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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 12-81907- -4	**FECHA**: 2014-01-24 11:04:31
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	**EVE:** 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	**FOLIOS**: 5
ACT: 519 PRESENTACION	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
CARLOS REINALDO OLARTE GARCIA

Asunto: Radicación: 12-81907- -4
Trámite: 11
Evento: 378
Actuación: 519
Oficio: 666
Folios: 5

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/US2010/056926				
Fecha de Presentación Internacional	17/11/2010				

1. Documentos estudiados

Descripción:	Radicación 12-081907-00000	17/Mayo/2012
Reivindicaciones:	Radicación 12-081907-00000	17/Mayo/2012
Prioridad(es):	US 61/261812	17/Noviembre/2009

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque su contenido técnico corresponde con el de la prioridad reivindicada (Art. 9 D 486) y fue presentada dentro del plazo establecido por la D. 486.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Título X de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En el presente caso se estudiarán las reivindicaciones 1 a 10 del capítulo reivindicatorio.

Título de la solicitud: “Método para el tratamiento de trastornos proliferativos y otras condiciones patológicas mediadas por la actividad de cinasa de BCR-ABL, C-KIT,

DDR-1, DDR-2 o PDGF-R".

El problema planteado en esta solicitud consiste en proporcionar una forma de dosificación alternativa que permita administrar el fármaco nilotinib a pacientes pediátricos y geriátricos con dificultad para tragar una capsula dura.

Para resolver este problema técnico la solicitud en estudio proporciona una forma de dosificación para administración oral de nilotinib que comprende el fármaco dispersado en una preparación de fruta.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K31/506, A61K9/00, A61P35/00.

4. Excepción a la Patentabilidad (Art 20 D 486 literal d))

Las reivindicaciones 1 a 8 definen un método de tratamiento de un trastorno proliferativo, materia que se encuentra exceptuada de patentabilidad de acuerdo con el art. 20 lit d) D 486.

La reivindicación 9 aunque está encabezada como un paquete comercial no corresponde a una unidad funcional conformada por componentes que provienen de preparaciones individuales (kit de partes), por lo que se entiende como un método de tratamiento, ya que únicamente se caracteriza por la forma de preparación de los compuestos de fórmula I para su administración. No obstante, la reivindicación corresponde a un método de tratamiento se realizará la determinación del estado de la técnica para los compuestos de fórmula I.

5. Reivindicaciones relativas a un uso (Art 14 D 486)

La reivindicación 10 aunque está encabezada como un compuesto pirimidil-amino-benzamida de fórmula I hace referencia al uso de los compuestos de fórmula I en tratamiento de un trastorno proliferativo. El uso no es una categoría inventiva de acuerdo con el art 14 D 486, por lo que se sugiere retirarla del capítulo reivindicatorio.

6. De la solicitud de patente

Titulo

El título no corresponde con el objeto de la solicitud porque hace referencia al uso terapéutico. Se sugiere a la solicitante asignar un nuevo título a la solicitud indicando los elementos combinados.

Reivindicaciones (Art. 30 D 486)

La reivindicación 9 no es clara porque está encabezada como un paquete comercial, se sugiere a la Solicitante encabezarlo como un kit de partes si el objeto corresponde a una unidad funcional conformada por componentes que provienen de preparaciones individuales, los cuales presentan una interacción directa entre si necesaria para obtener un efecto técnico.

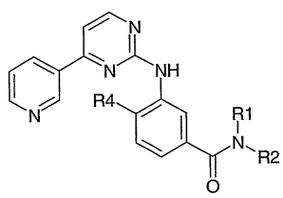
Por otra parte, se recuerda a la solicitante que el compuesto nilotinib por sí solo se encuentra comprendido en el estado de la técnica por lo que no se puede formular una reivindicación en los términos del compuesto porque esto equivale a solicitar la exclusividad nuevamente sobre la estructura molecular.

7. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación internacional: noviembre 17 de 2009 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud.

