP patients are reported in Table 6.

Table 6 Efficacy of Tasigna in CML

Cytogenetic Response Rate (Unconfirmed) (%)^a	Chronic Phase n=232
Major (95%CI)	40% (33,46)
Complete (95% CI)	28% (22,34)
Partial (95% CI)	12% (8,16)
	Accelerated Phase n=105
Hematologic Response Rate (95%CI)^b	26% (18,35)
Complete Hematologic Response Rate (95% CI)	18% (11,27)
No evidence of Leukemia (95% CI)	8% (3,15)

^a Cytogenetic response criteria: Complete (0% Ph + metaphases) or partial (1-35%). Cytogenetic responses were based on the percentage of Ph-positive metaphases among ≥ 20 metaphase cells in each bone marrow sample.

^b Hematologic response = CHR + NEL (all responses confirmed after 4 weeks).

CHR (CML-CP): WBC $< 10 \times 10^9$ /L, platelets $< 450,000/\text{mm}^3$, no blasts or promyelocytes in peripheral blood, $< 5\%$ myelocytes + metamyelocytes in bone marrow, $< 20\%$ basophils in peripheral blood, and no extramedullary involvement.

CHR (CML-AP): neutrophils $\geq 1.5 \times 10^9$ /L, platelets $\geq 100 \times 10^9$ /L, no myeloblasts in peripheral blood, myeloblasts $< 5\%$ in bone marrow, and no extramedullary involvement.

NEL: same criteria as for CHR but neutrophils $\geq 1.0 \times 10^9$ /L and platelets $\geq 20 \times 10^9$ /L without transfusions or bleeding.

The median duration of response has not been reached for CML-CP and CML-AP. Based on current follow-up, 59% of CML-CP patients with a major cytogenetic response had a duration of response of at least 6 months. Based on current follow-up, 63% of CML-AP patients with a confirmed hematologic response had a duration of response of at least 6 months.

After imatinib failure, 24 different BCR-ABL mutations were noted in 19% of chronic phase and 25% of accelerated phase CML patients who were evaluated for mutations. Patients harbouring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I, responded to Tasigna.

7.2.3. Other efficacy studies

Not applicable.

7.2.4. Discussion of primary and secondary reviewers' comments and conclusions

The Clinical Review made the following recommendation on regulatory action:

The reviewers recommend subpart H (accelerated) approval of nilotinib for use in the treatment of adults with chronic phase (CML-CP) and accelerated phase (CML-AP) chronic myeloid leukemia (CML) patients with resistance or intolerance to prior therapy including imatinib mesylate.

Patients with CML that is resistant to imatinib or who can not tolerate imatinib have limited therapeutic options, although dasatinib has also received accelerated approval for these indications. The clinical data presented in the NDA provide substantial evidence of effectiveness of nilotinib in the form of hematologic responses in the CML-AP population and cytogenetic responses in the CML-CP population which appear to be durable. Final characterization of this durability will require a longer follow-up period. This follow-up data could potentially be the basis for regular approval. The safety profile of dasatinib is acceptable, given the serious life-threatening nature of these disease entities. Since nilotinib prolongs the QT interval and has resulted in sudden deaths, the reviewers recommend a black box warning regarding sudden deaths and QT interval prolongation to be included in the label and the applicant has agreed to a black box warning.

The review recommended the following risk management activity:

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. A black box warning describing the risk of sudden death and QT interval prolongation will be included in the label. Drug-drug interactions are seen with nilotinib and will be described in the labeling. The applicant will conduct post-marketing pharmacovigilance activities to evaluate safety signals associated with nilotinib including QT interval prolongation.

The review recommended the following phase 4 commitment under subpart H:

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.

The review also concurred with the clinical pharmacology recommendations for Phase 4 studies.

The medical team leader/CDTL memo provided the following 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.

7.2.5. Pediatric use/PREA waivers/deferrals

Not applicable. Tasigna has orphan drug exclusivity.

7.2.6. Notable issues

There are no unresolved efficacy issues.

7.3. Safety

7.3.1. General safety considerations

The safety database consists of 438 patients and is adequate for this indication.

7.3.2. Safety findings from submitted clinical trials

The safety data are summarized in the following excerpt from the agreed-upon package insert:

In the single open-label multicenter clinical trial, a total of 438 patients were treated (CML-CP=318; CML-AP=120).

The median duration of exposure in days for CML-CP and CML-AP patients is 245 (range 1-502) and 138 (range 2-503), respectively. The

median dose intensity of 797 mg/day (range 145 – 1149) was similar for both the chronic and accelerated phase patients and corresponded to the planned 400 mg twice daily dosing.

