

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210806Orig1s000

210807Orig1s000

Trade Name: PIFELTRO™ tablet, 100 mg
DELSTRIGO™ tablets, 100/300/300 mg

Generic or Proper Name: doravirine
doravirine, lamivudine, and tenofovir disoproxil fumarate

Sponsor: Merck Sharp & Dohme Corp.

Approval Date: August 30, 2018

Indication: for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210806Orig1s000

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APPROVAL LETTER



NDA 210806

NDA APPROVAL

Merck Sharp & Dohme Corp.,
a subsidiary of Merck & Co., Inc.
Attention: Donnette Staas, PhD
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Staas:

Please refer to your New Drug Application (NDA) dated and received October 23, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for PIFELTRO™ (doravirine) tablet, 100 mg.

This new drug application provides for the use of PIFELTRO™ (doravirine) tablet in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients with no prior antiretroviral treatment history.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABEL

Submit final printed immediate container label that is identical to the immediate container label submitted on July 17, 2018, as soon as it is available, but no more than 30 days after it is printed. Please submit the label electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Container Label for approved NDA 210806.**” Approval of this submission by FDA is not required before the labeling is used.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Christine Kim, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6391
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for PIFELTRO™ (doravirine) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for doravirine’s drug class and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to less than 28 days of age because the product fails to represent a meaningful therapeutic benefit over existing therapies in this age group and is unlikely to be used in a substantial number of pediatric patients in this age group.

We are deferring submission of your pediatric studies for ages 28 days to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

- 3415-1 Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of doravirine in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg. The safety and antiviral activity of doravirine in pediatric subjects must be evaluated for a minimum of 24 weeks.

Final Protocol Submission: submitted
Study/Trial Completion: 07/2021
Final Report Submission: 01/2022

- 3415-2 Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of doravirine in HIV-1 infected pediatric subjects at least 2 years of age and weighing less than 35 kg. The study participants must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine.

Final Protocol Submission: 01/2020
Study/Trial Completion: 11/2023
Final Report Submission: 05/2024

- 3415-3 Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of doravirine in HIV-1 infected pediatric subjects 4 weeks of age to 23 months of age. The study participants must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine.

Final Protocol Submission: 05/2022
Study/Trial Completion: 08/2028
Final Report Submission: 02/2029

Submit the protocol(s) to your INDs 112796 or 124997, if applicable, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must 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 REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS
UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 3415-4 Assess the phenotypic susceptibility in cell culture of doravirine and approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) against Y318F alone and in combination with the following substitutions, which have been associated with doravirine and/or other NNRTIs: K103N; Y181C; K103N/Y181C; L100I; L100I/K103N; V106A; P225H; V106A/P225H; H221Y; V106M; F227C; V108I.

The timetable you submitted on June 25, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2018
Study/Trial Completion: 06/2019
Final Report Submission: 09/2019

- 3415-5 Conduct a drug-drug interaction study to evaluate the pharmacokinetics of doravirine and its primary metabolite (M9) when doravirine 100 mg BID is coadministered with rifabutin as compared to the administration of doravirine 100 mg QD alone in healthy subjects.

The timetable you submitted on June 25, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2019
Study/Trial Completion: 06/2020
Final Report Submission: 12/2020

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your INDs 112796 or 124997, if applicable for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Christine Kim, PharmD, Regulatory Project Manager, at (301) 796-5964 or 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

Enclosures:

Content of Labeling
Immediate Container Label

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN J FARLEY
08/30/2018



NDA 210807

NDA APPROVAL

Merck Sharp & Dohme Corp.,
a subsidiary of Merck & Co., Inc.
Attention: Donnette Staas, PhD
Director, Global Regulatory Affairs and Clinical Safety
351 N. Sumneytown Pike
P.O. Box 1000, UG2D-68
North Wales, PA 19454-2505

Dear Dr. Staas:

Please refer to your New Drug Application (NDA) dated and received October 23, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DELSTRIGO™ (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, 100/300/300 mg.

This new drug application provides for the use of DELSTRIGO™ (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets as a complete regimen for the treatment of HIV-1 infection in adult patients with no antiretroviral treatment history.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the prescribing information and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories.

IMMEDIATE CONTAINER LABEL

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MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Christine Kim, PharmD
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6391
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for DELSTRIGO™ (doravirine, lamivudine, and tenofovir disoproxil fumarate) was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for the drugs or drug classes contained in DELSTRIGO™ and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to less than 2 years of age because the product (doravirine, lamivudine, and tenofovir disoproxil fumarate) fails to represent a meaningful therapeutic benefit over existing therapies in this age group and one of the individual components (tenofovir disoproxil fumarate) is not indicated for use in children below 2 years of age.

We are deferring submission of your pediatric studies for ages 2 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3416-1 Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of doravirine/lamivudine/tenofovir disoproxil fumarate fixed dose combination (FDC) product in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg. Subjects must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of doravirine/lamivudine/tenofovir disoproxil fumarate FDC product. A clinical trial in pediatric subjects weighing at least 35 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials already conducted with the individual drug products.

Final Protocol Submission: submitted
Study/Trial Completion: 07/2021
Final Report Submission: 01/2022

3416-2 Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of doravirine/lamivudine/tenofovir disoproxil fumarate fixed dose combination (FDC) product in HIV-1 infected pediatric subjects age 2 years and older, and weighing less than 35 kg. The study participants must be followed for a minimum of 24 weeks to assess the safety and antiviral activity of the FDC product, doravirine/lamivudine/tenofovir disoproxil fumarate. A clinical trial in pediatric subjects 2 years and older and weighing less than 35 kg may not be required if dosing recommendation for the FDC tablets can be supported by pediatric trials conducted with the individual drug products.

Final Protocol Submission: 01/2020
Study/Trial Completion: 11/2023
Final Report Submission: 05/2024

Submit the protocol(s) to your IND 112796 or 124997, if applicable, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must 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 REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 3416-3 Assess the phenotypic susceptibility in cell culture of doravirine and approved non-nucleoside reverse transcriptase inhibitors (NNRTIs) against Y318F alone and in combination with the following substitutions, which have been associated with doravirine and/or other NNRTIs: K103N; Y181C; K103N/Y181C; L100I; L100I/K103N; V106A; P225H; V106A/P225H; H221Y; V106M; F227C; V108I.

The timetable you submitted on June 25, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2018
Study/Trial Completion:	06/2019
Final Report Submission:	09/2019

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocol to your INDs 112796 or 124997, if applicable for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

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REPORTING REQUIREMENTS

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MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

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If you have any questions, call Christine Kim, PharmD, Regulatory Project Manager, at (301) 796-5964 or 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

Enclosures:

Content of Labeling
Immediate Container Label

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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JOHN J FARLEY
08/30/2018