APPLYING FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211994Orig1s000

OTHER REVIEW(S)
MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: March 29, 2019
Requesting Office or Division: Division of Antiviral Products (DAVP)
Application Type and Number: NDA 211994
Product Name and Strength: Dovato (dolutegravir and lamivudine) Tablets, 50 mg/300 mg
Applicant/Sponsor Name: ViiV Healthcare Company (ViiV)
FDA Received Date: March 19, 2019 and March 29, 2019
OSE RCM #: 2018-2265-1
DMEPA Safety Evaluator: Valerie S. Wilson, PharmD
DMEPA Team Leader: Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM
The Division of Antiviral Products (DAVP) requested that we review the revised container label for Dovato (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review\(^a\) and Information Request via email communication on March 26, 2019.

2 CONCLUSION
The revised container label for Dovato is acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 29, 2019

Container labels

(b) (4)
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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VALERIE S WILSON
03/29/2019 02:41:39 PM

SEVAN H KOLEJIAN
03/29/2019 02:53:50 PM
Memorandum

Date: March 29, 2019

To: Anitra Johnson, Regulatory Project Manager
Division of Antiviral Products (DAVP)

From: Wendy Lubarsky, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for DOVATO (dolutegravir and lamivudine) tablets, for oral use

NDA: 211994

In response to DAVP consult request dated October 30, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for DOVATO (dolutegravir and lamivudine) tablets, for oral use (Dovato). This submission proposes an indication for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato.

**PI and PPI:** OPDP’s comments on the proposed labeling are based on the draft PI link received by electronic mail from DAVP (Anitra Johnson) on March 26, 2019 and downloaded on March 29, 2019, and PPI received by electronic mail from DAVP (Anitra Johnson) on March 19, 2019. One OPDP comment in Section 14.1 of the PI is provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on March 28, 2019.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DAVP (Anitra Johnson) on March 26, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Wendy Lubarsky at (240) 402-7721 or wendy.lubarsky@fda.hhs.gov.
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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WENDY R LUBARSKY
03/29/2019 11:50:16 AM
PATIENT LABELING REVIEW

Date: March 28, 2019

To: Debra Birnkrant, MD
   Director
   Division of Antiviral Products (DAVP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
   Associate Director for Patient Labeling
   Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
   Team Leader, Patient Labeling
   Division of Medical Policy Programs (DMPP)

From: Ruth Lidoshore, PharmD
   Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

Wendy Lubarsky, PharmD
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): DOVATO (dolutegravir and lamivudine)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 211994

Applicant: ViiV Healthcare Company
1 INTRODUCTION
On October 18, 2018, ViiV Healthcare Company submitted for the Agency’s review an original New Drug Application (NDA) 211994 for DOVATO (dolutegravir and lamivudine) tablets. This submission proposes an indication for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no known substitutions associated with resistance to individual components of DOVATO (dolutegravir and lamivudine).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antiviral Products (DAVP) on October 30, 2018, for DMPP and OPDP to review the Applicant’s proposed Patient Package Insert (PPI) for DOVATO (dolutegravir and lamivudine) tablets.

2 MATERIAL REVIEWED
- Draft DOVATO (dolutegravir and lamivudine) tablets PPI received on October 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 19, 2019.
- Draft DOVATO (dolutegravir and lamivudine) tablets Prescribing Information (PI) received on October 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 19, 2019.
- Approved TIVICAY (dolutegravir) tablets NDA 204790 comparator labeling dated September 6, 2018.
- Approved EPIVIR (lamivudine) tablets NDA 020564 comparator labeling dated April 27, 2018.

3 REVIEW METHODS
To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:
- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

ensured that the PPI meets the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS
The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

• Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

• Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.
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/

RUTH I LIDOSHORE
03/28/2019 10:42:57 AM

WENDY R LUBARSKY
03/28/2019 02:23:44 PM

BARBARA A FULLER
03/28/2019 02:25:56 PM

LASHAWN M GRIFFITHS
03/28/2019 02:32:56 PM
I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The data from two identical Phase 3 studies of dolutegravir plus lamivudine (Study 204861 [GEMINI-1] and Study 205543 [GEMINI-2]) were submitted to the Agency in support of NDA 211994. Four clinical sites, Dr. Norma Porteiro, M.D. (Site 221100; Study 204861), Dr. Mezgebe Berhe, M.D. (Site 222181; Study 205543), Dr. Juan Sierra-Madero, M.D. (Site 222250; Study 205543), and Dr. Gustavo Lopardo, M.D. (Site 223550; Study 205543), were selected for audit.