The median cumulative duration in days of dose interruptions for the CML-CP patients was 18 (range 1-185), and the median duration in days of dose interruptions for the CML-AP patients was 22 (range 1 – 163).

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.

There were five sudden deaths reported in patients receiving nilotinib in an on-going study (n=867; 0.6%). A similar incidence was also reported in the expanded access program. The relative early occurrence of some of these deaths relative to the initiation of nilotinib suggests the possibility that ventricular repolarization abnormalities may have contributed to their occurrence.

Discontinuation for drug related adverse reactions was observed in 11% of CML-CP and 8% of CML-AP patients.

Table 4 shows the percentage of patients experiencing treatment-emergent adverse reactions (excluding laboratory abnormalities) regardless of relationship to study drug. Adverse reactions reported in at least 10% of patients who received at least one dose of Tasigna are listed.

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Table 4 Treatment-emergent Adverse Reactions Reported in $\geq 10\%$ of Patients in the Clinical Study^a

Body System and preferred term		CML-CP n=318		CML-AP n=120	
		All Grades (%)	CTC Grades ^b 3/4 (%)	All Grades (%)	CTC Grades ^b 3/4 (%)
Skin and subcutaneous tissue disorders:	Rash	33	2	28	0
	Pruritus	29	1	20	0
Gastrointestinal disorders:	Nausea	31	1	18	<1
	Diarrhea	22	3	19	2
	Constipation	21	<1	18	0
	Vomiting	21	<1	10	0
	Abdominal pain	11	1	13	3
Nervous system disorders	Headache	31	3	21	2
General disorders and administration site conditions	Fatigue	28	1	16	<1
	Pyrexia	14	1	24	2
	Asthenia	14	0	12	2
	Edema, peripheral	11	0	11	0
Musculoskeletal and connective tissue disorders	Arthralgia	18	2	16	0
	Myalgia	14	2	14	<1
	Pain in extremity	13	1	16	2
	Bone pain	11	<1	13	<1
	Muscle spasms	11	<1	14	0
	Back pain	10	<1	12	<1
Respiratory, thoracic and mediastinal disorders	Cough	17	<1	13	0
	Dyspnea	11	1	8	3
Infections and infestations	Nasopharyngitis	16	<1	11	0

^a Excluding laboratory abnormalities

^b NCI Common Terminology Criteria for Adverse Events, Version 3.0

Table 5 shows the percentage of patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna.

Table 5 Incidence of Clinically Relevant Grade 3/4 Laboratory Abnormalities

	CML-CP N=318	CML-AP N=120
	Grades 3/4 *	Grades 3/4 *
Hematologic Parameters		
-Thrombocytopenia	28% ¹	37% ²
-Neutropenia ²	28%	37% ³
-Anemia	8%	23%
Biochemistry Parameters		
-Elevated lipase	15%	17%
-Hyperglycemia	11%	4%
-Hypophosphatemia	10%	10%
-Elevated Bilirubin (total)	9%	10%
-Elevated SGPT (ALT)	4%	2%
-Hyperkalemia	4%	3%
-Hyponatremia	3%	3%
-Hypokalemia	1%	5%
-Elevated SGOT (AST)	1%	1%
-Decreased albumin	1%	1%
-Hypocalcemia	1%	4%
-Elevated alkaline phosphatase	1%	3%
-Elevated creatinine	<1%	0%

*NCI Common Terminology Criteria for Adverse Events, version 3.0

¹CML-CP: Thrombocytopenia: 11% were grade 3, 17% were grade 4

²CML-AP: Thrombocytopenia: 7% were grade 3, 30% were grade 4

³CML-AP: Neutropenia: 12% were grade 3, 25% were grade 4

7.3.3. Safety update

The safety update did not identify any new safety signals.

7.3.4. Immunogenicity, where pertinent

Not applicable.

7.3.5. Special safety concerns

The potential for QTc prolongation and the unexplained sudden deaths were discussed in sections 5.5 and 7.3.2 above.

7.3.6. Discussion of primary and secondary reviewers' comments and conclusions

The reviewer's comments and conclusions are discussed in section 7.2.4 above.

7.3.7. Notable issues

See section 5.5 for discussion of QTc prolongation and unexplained sudden deaths. The package insert and Medguide address the precautions to be taken.

8. Advisory Committee Meeting

This application was not taken to the Oncologic Drugs Advisory Committee (ODAC) because 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.

9. Other Regulatory Issues

None.

10. Financial Disclosure

Financial disclosure was provided and was discussed in the Clinical Review and the CDTL Memo.

11. Labeling

11.1. Proprietary name

DMETS found the proprietary name to be acceptable.

11.2. Physician labeling

The major issue during the labeling negotiations was the inclusion of the boxed warning concerning QTc prolongation and sudden deaths. The applicant has agreed to the wording discussed in 5.5 and 7.3.2 above.