Ítem	Documento	Título	Fecha de Publicación
D1	WO2004005281	"Inhibitors of tyrosine kinases"	15/Enero/2004
D2	Hazarika, M.,et al. Clin Cancer Res 2008;14:5325-5331.	"Tasigna for Chronic and Accelerated Phase Philadelphia Chromosome Positive Chronic Myelogenous Leukemia Resistant to or Intolerant of Imatinib"	1/Septiembre/2008

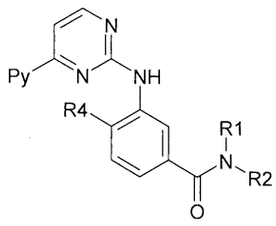
El documento D1[1] divulga compuestos de la fórmula I inhibidores de tirosina quinasas tales como Abl, Bcr-Abl, PDGF-R y c-kit útiles en el tratamiento de enfermedades neoplásicas (Pág. 1, Párr. [001] a Pág. 3, Párr. [003]). D1 divulga específicamente el compuesto nilotinib (4-metil-3-[[4-(3-piridinil)-2-pirimidinil]-amino]-N-[5-(4-metil-1H-imidazol-1-il)-3-(trifluoro-metil)fenil]benzamida) (Pág. 21 a 23)



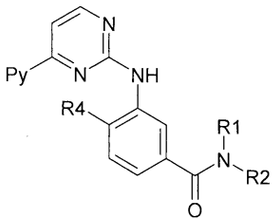
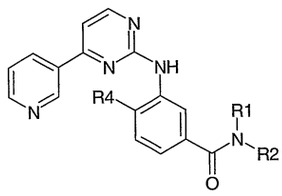
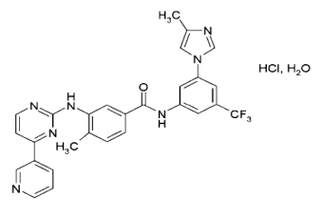
El documento D2[2] divulga un estudio clínico de los datos preclínicos y clínicos de seguridad y eficacia del compuesto nilotinib en el tratamiento de leucemia mieloide crónica en fase crónica o acelerada resistente o intolerante a imatinib (abstract). D2 revela los parámetros farmacocinéticos del nilotinib administrado por vía oral con un incremento en la biodisponibilidad por administración concomitante con una comida comparado con la administración en ayunas, observándose un incremento del 82% en el AUC cuando el nilotinib se administra 30 min después de una comida alta en grasa (Pág. 5326, Col. 2 a Pág. 5327, Col. 2).

La reivindicación 9 consiste en un paquete comercial que contiene una pirimidil-amino-benzamida de la fórmula I en donde (a) Py denota 3-piridilo…(Rad. No. 12-081907-00000 de 17/Mayo/2012)

1 http://worldwide.espacenet.com/publicationDetails/biblio?CC=WO&NR=2004005281A1&KC=A1&FT=D&ND=3&date=20040115&DB=worldwide.espacenet.com&locale=en_EP
2 http://clincancerres.aacrjournals.org/content/14/17/5325.full.pdf



(I)

Características esenciales	D1	D2
un paquete comercial que contiene:	Compuestos de la fórmula I inhibidores de tirosina quinasas tales como Abl, Bcr-Abl, PDGF-R y c-kit útiles en el tratamiento de enfermedades neoplásicas (Pág. 1, Párr. [001] a Pág. 3, Párr. [003]).	Compuesto nilotinib en el tratamiento de leucemia mieloide crónica en fase crónica o acelerada resistente o intolerante a imatinib (abstract).
contiene una pirimidil-amino-benzamida de la fórmula I  (I) en donde (a) Py denota 3-piridilo…(Rad. No. 12-081907-00000)	 El compuesto nilotinib (4-metil-3-[[4-(3-piridinil)-2-pirimidinil]-amino]-N-[5-(4-metil-1H-imidazol-1-il)-3-(trifluoro-metil)fenil]benzamida) (Pág. 21 a 23)	
Junto con instrucciones para dispersar el compuesto de la fórmula (I) o una sal farmacéuticamente aceptable del mismo en una preparación de fruta.	No menciona	Administrado por vía oral concomitantemente con una comida incrementa la biodisponibilidad comparado con la administración en ayunas, observando un incremento del 82% en el AUC cuando el fármaco se administra 30 min después de una comida alta en grasa (Pág. 5326, Col. 2 a Pág. 5327, Col. 2).

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2014-01-28

Elaboró: John Fredy Hernandez MontaÑo
Revisó: Gloria Jacqueline Alfonso Rozo
Revisó: Jose Luis Salazar Lopez

Clinical Cancer Research

Tasigna for Chronic and Accelerated Phase Philadelphia Chromosome –Positive Chronic Myelogenous Leukemia Resistant to or Intolerant of Imatinib

Maitreyee Hazarika, Xiaoping Jiang, Qi Liu, et al.

Clin Cancer Res 2008;14:5325-5331.