The data from Study 204861 and Study 205543 submitted to the Agency in support of NDA 211994, appear reliable based on available information.

There were no significant inspectional findings for clinical investigators Dr. Norma Porteiro, Dr. Mezgebe Berhe, and Dr. Gustavo Lopardo. However, there were noteworthy inspectional observations at Dr. Juan Sierra-Madero’s clinical site. The site deliberately deviated from the investigational plan, in requiring that all study subjects return to the site 4 weeks after the study Week 24 and 48 visits, to review in person the results of the HIV RNA copies/mL test, and, if the test results from Week 24 or 48 were >50 copies/mL a confirmatory blood draw would be collected for a repeat testing of HIV RNA copies/mL per the protocol. The majority of study
subjects didn’t have a HIV RNA count/mL >50, as such, they were made to attend an unnecessary study visit at the clinical site. While this site-specific practice was a protocol violation it should not have placed subjects at undue risk or have importantly affected overall study outcomes.

The sponsor Viiv Healthcare also submitted a parallel application to the EMA for approval of

The EMA findings from these inspections are not available at this time. OSI will submit a Clinical Inspection Summary Addendum if there are any significant findings from the EMA clinical site inspections that would change the overall recommendation from OSI.

II. BACKGROUND

ViiV Healthcare Co. seeks approval to market dolutegravir and lamivudine for use as a complete, single tablet regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. This request is based on the results from primarily two identical Phase 3 Studies: Study 204861 [GEMINI-1] and Study 205543 [GEMINI-2].

Study 204861 [GEMINI-1] is entitled, “Phase III, randomized, double blind, multicenter, parallel-group, NI study evaluating efficacy, safety, and tolerability of DTG + 3TC compared to DTG + TDF/FTC in HIV-1-infected treatment-naïve adults”. A total of 87 investigational centers in 18 countries randomized 719 subjects (HIV-1-infected, treatment-naïve adults) in this study.

Study 205543 [GEMINI-2] is entitled, “Phase III, randomized, double blind, multicenter, parallel-group, NI study evaluating efficacy, safety, and tolerability of DTG + 3TC compared to DTG + TDF/FTC in HIV-1-infected treatment-naïve adults”. A total of 104 investigational centers in 18 countries screened 1006 HIV-1-infected, treatment-naïve adults and randomized 719 subjects.

Primary Objective: To demonstrate non-inferior antiviral activity of dolutegravir plus lamivudine (DTG + 3TC) versus dolutegravir plus tenofovir/emtricitabine (DTG + TDF/FTC) at 48 weeks in human immunodeficiency type 1 (HIV-1)-infected, antiretroviral therapy (ART)-naïve subjects.

Key inclusion criteria: HIV-1 infected, ART-naïve women and men ≥18 years of age with screening plasma HIV-1 ribonucleic acid (RNA) of 1000 copies/mL to ≤ 500,000 copies/mL.

Subjects were randomized 1:1 to receive a 2-drug regimen of DTG + 3TC once daily or DTG + TDF/FTC fixed dose combination (FDC) tablet once daily until Week 148. Subjects were stratified by screening HIV-1 RNA (≤100,000 copies/mL or >100,000 copies/mL) and screening CD4+ cell count (≤ or >200 cells/mm3).
Primary efficacy endpoint: the proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the Snapshot algorithm for the Intent-to-Treat Exposed (ITT-E) population. The Snapshot algorithm was an analysis table that showed the percent responders between different treatment groups at various timepoints during the study.

