



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.

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 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 Study 1.

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

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-resistant or -intolerant chronic or accelerated phase chronic myeloid leukemia (CP or AP CML) and relapsed or refractory Philadelphia chromosome positive acute lymphocytic leukemia (Ph⁺ ALL).

Study 2: Pediatric patients with imatinib-resistant or –intolerant CP-CML or AP-CML and newly diagnosed CP-CML. If activity is shown in Study 1, pediatric patients with Ph⁺ ALL will also be studied.

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

Study 1: Children up to 17 years.

Study 2: Children and adolescents 1 to 20 years of age with an adequate distribution of patients that reflects the demographics of pediatric CP and AP CML and Ph⁺ ALL.

- *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., 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.

- *Study endpoints*

Study 1: Safety (including EKG monitoring) and tolerability, maximum tolerated dose (MTD), and pharmacokinetics.

Study 2: Objective response rates (including major cytogenetic response for patients with CP-CML and complete hematologic response for patients with AP-CML and Ph⁺ ALL), pharmacokinetics, safety (including EKG monitoring). Relevant pharmacokinetic parameters (such as AUC, elimination T_{1/2}, 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/m². 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 1 and Phase 2 studies should be combined to develop pharmacokinetic and pharmacodynamic (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)(1) 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 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) 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

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

/s/

Richard Pazdur
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