DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022068

**WRITTEN REQUEST – AMENDMENT 2**

Novartis Pharmaceuticals Corporation
Attention: Marilyn Brandt, PhD, RAC
Associate Director, Global Drug Regulatory Affairs - Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Brandt:

Please refer to your correspondence dated February 25, 2015, requesting changes to FDA's June 19, 2009, Written Request for pediatric studies for TASIGNA® (nilotinib).

We also refer to your amendments dated April 9 and 21, 2015.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on June 19, 2009, and as amended on March 7, 2014, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Number of patients to be studied:*

  Study 1: At least 14 patients with age distribution reflective of the disease population. If nilotinib pharmacokinetic (PK) measure is shown to be different, i.e., <u>either</u> a two-fold difference in the area under the curve (AUC) or the oral clearance (CL/F) is detected in either of the age groups as compared to that in the adult population, 5 additional patients will be recruited for that age group.

  Study 2: At least fifty evaluable patients. <u>At least 15 patients must be within the age cohort, 1 to <10 years.</u>

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated June 19, 2009, as amended by this letter and by previous amendment dated March 7, 2014, must be submitted to the Agency on or before June 30, 2021, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission TASIGNA® (nilotinib) via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

*{See appended electronic signature page}*

Gregory H. Reaman, MD
Associate Director for Oncology Sciences
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Rockville, MD 20857

**WRITTEN REQUEST**

NDA 22-068

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Attention: Darshan Wariabharaj
Senior Associate Director, Drug Regulatory Affairs

Dear Mr. Wariabharaj:

Reference is made to your December 17, 2008, Proposed Pediatric Study Request for Tasigna® (nilotinib) capsules.

These studies investigate the potential use of Tasigna in the treatment of Philadelphia chromosome positive (Ph+) hematologic malignancies in pediatric patients 1 to <18 years of age.

Chronic myelogenous leukemia (CML) is a hematologic cancer in which abnormal proliferation of a bone marrow stem cell results in the increased production of mature granulocytes (neutrophils, eosinophils, basophils) and their precursors and their accumulation in blood. While CML accounts for approximately 15-20% of all leukemias in adults, it comprises less than 3% of childhood leukemia, occurring most commonly in older children and adolescents, and not usually presenting in children younger than 6 years of age.

As in adults, CML in children is characterized by the presence of the Philadelphia chromosome (Ph), carrying the abnormal fusion oncogene BCR-ABL. Standard initial treatment of this leukemia in both children and adults consists of therapy with a first or second generation tyrosine kinase inhibitor (TKI), such as imatinib, dasatinib, or nilotinib, which target the tyrosine kinase BCR-ABL. However, imatinib is currently the only agent approved for use in pediatric CML. The availability of approved second generation TKIs would provide important treatment options for children with Ph+CML, both in the front-line setting, and in patients who are resistant or intolerant to prior TKI therapy.

Given the similar underlying pathobiology and clinical course of CML in pediatric patients and adults, the efficacy of TKIs in the treatment of children and adolescents with CML can be extrapolated from adult trials. Since Ph+CML is not diagnosed in children less than 1 year of age, neonates and infants are not included in this Written Request.

To obtain needed pediatric information on nilotinib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food Drug,

and Cosmetic Act (the ACT), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies.

Protocols for your studies must be submitted to the FDA for review and agreement prior to initiation of the studies. Each submission must review the overall development plan and justify the study design.

- *Type of studies:*

  Study 1: Dose escalation, safety and tolerability, PK study of nilotinib administered orally twice daily.

  The dose for Study 2 will be determined by the results of Study1.

  Study 2: Study to assess the activity, PK, and safety of nilotinib administered orally twice daily.