Updated version	Access the most recent version of this article at: http://clincancerres.aacrjournals.org/content/14/17/5325

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Tasigna for Chronic and Accelerated Phase Philadelphia Chromosome–Positive Chronic Myelogenous Leukemia Resistant to or Intolerant of Imatinib

Maitreyee Hazarika,[1] Xiaoping Jiang,[2] Qi Liu,[3] Shwu-Luan Lee,[1] Roshni Ramchandani,[3] Christine Garnett,[3] Micheal S. Orr,[3] Rajeshwari Sridhara,[2] Brian Booth,[3] John K. Leighton,[1] William Timmer,[4] Ravi Harapanhalli,[4] Ramzi Dagher,[1] Robert Justice,[1] and Richard Pazdur[1]

Abstract

Purpose: This Food and Drug Administration (FDA) approval report describes the data and analyses leading to the approval by the FDA of nilotinib (Tasigna, AMN-107; Novartis Pharmaceuticals Corporation), an inhibitor of Bcr-Abl tyrosine kinase, for the treatment of chronic-phase (CP) and accelerated-phase (AP) chronic myelogenous leukemia (CML) resistant to or intolerant of imatinib.

Experimental Design: The FDA approval of the efficacy and safety of nilotinib was based on the results of an ongoing single-arm, open-label, phase 2 clinical trial. The primary end point for CML-CP was unconfirmed major cytogenetic response. The efficacy end point for CML-AP was confirmed hematologic response.

Results: The major cytogenetic response rate in 232 evaluable CP patients was 40% (95% confidence interval, 33%, 46%). The hematologic response rate in 105 evaluable AP patients was 26% (95% confidence interval, 18%, 35%). The median duration of response has not been reached for both CML-CP and CML-AP responding patients. In CML-CP patients, the common serious drug-related adverse reactions were thrombocytopenia and neutropenia. In CML-AP patients, 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; these risks and appropriate risk minimization strategies are described in a boxed warning on the labeling.

Conclusions: On October 29, 2007, the U.S. FDA granted accelerated approval to nilotinib (Tasigna) for use in the treatment of CP and AP Philadelphia chromosome positive CML in adult patients resistant to or intolerant of prior therapy that included imatinib.

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder of the hematopoietic stem cell. CML accounts for 15% of cases of leukemia in adults. The median age of patients with CML is 67 years, but for patients enrolled in clinical studies, a median age of 50 to 60 years is reported. It is estimated that 4,570 new patients (2,570 men and 2,000 women) will be diagnosed with and 490 patients will die of chronic myeloid leukemia in 2007.[5]

CML has a triphasic clinical course: an initial indolent chronic phase (CP), which is present at the time of diagnosis in ~85% of patients with a median duration of 3 to 5 years; an accelerated phase (AP) lasting 6 to 18 months, in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with myelosuppressive medications; and a terminal blast crisis (BC), a condition resembling acute leukemia lasting 3 to 6 months in which myeloid or lymphoid blasts fail to differentiate.

CML is characterized by the Philadelphia chromosome (Ph), which represents a reciprocal translocation between the long arms of chromosomes 9 and 22, t (9; 22) (q34; q11) which forms and creates a novel fusion gene Bcr-Abl. The Ph links the Bcr of chromosome 22 with the Abl proto-oncogene of chromosome 9. The normal Abl gene product is a tightly regulated tyrosine kinase involved in cell division and apoptosis. The Bcr-Abl fusion gene product is a constitutively active tyrosine kinase, the

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Received 2/5/08; revised 4/10/08; accepted 4/27/08.

Note: Full prescribing information is available at http://www.fda.gov/cder/foi/label/2007/022068lbl.pdf.

Requests for reprints: Ramzi Dagher, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Building 22, Room 2389, Silver Spring, MD 20993. E-mail: ramzi.dagher@fda.hhs.gov.
doi:10.1158/1078-0432.CCR-08-0308

[5] Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, et al. *SEER Cancer Statistics Review, 1975 to 2004*, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975.2004/, based on November 2006 SEER data. submission, posted to the SEER website, 2007.

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presence of which seems sufficient to induce leukemia in both experimental animals and humans (1, 2).

Imatinib resistance can be defined as lack of a complete hematologic response in patients with CP-CML or as a failure to return to CP for patients with CML in AP or BC. The majority of patients with imatinib-resistant CML have secondary Bcr-Abl mutations that either impair the ability of the kinase to adopt the closed conformation to which imatinib binds or directly interfere with drug binding. Drug resistance is associated with the reactivation of BCR-ABL signal transduction (3–6).

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 after failure of IFN (7). This approval was based on cytogenetic and hematologic responses in three non-randomized, single-arm trials including a total of 1,027 patients with CML. Follow-up data from those studies led to the conversion of imatinib from accelerated to regular approval in 2003 (7–9). In 2002, imatinib mesylate was approved for the treatment of newly diagnosed adult patients with Ph+ CML in chronic phase. Treatment options for patients with imatinib resistance are limited. Higher doses of imatinib mesylate are reported to overcome disease-poor responses to conventional doses in patients who relapse or are resistant to the recommended approved doses of imatinib (10).