11.3. Patient labeling/Medication guide

Agreement has been reached on a medication guide.

12. DSI Audits

The following sites were inspected:

Name of CI and site #, if known	City, State*	Country	Insp. Date	EIR Received Date	Final Classification
J. Pinilla-Ibarz (502)	Tampa, FL		26 Mar 07	25 Apr 07	Pending
H. Kantarjian (501)	Houston, TX		14 Mar 07	4 Apr 07	Pending
P. LeCoutre (304)	Berlin	Germany	16 Apr 07	Pending	Pending
Ottman & Wolfgang	Frankfurt	Germany	16 Apr 07	Pending	Pending
Novartis	E. Hanover NJ		9 Jul 07	Pending	Pending

The Clinical Inspection Summary of 7/16/07 stated that no significant problems were found at the clinical sites or at the sponsor.

13. Conclusions and Recommendations

13.1. Regulatory action

I concur with the review team's recommendation that this application should be approved. The applicant has demonstrated that Tasigna is effective in the treatment of chronic phase and accelerated phase CML in patients whose disease is refractory to therapy that included imatinib or who do not tolerate imatinib. The safety profile of Tasigna is generally acceptable for this indication, although the potential for QTc prolongation and sudden death is a concern. This safety concern will be addressed by the package insert, which includes a boxed warning, the Medguide, a RiskMAP, and enhanced post-marketing reporting.

I also concur with the required subpart H postmarketing commitment and with the clinical pharmacology postmarketing study commitments.

13.2. Safety concerns to be followed postmarketing

QTc prolongation (see above).

13.3. Risk Minimization Action Plan

13.3.1. General considerations on the need for, and goals of, any RiskMAP beyond standard labeling and pharmacovigilance

The applicant proposed a RiskMAP to minimize the risks of QTc prolongation. The OSE summary and assessment of the RiskMAP are quoted below:

...The Sponsor proposes an education-based RiskMAP, in addition to labeling, to minimize the risks of QTc prolongation, drug-drug interactions, and food effects (i.e., food-drug interactions).

The stated goal for the Tassigna RiskMAP is to ensure that important information on the proper use and safety profile of Tassigna is appropriately communicated to healthcare professionals and patients.

We agree with the scope and tools of the RiskMAP. Issues remaining to be resolved to allow final acceptance of the RiskMAP include:

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13.3.2. Important issues

The applicant has agreed to the following phase 4 commitment regarding the RiskMAP:

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.

Submission: by November 30, 2007

The applicant also agreed that in addition to the usual postmarketing reporting of adverse drug experiences (21 CFR 314.80(c)), it will initiate a 15-day Alert report and follow-up for each of the following:

1. Medication errors involving dosing outside of the Tassigna (nilotinib) labeled recommendations including, but 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)
2. QTc prolongation. These reports will include information and follow-up as to whether the event was the result of a medication error (e.g., dosing with food, dosing outside of the 12 hr frequency, etc).

13.4. Postmarketing studies

13.4.1. Required studies

The applicant has agreed to the following subpart H postmarketing study commitment:

To submit the complete study report (with at least 24 months follow-up of all patients) and data from study 2101, a phase 2 multicenter study of nilotinib in patients with imatinib resistant or intolerant chronic myeloid leukemia in chronic and accelerated phases respectively (arms 4 & 3, respectively).

Protocol Submission:	Study 2101 filed to IND 69,764 in April 2004 (SN 000)
Study Start:	May 2004
Final Report Submission:	by August 2010

13.4.2. Commitments (PMCs)

The applicant has also agreed to the following postmarketing study commitments:

2. Submit the completed study report and datasets for the hepatic impairment study.

Protocol Submission:	Study 2116 filed to IND 69,764 on 10/9/06 (SN 326)
Study Start:	October 2006
Final Report Submission:	by June 2008

3. Conduct a relative bioavailability study (using a liquid formulation as the reference).

Protocol Submission:	by August 2009
Study Start:	by November 2009
Final Report Submission:	by July 2010

4. Conduct a clinical study or studies to evaluate whether multiple doses of nilotinib alter the metabolism of a sensitive CYP2C9 substrate (for example, S-warfarin). If a significant interaction is demonstrated, additional clinical studies may be needed to evaluate whether multiple doses of nilotinib alter the metabolism of a sensitive CYP2C8 substrate (for example, repaglinide) and/or a sensitive CYP3A4 substrate (for example, midazolam).

Protocol Submission: by July 2008
Study Start: by September 2008
Final Report Submission: by June 2009

5. Conduct a clinical study to evaluate if H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib.

Protocol Submission: by July 2008
Study Start: by September 2008
Final Report Submission: by June 2009

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/s/

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