DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20857

NDA 22145
NDA 203045
NDA 205786

WRITTEN REQUEST – AMENDMENT 4

Merck Sharp & Dohme Corp.
Attention: Chitrananda Abeygunawardana, Ph.D.
Director, Regulatory Liaison, Global Regulatory Affairs
351 North Sumneytown Pike
P.O. Box 1000, UG2D-68
North Wales, PA 19454

Dear Dr. Abeygunawardana:

Please refer to your correspondence dated May 12, 2016, to NDA 205786, and NDA 203045 and to your May 20, 2016, correspondence to NDA 22145 requesting changes to FDA's August 18, 2006 Written Request for pediatric studies for ISENTRESS™ (raltegravir potassium; formerly MK-0518).

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 August 18, 2006, and as amended on June 27, 2007, October 19, 2010, and November 6, 2014, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

Timeframe for submitting reports of the studies:
Reports of the above studies must be submitted to the Agency on or before ~~December 30, 2016~~ September 30, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:
Submit reports of the studies as a new drug application (NDA) or 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, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, ~~HFD-600,~~ CDER, FDA, Document Control Room, Metro Park North ~~IV~~ VII, ~~7619~~ 7620 Standish Place, Rockville, MD 20855-2773.

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 August 18, 2006, as amended by this letter and by the previous amendments dated June 27, 2007, October 19, 2010, and November

6, 2014, must be submitted to the Agency on or before September 30, 2017, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) or 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, 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.

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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), 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 approval);
    2) the Agency grants pediatric exclusivity, including publishing 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 indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that raltegravir potassium 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).

- 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, approvable, not approvable); 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 your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be 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 these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Christian P. Yoder, MPH, Regulatory Project Manager, at (240) 402-9990 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment (Complete Clean Copy of Written Request as amended)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20857

NDA 22145
NDA 203045
NDA 205786

WRITTEN REQUEST – AMENDMENT 4

Merck Sharp & Dohme Corp.
Attention: Chitrananda Abeygunawardana, Ph.D.
Director, Regulatory Liaison, Global Regulatory Affairs
351 North Sumneytown Pike
P.O. Box 1000, UG2D-68
North Wales, PA 19454

Dear Dr. Abeygunawardana:

Reference is made to your April 25, 2006 Proposed Pediatric Study Request submitted to IND 69,928 for raltegravir potassium (formerly MK-0518).

To obtain needed pediatric information on raltegravir potassium, 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), that you submit information from the following studies:

Types of studies:

Multiple-dose pharmacokinetic, safety, and activity study of raltegravir potassium in combination with other antiretroviral agents in HIV-infected pediatric patients.

Multiple-dose pharmacokinetic and safety study of raltegravir potassium in addition to the standard of care in HIV-exposed neonates (born to HIV-infected mothers).

The objective of these studies will be to determine the pharmacokinetic and safety profile of raltegravir potassium across the age range studied, identify an appropriate dose for use in HIV-infected pediatric patients and exposed neonates, and evaluate the activity of this dose (or doses) in treatment and/or prophylaxis.

Indication to be studied:

Treatment of HIV infection in pediatric patients and/or prophylaxis of HIV infection in exposed neonates.

Age group in which studies will be performed:

HIV-infected pediatric patients from 1 month to adolescence and HIV-exposed neonates (born to HIV-infected mothers).

Drug Information:

Dosage form: Age-appropriate formulation.

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

Development of a commercially marketable formulation is preferable. If you cannot develop a commercially marketable age-appropriate formulation, 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 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 label 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 should be characterized, and if necessary, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide safety data including gastrointestinal disorders, headache, hepatic toxicity, metabolic disturbances, and any other parameters pertinent to use in the pediatric population.

Safety of raltegravir potassium must be studied in an adequate number of pediatric patients or neonates to characterize adverse events across the age range. A minimum of 100 patients with at least 24 weeks safety data is needed.

Statistical information, including power of study and statistical assessments:

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients and descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).

A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic studies conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

Birth to < 6 weeks: 8

6 weeks to < 6 months: 6

6 months to < 2 years: 6

2 years to < 6 years: 12

6 years to < 12 years: 8

12 years to 18 years: 6

Studies must include an adequate number of patients to characterize pharmacokinetics and select a therapeutic dose for the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be approximately evenly distributed across the age range studied.

Study Endpoints:

Pharmacokinetics

Parameters including: C_{max}, C_{min}, T_{max}, and AUC_{0-12}, will be characterized.

Safety and tolerability

HIV-infected pediatric patients should be followed for safety for a minimum of 24 weeks at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments, on or off treatment (as appropriate), for a minimum of 24 weeks after start of therapy.

Activity

Assessment of changes in plasma HIV RNA levels and in $CD4^+$ cell counts.

Resistance

Collect and submit information regarding the resistance profile (genotypic and phenotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving raltegravir potassium, particularly from those who experience loss of virologic response.

Labeling that may result from the studies:

Information regarding dosing, safety, and activity in the HIV-infected pediatric population and information regarding dosing and safety in HIV-exposed neonates (born to HIV-infected mothers).

Format of reports to be submitted:

You must submit full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to 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 one of the following designations should be used: Hispanic/Latino or not Hispanic/ Latino.

Timeframe for submitting reports of the studies:

Reports of the above studies must be submitted to the Agency on or before September 30, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency of your intent to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

Please 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. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission "**PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a new drug application (NDA)/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.

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, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), 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 approval);
  2) the Agency grants pediatric exclusivity, including publishing 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 indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that raltegravir potassium 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).

- 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, approvable, not approvable); 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 your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be 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 these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, please contact Christian P. Yoder, MPH, at (240) 402-9990 or the Division's main number at (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

John Farley, MD, MPH
Deputy Director
Office of Antimicrobial 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/

JOHN J FARLEY
06/29/2016