Dasatinib (Sprycel) received accelerated approval in 2006 for the treatment of patients with imatinib-resistant CML-CP, CML-AP, and CML-BC, and received regular approval for patients with Ph+ ALL (11). Accelerated approval for CML-CP, CML-AP, and CML-BC was based on cytogenetic and hematologic responses in four single-arm phase 2 studies, and one randomized phase 2 study.

Nilotinib (Tasigna, AMN-107; Novartis Corporation) is a multiprotein kinase inhibitor, targeting the Bcr-Abl fusion protein, c-Kit and PDGFRα (platelet-derived growth factor receptor), and PDGFRβ (12, 13). As shown by X-ray crystallographic data of nilotinib with unphosphorylated human Abl kinase, nilotinib stabilized the inactive configuration of the kinase by binding between the NH_2- and COOH-terminal lobes of the kinase domain (14). In murine (transfected with Bcr-Abl expression vectors, both wild-type and point mutant forms) and human leukemic cell lines, nilotinib showed inhibitory effects against Bcr-Abl autophosphorylation and Bcr-Abl–mediated cell proliferation. Although nilotinib has shown *in vitro* inhibitory effects toward several mutant forms commonly found in the human Ph+ leukemia (such as E255V, M351T, Q252H/R, Y253F, F317L and E355G, IC_{50} 30-400 nmol/L), it exerted no effects against mutant T315I. Orally administered nilotinib at tolerated doses reduced tumor burden in nude mouse models.

The initial investigational new drug application for nilotinib was submitted on April 24, 2004. Nilotinib received orphan drug designation on April 27, 2006. Fast track designation for the treatment of imatinib-resistant or intolerant Ph + CML was granted on March 11, 2006. The New Drug Application was submitted for review on September 28, 2006. This article summarizes the preclinical and clinical data submitted to the FDA for marketing approval for nilotinib and the FDA analyses leading to nilotinib approval.

Chemistry

The nilotinib drug substance, a monohydrate mono-hydrochloride, is a yellow powder with a molecular weight of 565.98 Da. The solubility of nilotinib in aqueous solutions decreases with increasing pH. The chemical name of nilotinib is 4-methyl-*N*-[3-(4-methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl) phenyl]-3-[4-(3-pyridinyl)-2-pyrimidinyl] amino]-benzamide, monohydrochloride, monohydrate (Fig. 1). Nilotinib capsules for oral use contain 200 mg nilotinib base, anhydrous with several inactive ingredients. The capsules contain gelatin, iron oxide (red), iron oxide (yellow), and titanium dioxide.

Toxicology

The safety assessment of nilotinib was conducted in *in vitro* and *in vivo* safety pharmacology, pivotal general toxicology (4- and 26-week rats, 4-week dog, and 39-week monkey), genetic toxicology, and reproductive and developmental toxicology (rat and rabbit) studies, and identified liver, bile duct, and gall bladder as the target organs. Minor but salient toxic effects were also noted in spleen, heart, pancreas, and thyroid.

In cardiovascular safety pharmacology studies, nilotinib was a hERG channel blocker with an IC_{50} value at 0.13 μmol/L. It also prolonged action potential duration and induced triangulation and beat-to-beat variability in isolated rabbit hearts. The coronary vasoconstrictive effect was illustrated in rabbit hearts as well as in isolated human coronary arteries. The clinical relevance of the observed changes is not clear. Neither dogs nor monkeys showed remarkable results in electrocardiography, as similarly shown in the negative telemetry test in conscious dogs. In general toxicology studies, nilotinib exhibited minimal histopathologic changes in the heart: cardiomyopathy in rats; focal mesothelial cell proliferation, coronary medial hypertrophy, and fibrosis in dogs; and slight hemorrhage in monkeys.

The hematologic findings, common in rats and monkeys but not dogs, included suppressed erythroid parameters with or without an increase in reticulocyte counts, and increased WBC counts. The latter could be likely the consequence of infection/inflammation, as evidenced by the observation of leukocyte

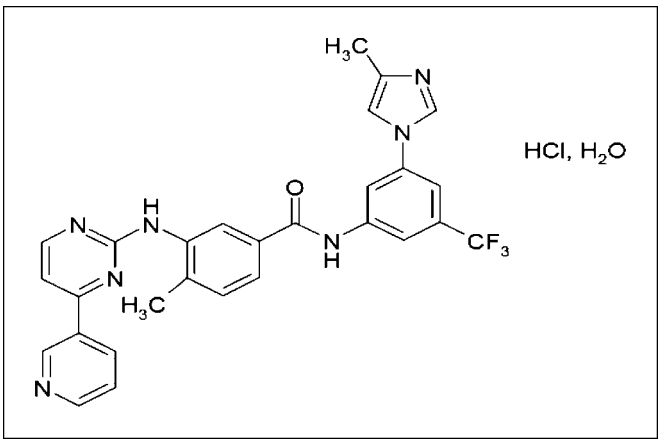

Fig. 1. Structure of nilotinib.

