DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21985

WRITTEN REQUEST – AMENDMENT 3

Novartis Pharmaceuticals Corporation
Attention: Anne-Marie van der Merwe
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. van der Merwe:

Please refer to your correspondence dated 11 May 2016, requesting changes to FDA's 13 May 2008 Written Request for pediatric studies for aliskiren.

We have reviewed your proposed changes and acknowledge your request to resume technical development of your pediatric formulation (b) (4) Accordingly, we are amending the below listed section of the Written Request.

All other terms stated in our Written Request issued on 13 May 2008, with amendments issued 13 March 2009 and 6 August 2012, remain the same. (Text added is underlined. Text deleted is strikethrough.)

TIMEFRAME FOR REPORTS

Reports of the above studies must be submitted to the Agency on or before 20 April 2017 ~~31 January 2016~~. 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.

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

Submit reports of the studies as a new 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 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, please call Bridget Kane, Regulatory Project Manager, at 240-402-2170.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21985

WRITTEN REQUEST – AMENDMENT 3

Novartis Pharmaceuticals Corporation
Attention: Anne-Marie van der Merwe
Global Program Regulatory Director
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. van der Merwe:

Reference is made to your new drug application (NDA) amendment dated 17 December 2007, received 17 December 2007, requesting the issuance of a Written Request letter for Tekturna (aliskiren) 150 mg and 300 mg Tablets

Reference is also made to previous versions of this Written Request dated 13 May 2008, 13 March 2009, and 6 August 2012.

To obtain needed pediatric information on aliskiren, 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 studies described below.

This Written Request contains a mixture of requirements (failure to fulfill these would result in denial of exclusivity) *and* advice. We have highlighted formal requirements to make this distinction clear.

- *Type of studies*:

  - pharmacokinetic sampling in patients spanning the same age range as those to be studied for effectiveness,
  - a dose-response trial of effectiveness in hypertensive pediatric patients; and
  - safety data derived from a controlled trial and a 1-year open treatment phase following the effectiveness trial, and a summary of all available information on the safety of the drug in hypertensive pediatric patients. The safety evaluation in children must include a summary of the published literature and formal analyses of published and unpublished data. Unpublished data may be obtainable from organizations participating in healthcare delivery to the pediatric population.

- *Indication to be studied:* reduction of blood pressure in pediatric patients

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

  The five pediatric age groups to which we refer in this document are:
  - Neonates (age less than 1 month)
  - Infants and toddlers (age 1 month to <24 months)
  - Preschool children (age 2 to <6 years)
  - School age children (age 6 to Tanner stage 2)
  - Adolescents (Tanner stage 3 to 16 years)

Pharmacokinetic Trials

Pharmacokinetic data must be obtained over the range of doses and ages studied for effectiveness. Patients must have grossly normal metabolic function. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters.

Data must be collected with respect to aliskiren and any metabolites that make substantial contributions to its efficacy or toxicity. For the parent and each metabolite followed, the data collected must provide estimates of the exposure (AUC), half-life, oral apparent clearance, volume of distribution, C_{max} , and t_{max} in pediatric subjects of the various age groups. These results should be discussed in comparison with results in adults.

Dose-Ranging Trial

Trial design

The dose-ranging study must be double-blind in design and it must evaluate at least three dose levels of aliskiren. You must obtain agreement from the Division on the doses incorporated into this study. The doses chosen should result in blood levels that range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the highest approved adult dose[1]. Randomization should be stratified by age and race (see racial groups). The duration of the parallel portion of the study must be at least 2 weeks after titration to target doses is completed. The primary end point must be either absolute or percentage change in systolic or diastolic pressure. The statistical approach will depend on the specific trial design, but, broadly, you can allocate alpha to each active arm in the placebo-controlled comparison, or to some combination of treatment arms (highest 2) or you can look for a positive slope in the dose-response relationship. The primary analysis must include all patients with data on randomized treatment.

If the pharmacokinetics of the drug in children, derived from the pharmacokinetic trial described above, differ substantially from the reported pharmacokinetics in adults, such that the serum half-life is appreciably altered, the trial must include an assessment of the effect of varying dosing interval on trough antihypertensive effect. This must include measurement of the effects of the drug throughout the dosing interval.

Acceptable options for trial design are as follows:

---

[1] *Doses would usually be derived from adult doses scaled by body surface area, but there should be, from pharmacokinetic data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.*

The most straightforward, acceptable trial (Trial A) would be one in which each patient is randomized to placebo or to one of three doses of study drug.