Secondary efficacy endpoints:
- the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Weeks 24, 96, and 144 using the Snapshot algorithm for the ITT-E population
- time to viral suppression (HIV-1 RNA <50 copies/mL)
- absolute values and changes from baseline in CD4+ cell counts
- the incidence of disease progression (HIV-associated conditions, AIDS, and death)
- the proportion of subjects by subgroups (e.g. by age, gender, baseline CD4+ cell count) with plasma HIV-1 RNA <50 copies/mL using the Snapshot algorithm for the ITT-E population
- change from baseline in CD4+ cell counts by subject subgroups

Objectives of Inspections:
- verify efficacy endpoints using source documents at the clinical site for each subject
- Identification, documentation, and reporting of adverse events (AEs) for a sample of enrolled subjects.
- General compliance with the investigational plan.

III. RESULTS (by site):

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<tr>
<th>Name of CI, Site #, Address</th>
<th>Protocol # and # of Subjects</th>
<th>Inspection Date</th>
<th>Final Classification</th>
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<tbody>
<tr>
<td>CI: Dr. Mezgebe Berhe, M.D. (Site 222181) 3409 Worth Street Dallas, TX 75246</td>
<td>Protocol: 205543 Subjects: 25</td>
<td>December 12-14, 2018</td>
<td>NAI</td>
</tr>
<tr>
<td>CI: Dr. Norma Porteiro, M.D. (Site 221100) Neuquén 677 Ciudad Autónoma de Buenos Aires, Buenos Aires C1405CKC Argentina</td>
<td>Protocol: 204861 Subjects: 34</td>
<td>February 11-13, 2019</td>
<td>NAI</td>
</tr>
<tr>
<td>CI: Dr. Juan Sierra-Madero, M.D. (Site 222250) Vasco de Quiroca 15 Mexico, 14000</td>
<td>Protocol: 205543 Subjects: 20</td>
<td>February 5-8, 2019</td>
<td>*VAI</td>
</tr>
</tbody>
</table>
Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Dr. Mezgebe Berhe, M.D. (Site 222181; Study 205543)

The site screened 37 subjects that consisted of 24 subjects enrolled/randomized (plus 1 subject transfer to the site). At the time of this inspection four subjects had discontinued; Subject withdrew consent due to moving out of the area, Subject was lost to follow-up at Week 50, Subject withdrew consent due to moving out of the area, and Subject was a viral load failure at Week 120 (Virus RNA copies/mL >200 after Week 120. Sixteen subjects had completed study activities through Week 96, and five subjects were currently in the double-blind treatment phase.

Of the 25 enrolled subjects, all subject records were reviewed for the following topics: informed consent, eligibility, investigational product, primary efficacy endpoint, adverse events (to include neuropsychiatric events), protocol deviations, discontinuations, laboratory abnormalities and liver/renal/lipid profiles. All records were adequate and were consistent with data submitted to the application in support of NDA 211994. Protocol deviations were reported as appropriate to the sponsor and IRB.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. The primary endpoint was verifiable, and all source data matched with the data listings submitted to the application. The data from Site 222181, associated with Study 205543 appear reliable.

2. Dr. Gustavo Lopardo, M.D. (Site 223550; Study 205543)

The site screened 30 subjects and 24 subjects were enrolled and received test article. At the time of this inspection of the 24 subjects enrolled, 23 had completed the study and are currently participating in the open-label phase of the study. One subject was discontinued by the clinical investigator due to suicidal ideation. Informed consents were reviewed for all study subjects. The inspection covered a review of the source data and compared it to the data listings submitted to the application. Special attention was given to screening, entry criteria compliance, randomization, documentation of study-specific assessments, primary and secondary efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol. Review of regulatory documentation, monitoring practices, study medication accountability, and delegation of authority was also completed.

Records were sufficient to document the existence of each subject, as well as their
historical and current medical conditions. Site data recorded in the study records was compared to endpoint events and adverse events in the data listings submitted to the application. No discrepancies were observed.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. The efficacy endpoint data were verifiable, and consistent with the data listings submitted to the application. The data from Site 223550, associated with Study 205543, appear reliable.