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infiltration in multiple organs, or secondary to the drug-effects in the lymphoid tissues, shown by findings in spleen and lymph nodes, such as lymphoid hyperplasia, fibrosis, hemorrhage, and hypocellularity. These findings may also be a result of the pharmacologic activity of nilotinib on c-Kit and PDGF receptors, which play a crucial role in normal hematopoiesis. Increased platelet counts and prolonged activated partial thromboplastin time were seen in monkeys.

Nilotinib induced prominent hepatobiliary toxicities in dogs and monkeys. These toxicities included increased levels of alanine aminotransferase, total bilirubin, cholesterol, and triglyceride, as well as gross and histopathologic findings (enlargement, discoloration, Kupffer cell hypertrophy, hyperplasia, vacuolation, proliferation and hyperplasia in bile ducts, as well as increased luminal mucus in gall bladder).

Carcinogenicity studies were not conducted with nilotinib. Nilotinib was negative in the bacterial Ames test, *in vitro* chromosomal aberration test in human peripheral lymphocytes, Comet test, and *in vivo* micronucleus test in rats. However, two impurities, as synthetic intermediates and present in small quantities in the final product, were positive in the bacterial mutagenicity test.

Nilotinib did not affect male or female fertility. Nilotinib induced dose-dependent embryo-fetal toxicities: increased resorption, postimplantation loss, as well as decreased viable fetuses and litter size. Other than uterine dilation in a 26-week study in rats, nilotinib was devoid of toxicities in male or female reproductive organs. Nilotinib was not teratogenic in either rats or rabbits.

Clinical Pharmacology

Pharmacokinetics. Peak concentrations of nilotinib are reached 3 hours after oral administration. The bioavailability of nilotinib was increased when given with a meal. Compared with the fasted state, the systemic exposure (AUC, area under the curve) 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 ~17 hours. Inter-patient variability in nilotinib AUC was 32% to 64%. Steady state conditions were achieved by day 8. 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. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice daily to 600 mg twice daily. Serum protein binding is ~98% on the basis of *in vitro* experiments. Age, body weight, gender, or ethnic origin did not significantly affect the pharmacokinetics of nilotinib.

After a single dose of radiolabeled nilotinib in healthy subjects, >90% of the administered dose was eliminated within 7 days, mainly in feces. 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 ~3-fold. In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased ~80%. Nilotinib has not been investigated in patients with hepatic impairment. Caution is recommended in patients with hepatic impairment, because nilotinib metabolism is mainly hepatic. Nilotinib is a substrate of the efflux transporter P-glycoprotein (Pgp, ABCB1). If nilotinib is administered with drugs that inhibit Pgp, increased concentrations of nilotinib are likely, and caution should be exercised.

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 nilotinib with midazolam (a CYP3A4 substrate) to healthy subjects increased midazolam exposure by 30%. Caution should be exercised when coadministering nilotinib with substrates for these enzymes that have a narrow therapeutic index. *In vitro* studies also suggest that nilotinib may induce CYP2B6, CYP2C8, and CYP2C9, and thereby has the potential to decrease the concentrations of drugs that are eliminated by these enzymes. Nilotinib inhibits human P-gp.

Pharmacogenomics. A pharmacogenetic analysis of 97 patients evaluated the polymorphisms of UGT1A1 and its potential association with hyperbilirubinemia during nilotinib treatment. In this study, the (TA)7/(TA)7 genotype was associated with a statistically significant increase in the risk of hyperbilirubinemia relative to the (TA)6/(TA)6 and (TA)6/(TA)7 genotypes for both CML-CP and CML-AP patients. In the AP arm of the phase 2 component, the relative risk was 7.3 (95% confidence interval: 1.5, 34.4) for grade 3 or greater hyperbilirubinemia. In the CP arm, the relative risk was 18 (95% confidence interval: 4.1, 78.5) for grade 3 or greater hyperbilirubinemia. For both comparisons, the results were significant at the 0.05 level (15).