Although, with appropriate monitoring, we believe that there is no risk associated with a few weeks of placebo treatment, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be a two-stage trial, where the first stage is randomization to the three doses of active drug and the second stage is randomization to continuation of the original dose or to placebo (randomized withdrawal study).

The analysis of Trial B would first be a slope analysis for the first phase. If the first phase failed to reveal a statistically significant non-zero slope, an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. No alpha adjustment would be required for testing these two hypotheses. This design would allow you to distinguish between failure to see dose-response because all doses were similarly effective and failure to see a dose-response because none of the doses had an effect.

Measurement of blood pressure

You must consistently measure both systolic pressure and diastolic pressure in all patients. You must prospectively identify either the systolic or diastolic blood pressure as the primary end point. For the trial designs other than randomized withdrawal from active drug (see above), the primary efficacy measurement must be the change in blood pressure from baseline to the time of the last dose plus the inter-dosing interval. Additional measurements of blood pressure should be performed at the anticipated peak drug effect (estimated from adult data or based on the results of the pharmacokinetic studies in children). For randomized withdrawal trial designs, the primary efficacy measurement must be the change in blood pressure at the interdosing interval from the last on-treatment visit to the end of the withdrawal period, or to the time at which an acceptable blood pressure is exceeded. Patients should be followed at least weekly, so that unacceptable increases in blood pressure can be detected and treated promptly.

Drug information

An age-appropriate formulation must be used in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test one, and, if it is found safe and effective in the studied pediatric populations, 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 population(s) 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.

Recruiting

The trial must be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must be included, and 50% of the patients in the trial must be ≤12 years old. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They must not be recruited if other interventions known to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment.

These studies should take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, please provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Eligibility

Prior treatment with aliskiren or other therapy should be neither required nor disqualifying. A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving antihypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period.

Statistical considerations

The trial must be designed to detect a treatment effect of conventional ($p<0.05$) statistical significance. You must obtain agreement on the final statistical analysis plan, including handling of missing data, prior to 25% enrollment.

Your study must be powered to be able to detect a "clinically meaningful" treatment benefit on the primary end point. For the purpose of satisfying the Written Request, a clinically meaningful treatment benefit is considered to be a 3-mmHg effect (placebo-subtracted change from baseline) on either systolic or diastolic pressure.

This requires you to show that if the true treatment effect for one of the treatment groups were minimally "clinically meaningful", the pre-planned analysis would have at least 90% power to infer that at least one dose or the high dose is significantly different from placebo. You may wish to obtain an estimate of variability to use in power calculations from a preliminary study. However, to ensure

that the study is adequately powered, you must obtain an estimate of variability from an interim analysis and then follow a pre-specified rule to adjust the sample size to achieve the specified target power. This interim analysis must be performed at >90% of initially planned enrollment. Options for estimating variability are (1) a blinded, pooled analysis of all groups, (2) a blinded analysis of one group, or (3) a partially unblinded analysis of variability within each group (performed by an independent third party). No alpha-spending adjustment is required for this interim analysis to assess the variability, but if you want to perform an efficacy assessment at this or some other interim analysis, an appropriate alpha adjustment is required.

Long-term safety

Patients in the trial(s) of clinical efficacy should be enrolled in an open-label follow-on study with safety (adverse events), growth (change in head circumference[2], weight, and length or height), and development (milestones, school performance, or neurocognitive testing) assessed at baseline and at one year. This long-term safety study should include a randomized control group treated per standard of care.

Extraordinary results

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected, useful results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Labeling

Under section 505A(j) of the Act, regardless of whether the studies demonstrate that aliskiren is safe and effective, or whether such study results are inconclusive in the studied pediatric population, you must submit labeling to include information about the results of the studies. 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 studies.

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 studies. 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.

---

[2] *Up to age of 3 years.*

Protocols
Submit protocols for the above study(ies) 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.

Amendments
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.

Trial registration
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.

Reporting
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 reports
Reports of the above studies must be submitted to the Agency on or before 20 April 2017. 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.
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 II, 7500 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 301-827-5911.

Dissemination of information
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 have any questions, please call Bridget Kane, Regulatory Project Manager, at (240) 402-2170.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I
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/

ELLIS F UNGER
08/09/2016