  Study 2 will start in each age group (from 1 to <10 years; from 10 years to <18 years) once the nilotinib pediatric dose is confirmed in the respective age group in Study 1.
  If the dose is confirmed first in the older age group, Study 2 will start only in the older age group and it will only be opened to the younger age group when dose is confirmed in this group.
  These studies must take into account adequate (e.g., proportionate to the disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Populations to be studied:*

  Study 1: Pediatric patients with imatinib and/or dasatinib-resistant or -intolerant chronic or accelerated phase chronic myeloid leukemia (CP or AP CML), with newly diagnosed chronic phase Ph+ CML, and relapsed or refractory Philadelphia chromosome positive acute lymphocytic leukemia (Ph+ ALL).

  Study 2: Pediatric patients with either imatinib or dasatinib-resistant or -intolerant CP-CML or AP-CML and newly diagnosed CP-CML.

- *Age group in which studies will be performed:*

  Study 1: Children from 1 to < 18 years.

  Study 2: Children from 1 to < 18 years.

- *Number of patients to be studied:*

Study 1: At least 14 patients with age distribution reflective of the disease population. If nilotinib pharmacokinetic (PK) measure is shown to be different, i.e., either a two-fold difference in the area under the curve (AUC) or the oral clearance (CL/F) is detected in either of the age groups as compared to that in the adult population, 5 additional patients will be recruited for that age group.

Study 2: At least fifty evaluable patients. At least 15 patients must be within the age cohort, 1 to <10 years.

- *Study endpoints*

  Study 1: Safety (including EKG monitoring) and tolerability, nilotinib pediatric dose (recommended Study 2 dose), and pharmacokinetics.

  Study 2: Objective response rates (including rate of major molecular response (MMR) in newly diagnosed Ph+CML CP and in Ph+CML CP/AP patients resistant/intolerant to either imatinib or dasatinib (MMR is defined as ≥ 3 log reduction of BCR-ABL transcript from standardized baseline or ≤ 0.1% BCR-ABL/ABL % by international scale, measured by RQ-PCR), rate of major cytogenetic response (MCyR) and complete cytogenetic response (CCyR) in newly diagnosed Ph+ CML CP and in Ph+ CML CP/AP patients resistant/intolerant to either imatinib or dasatinib, and complete hematologic response (CHR) in Ph+ CML AP patients resistant/intolerant to either imatinib or dasatinib, pharmacokinetics, safety (including EKG monitoring). Relevant pharmacokinetic parameters (such as AUC, elimination Tl/2, $C_{max}$, and $T_{max}$) should be derived through approaches such as optimal sparse sampling in all patients with rich sampling in a sub-group.

- *Drug information*

  *Dosage form:* Age appropriate formulation

  *Route of administration:* Oral

  *Regimen:* Studies 1 and 2 will evaluate twice daily oral doses. The starting dose for Study 1 will be 230 mg/m$^2$. The dose for Study 2 will depend upon the results of Study 1.

  Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric populations studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the

approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Drug specific safety concerns:* QT prolongation and sudden death, myelosuppression, elevated serum lipase, liver function abnormality, hepatic impairment, drug interactions, food effect, and fetal harm.

- *Statistical information, including power of studies and statistical assessments:*

    - Study 1: Efficacy data will be for exploratory analyses only, no formal statistical tests will be conducted. Descriptive statistics for PK will be calculated.

    - Study 2: Efficacy data will be for exploratory analyses only, no formal statistical tests will be conducted. Hematological and cytogenetic responses will be summarized by descriptive statistics and the raw data will be listed. The pharmacokinetic data should be appropriately analyzed using methods such as nonlinear mixed effects modeling. Data from the Phase 1and Phase 2 studies should be combined to develop pharmacokinetic and pharmacodynamics (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

- *Labeling that may result from the studies:* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the studies demonstrate that nilotinib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the

public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format-Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before June 30, 2021. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

  *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS -PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(l) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402G)(l)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402G) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Christy Cottrell, Regulatory Project Manager, at (301) 796-4256.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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GREGORY H REAMAN
08/28/2015