Overview of Clinical Data

The source of the clinical data was a single nonrandomized phase 1/2 trial conducted by the applicant. The phase 1 component was designed to establish the maximum tolerated dose, define dose limiting toxicity, and guide dosing in the phase 2 component. The phase 2 study component, which is currently ongoing, had several cohorts of patients, some of which were the basis for the approved indications.

Phase 1 component. The phase 1 component evaluated nilotinib on an initial once-daily and later twice- daily continuous dosing regimen from 50 mg to 1,200 mg/d in 119 patients. Dose-limiting toxicities were primarily related to hematologic toxicities such as thrombocytopenia and neutropenia, hepatobiliary toxicities such as transaminase elevations, hyperbilirubinemia and increased lipases, and rash that occurred at and beyond doses 600 mg once daily. There was no further increase in exposure with the 600 mg twice-daily dose compared with the 400 mg twice-daily dose. The maximum tolerated dose was determined to be 600 mg twice daily by a two-stage modified continuous reassessment method. However, the 400 mg twice-daily dose regimen was selected for evaluation in the Phase 2 component of the study according to criteria based on safety, pharmacokinetics, and preliminary evidence of activity.

Phase 2 component. The primary efficacy end point in the CP-CML population was unconfirmed major cytogenetic response (MCyR), which included complete cytogenetic response (0% Ph+ cells) and partial response (1-35% Ph+ cells).

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The primary efficacy end point in CML-AP was confirmed overall hematologic response that included complete hematologic response (CHR), no evidence of leukemia (NEL), and return to chronic phase. For the purpose of accelerated approval, only CHR and NEL were considered as surrogates reasonably likely to predict clinical benefit. Hematologic responses had to be confirmed ≥4 weeks after the initial response was noted. The total number of patients reviewed in the submission consisted of 280 patients with CML-CP and 105 patients with CML-AP. The median duration of treatment with nilotinib in patients with CML-CP was 8.7 months and with CML-AP was 5.6 months. Nilotinib was administered orally at 400 mg twice daily not to be taken with food. The capsules were swallowed whole with water.

Efficacy results. Baseline characteristics in the CML-CP and CML-AP patients are shown in Table 1. 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.

In patients with imatinib-resistant or -intolerant CML-CP, 92 of 232 (40%) evaluable patients achieved an unconfirmed MCyR (Table 2). Results were based on bone marrow cytogenetics. There was no difference in MCyR between patients ages <65 years and those ≥65 years. Based on current follow-up, 59% of CML-CP responding patients with a MCyR had a duration of response of at least 6 months.

In patients with imatinib-resistant or -intolerant CML-AP, the confirmed hematologic response rate (CHR + NEL) was 26% (Table 2). The major hematologic response rate was 31% in patients <65 years of age and 15% in patients ≥65 years. Based on current follow-up, 63% of CML-AP responding patients with

Table 1. Baseline characteristics in CML-CP and CML-AP

Baseline characteristics	CML-CP, *n* = 280 (%)	CML-AP, *n* = 105 (%)
Age (y) category		
<65	70	69
≥65	30	31
Gender		
Male	51	54
Female	49	46
Race		
Caucasian	92	83
African American	5	7
Asian	1	8
Other	2	2
WHO performance status		
Grade 0	71	50
Grade 1	26	44
Grade 2	2	6
Missing	<1	1
Time since first diagnosis (mo)		
Median	57	75
Prior imatinib		
Imatinib-resistant	69	81
Imatinib-intolerant	31	19
Prior highest imatinib dose		
<600 mg	28	16
≥600-<800 mg	33	31
≥800 mg	40	52
Missing	<1	0
Other prior treatment		
IFN	66	58
Transplants	8	8
Baseline CHR		
Yes	34	N/A
No	66	

Table 2. Efficacy of nilotinib in CML-CP and CML-AP

Cytogenetic response rate (unconfirmed)*	CML-CP % (*n* = 232)
Major (95%CI)	40 (33,46)
Complete (95% CI)	28 (22,34)
Partial (95% CI)	12 (8,16)
	CML-AP % (*n* = 105)
Hematologic response rate,† confirmed (95%CI)	26 (18,35)
CHR (95% CI)	18 (11,27)
NEL (95% CI)	8 (3,15)

NOTE: CHR: neutrophils ≥1.5 × 10^9/L, platelets ≥100 × 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 ≥1.0 × 10^9/L and platelets ≥20 × 10^9/L without transfusions or bleeding.

*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.

†Hematologic response (all responses confirmed after 4 wk) = CHR + NEL.