3. Dr. Norma Porteiro, M.D. (Site 221100; 204861)

The site screened 43 subjects and 34 subjects were enrolled and received test article. At the time of this inspection 33 subjects had completed the study and 33 subjects are currently participating in the open-label phase of the study. One subject was discontinued by the clinical investigator due to medication non-compliance. Informed consents were reviewed for all study subjects. The inspection covered a review of the source data and compared it to the data listings submitted to the application. Special attention was given to screening, entry criteria compliance, randomization, documentation of study-specific assessments, primary and secondary efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol. Review of regulatory documentation, monitoring practices, study medication accountability, and delegation of authority was also completed.

Records were sufficient to document the existence of each subject, as well as their historical and current medical conditions. Site data recorded in the study records was compared to endpoint events and adverse events in the data listings. No discrepancies were observed.

The inspection revealed no significant deficiencies. There was no evidence of under-reporting of AEs. The efficacy endpoint data were verifiable, and consistent with the data listings submitted to the application. The data from Site 221100, associated with Study 204861, appear reliable.

4. Dr. Juan Sierra-Madero, M.D. (Site 222250; Study 205543)

The site screened 27 subjects, of which 24 were unique subjects as there were three subjects who were re-screened with a new subject identifier and enrolled on the second screening attempt. Twenty subjects were enrolled/randomized. At the time of this inspection two subjects had discontinued; one subject was removed from the study prior to Week 48 due to liver toxicity and one subject withdrew consent after Week 48 but prior to Week 96 because they were leaving the area for an extended period. Seventeen subjects had reached the open-label phase of the study.

A total of 20 subjects’ records were audited during this inspection.

The inspection covered a review of the source data and compared it to the data listings submitted to the application focusing on screening, entry criteria compliance,
randomization, documentation of study-specific assessments, primary and secondary efficacy endpoints, adverse events reporting, concomitant medications, and adherence to protocol. Review of regulatory documentation, monitoring practices, study medication accountability, and delegation of authority was also completed.

Overall the study site was found to be well-run, however, there were noteworthy inspectional observations. The protocol was not always followed with respect to study visits. Briefly, the Protocol, Section 5.4.1.4., ‘Managing subjects with HIV-1 RNA ≥ 50 c/mL at study Weeks 24, 48, 96, and 144’ specifies that, at study Weeks 24, 48, 96, and 144 (key study efficacy endpoint visits), a repeat HIV-1 RNA testing is required for any HIV-1 RNA ≥ 50 c/mL, and it must be performed at the Week 28, Week 52, Week 100, and Week 148 study visits, respectively. The protocol also states that those subjects whose HIV-1 RNA is <50 c/mL at Weeks 24, 48, and 96 did not need to attend the Week 28, Week 52, and Week 100 study visits, respectively. However, this site had all study subjects return to the study site on Week 28. Of the 20 subjects who attended the Week 28 study visit, only four subjects had an HIV-1 RNA value of ≥ 50 c/mL at their Week 24 visit. Therefore, 16 of 20 subjects (80%) who attended this study visit were not required to do so according to the protocol. Likewise, of the 19 subjects who attended the Week 52 study visit, only three subjects had an HIV-1 RNA value of ≥ 50 c/mL at their Week 48 study visit. Therefore, 16 of 19 subjects (84%) who attended this visit were not required by protocol to do so. The FDA field investigator was told by site staff that the study site intentionally required all subjects to attend the Week 28 and Week 52 study visits. They enforced this local policy by only dispensing a four-week supply of each study medication to subjects at the Week 24 and Week 48 study visits and withholding the remaining eight weeks' worth of IVRS-assigned medication for these visits until the subjects returned at Week 28 and Week 52. While no subjects were placed at risk, it is a deviation from the protocol to require all subjects to return to the clinical for extra study visits.