Table 3. Incidence of clinically relevant treatment-emergent grade 3/4 laboratory abnormalities

	CML-CP (*n* = 318) Grades 3/4* (%)	CML-AP (*n* = 120) Grades 3/4* (%)
Hematologic parameters		
Thrombocytopenia	28 †	37 ‡
Neutropenia	28	37§
Anemia	8	23
Biochemistry parameters		
Elevated lipase	15	17
Hyperglycemia	11	4
Hypophosphatemia	10	10
Elevated bilirubin (total)	9	10
Hypokalemia	1	5

*National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

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

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

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

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a confirmed hematologic response had a duration of response of at least 6 months.

Complete hematologic response and unconfirmed MCyR were secondary end points evaluated in CML-CP and CML-AP patients, respectively. Only a subgroup of patients was evaluable for these end points. Therefore, these results were considered exploratory and were not included in labeling.

The number of patients in the population who received prior imatinib and dasatinib were too small for interpretation and this information was not included in the labeling.

Safety. Four hundred and thirty-eight patients comprised the safety population of 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 in days for CML-CP and CML-AP patients were 245 (range 1-502) and 138 (range 2-503), respectively. The median dose intensity of 797 mg/d (range 145-1,149) was similar for both CML-CP and CML-AP 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).

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

Treatment-emergent grade 3/4 myelosuppression was the most common laboratory adverse reaction. Grade 4 thrombocytopenia occurred with a greater incidence than grade 3 thrombocytopenia in patients with CML-CP and CML-AP (Table 3). Grade 4 neutropenia occurred with a greater incidence than grade 3 neutropenia in patients with CML-AP. Clinically relevant treatment-emergent grade 3/4 laboratory abnormalities occurring at an incidence >5% in CML patients receiving nilotinib included elevated lipase, hyperglycemia, hypophosphatemia, and elevated bilirubin (Table 4). Pancreatitis related to nilotinib administration occurred in 1% of the patients. Other relevant treatment-emergent adverse reactions that occurred at an incidence <5% included elevated change to aspartate aminotransferase or change to alanine aminotransferase, decreased albumin, and elevated alkaline phosphatase; electrolyte abnormalities included hyperkalemia, hypokalemia, hyponatremia and hypocalcemia, and elevated creatinine.

In CML-CP patients, the most commonly reported nonlaboratory drug-related adverse reactions (>10%) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea, and vomiting. In CML-AP patients, the most commonly reported nonlaboratory drug-related adverse reactions (>10%) were rash, pruritus, and constipation (Table 4).

The common serious drug-related adverse reactions in patients with CML-CP were thrombocytopenia and neutropenia. The common serious drug-related adverse reactions in patients with CML-AP were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase, and pyrexia.

The potential for nilotinib to prolong QT was assessed in both a placebo-controlled study with healthy volunteers and the nonrandomized phase 1/2 trial with patients. In the placebo-controlled study with healthy volunteers designed to assess the effects of nilotinib on the QT interval, the administration of nilotinib was associated with concentration-dependent QT prolongation; the maximum mean placebo-adjusted QTcF change from baseline was 18 ms (1-sided 95% upper confidence interval, 26 ms). A positive control was not included in the QT study. Peak plasma concentrations in the QT study were 26% lower than those observed in patients enrolled in the ongoing single-arm study.

Table 4. Treatment-emergent adverse reactions reported in ≥10% of patients in the clinical study

Adverse Reactions	CML-CP (*n* = 318)		CML-AP (*n* = 120)	
	All grades* (%)	Grades 3/4 (%)	All grades (%)	Grades 3/4 (%)
Rash	33	2	28	0
Pruritus	29	1	20	0
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
Headache	31	3	21	2
Fatigue	28	1	16	<1
Pyrexia	14	1	24	2
Asthenia	14	0	12	2
Edema, peripheral	11	0	11	0
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
Cough	17	<1	13	0
Dyspnea	11	1	8	3
Nasopharyngitis	16	<1	11	0

NOTE: Treatment-emergent adverse reactions regardless of relationship to study drug and excluding laboratory abnormalities.
*National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

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In the phase 1/2 study, a number of patients experienced QTcF prolongations from a baseline of >30 ms (33.0% of CML-CP patients, 40.8% of CML-AP patients). QTcF increases of >60 ms were reported in 1.9% of CML-CP and 2.5% of CML-AP patients. Grade 3/4 drug-related QT prolongations were reported in ≤3%, whereas syncope, gastrointestinal and central nervous system hemorrhages, fluid retention, arrhythmias, and myocardial infarction reactions were reported in ≤2% of patients.

Nilotinib should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected before nilotinib administration and should be periodically monitored during therapy. 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. Electrocardiograms should be obtained to monitor the QTc at baseline 7 days after initiation, and periodically following any dose adjustments.

There were 5 sudden deaths reported in patients receiving nilotinib in the ongoing phase 1/2 study (n = 867; 0.6%) considered at least possibly related to nilotinib use. Two additional sudden deaths were considered likely due to other causes. A similar incidence was also reported in the expanded access program or compassionate use protocol. 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. Some patients were on concomitant medications which either prolonged QT interval or were CYP inhibitors.

Phase IV Postmarketing Commitments

The applicant has agreed to several phase IV commitments. The commitment to submit the results of the ongoing, single-arm, phase 2 study in the CML-CP and CML-AP patients resistant to or intolerant of prior imatinib with a minimum follow-up of 24 months is intended to determine the duration of responses observed. This could possibly convert the accelerated approval to a regular approval. The applicant has also agreed to the implementation of postmarketing pharmacovigilance activities to evaluate safety signals associated with nilotinib, including QT interval prolongation and sudden deaths. Other commitments include evaluation of the pharmacokinetics of nilotinib in patients with impaired hepatic function; a relative bioavailability study; studies to evaluate the effect of nilotinib on the metabolism of a sensitive CYP2C9 substrate and if a significant interaction is shown, additional clinical studies to evaluate the effect of nilotinib on the metabolism of a sensitive CYP2C8 substrate and/or a sensitive CYP3A4 substrate; and a study to evaluate if H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib.

Regulatory Basis for Approval

For CML-CP, accelerated approval was based on the surrogate end point of MCyR (which included complete and partial CyR) assessed with standard bone marrow cytogenetics. The response rate by bone marrow cytogenetics was considered a surrogate end point reasonably likely to predict clinical effectiveness for accelerated approval. MCyR based on bone marrow cytogenetics has been used previously as a surrogate in the accelerated approvals of both imatinib and dasatinib (7, 11).

For CML-AP, accelerated approval was based on the surrogate end point of confirmed hematologic response. The protocol specified primary efficacy end point in CML-AP was overall hematologic response which included CHR or NEL and return to chronic phase. Only CHR and NEL (a major hematologic response) were considered as surrogates reasonably likely to predict clinical effectiveness for accelerated approval. This end point has also been used previously as a surrogate in the accelerated approvals of both imatinib and dasatinib (7, 11).

There were several limitations to the data. Efficacy was based on a single ongoing clinical trial with interim data submitted. All CML-CP patients had at least a 6-month follow-up and all CML-AP patients had at least a 4-month follow-up. These follow-up periods were sufficient for the evaluation of response rates, but not for the durations of responses. The median duration of response had not been reached in both the CML-CP and CML-AP populations. The ability to assess the causality of adverse events in this application is limited by the lack of randomized comparative data.

Patients who presented with cardiac events within 12 months before nilotinib administration, such as myocardial infarction, unstable angina, clinically significant atrial and ventricular arrhythmia, congestive heart failure and QT interval of > 450 were excluded from the nilotinib trial. It is therefore unknown whether patients with these concomitant conditions may be safely treated with nilotinib.

The use of concomitant medications and the timing of administration relative to food are important to reduce the potential for QT interval prolongation. A medication guide incorporates these instructions. Dose adjustments for QT interval prolongations, myelosuppression and elevations of lipase, amylase, bilirubin, and hepatic transaminases have been addressed in the label.

A boxed warning was also included on the label. This warning describes the extrinsic and intrinsic factors discussed above that increase nilotinib exposure and the factors that increase the risk of torsade. The warning also incorporates strategies to minimize risk, including electrolyte correction, avoiding drugs known to prolong the QT interval and strong CYP3A4 inhibitors, avoiding taking nilotinib with food, using caution in patients with hepatic impairment, and monitoring for QT interval prolongation.

The efficacy data show that nilotinib treatment results in cytogenetic and hematologic responses in patients with CML-CP and CML-AP who are resistant to or intolerant of imatinib. Most responses occurred within 3 months of initiation of therapy. Responses that lasted for as long as 14 months were observed. The results of the trial provide evidence that nilotinib is effective as a single agent in patients with CML-CP and CML-AP who are resistant to or intolerant of prior imatinib. Cytogenetic and hematologic responses in imatinib resistant or intolerant CML-CP and CML-AP patients, who have limited treatment options, are reasonably likely to predict clinical benefit and therefore support accelerated approval.

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Conclusions

On the basis of data summarized in this report, nilotinib received accelerated approval by the US FDA for the treatment of chronic phase and accelerated phase Ph+ CML in adults resistant to or intolerant of at least one prior therapy that included imatinib.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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