**OSI Reviewer Notes:** In a written response to the inspectional observations, dated February 25, 2019, Dr. Sierra Madero stated that he agreed with the inspectional observation and stated that it was discovered during a clinical monitoring visit on January 31, 2018. However, Dr. Sierra Madero explained that this practice was done intentionally. Briefly, detection of HIV-1 viral load ≥ 50 c/mL at weeks 24 and 48 required calling the subjects back to attend a new visit for a repeat viral load test after only 4 weeks. He explained that the time from obtaining the results of the Week 24 and 48 viral load results and the new subsequent visit was very short. It was Dr. Sierra Madero’s judgement this could result in the risk of subjects refusing (or not being able) to return to the clinic with such short notice. To prevent this from happening the investigator asked all the subjects to attend the study week 28 and 52 visits, just 4 weeks after the study week 24 and 48 visits, respectively, and be informed of the results of the viral load. If the subject’s study Week 24 or 48 results indicated a HIV RNA value ≥ 50 c/mL, blood draws would be taken to confirm virologic failure as required by the protocol. Dr. Sierra Madero provided a corrective action plan in his written response the to the Form FDA 483 that included submission of these protocol deviations to the local Ethics Committee and cancelling the practice of extra subject...
visits moving forward. Furthermore, Dr. Sierra Madero agreed that these were planned protocol deviations that should have been discussed with the study sponsor prior to implementation. These protocol deviations, do not appear to have placed subjects at undue risk, or have importantly impacted overall study outcomes.

Inspectional observations also found that the protocol was not followed with respect to Investigational Product (IP) dispensing. The site also failed to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation as it related to IP dispensing. Specifically, per protocol, for subject visits for study Weeks 24 and 48, the study subjects were supposed to receive twelve weeks of study medication to use until their Week 36 and Week 60 visits. However, IP was not dispensed according to the protocol at this clinical site.

First, the field investigator found that for all enrolled subjects at this study site, there are source documents (test article-dispensing log) indicating that all 12 weeks of the IVRS assigned study medication were dispensed for a total of 20 subjects at Week 24 and 19 subjects at Week 48. However, other documentation at the site indicated that the site only dispensed 4 weeks of study medication to subjects at these visits and the remaining IP was dispensed to each returning subject at the Week 28 and Week 52 study visits. The test article-dispensing log was initially completed documenting that all protocol-required study medication was dispensed at the Week 24 and 48 visits despite bottles actually being withheld at each of these visits. The records were later corrected to reflect the actual dispense dates on Weeks 28 and 52 for all subjects, as appropriate.

Second, the pharmacy records did not indicate that medication was dispensed to subjects at Weeks 28 and 52. There was no information in the subject records regarding study procedures which occurred regarding IP dispensing practices.

OSI Reviewer Notes: In a written response to the inspectional observations, dated February 25, 2019, Dr. Sierra Madero stated that he agreed with the inspectional observation. This issue was also discovered initially during a clinical monitoring visit on January 31, 2018. He explained that there was a miscommunication between the study coordinator and the pharmacy personnel resulting in these inconsistencies in IP dispensing documentation. The IP dispensing log documented the provision of medication for study subjects for one month whereas the notes in the subjects’ chart documented providing study medication for 3 months. Corrective actions included adding notes to the medical charts to reflect the true IP dispensing procedures for the affected subjects. The EC was also informed of the issues as described above. Preventative actions have since been implemented and included site staff training for dispensing study medications per the IVRS and protocol requirements, and the addition of clarifications and/or corrections to study source documents. The IP distribution practices, and corresponding IP accountability discrepancies, are serious protocol deviations. However, the explanation and corrective and preventative actions should mitigate these inspectional observations moving forward. The inspectional evidence supports that subjects did receive, albeit not according to the protocol, their
assigned IP for use during the conduct of the study. Subjects were not placed at undue risk and this local procedure should have no impact on overall study outcomes.

Finally, the site failed to assure that an IRB/EC was responsible for the initial and continuing review and approval of a clinical study. The inspection found that the EC responsible for the oversight of the study site originally approved the conduct of Protocol 205543 July 21, 2016, with an indicated expiration date of the approval on July 21, 2017. There is no record at the study site of the EC reapproving the study at this site until February 26, 2018, a period gap of approximately 7 months. During this time, the study site continued to see study subjects for assessments and distribution of investigational medicinal products.

OSI Reviewer Notes: In a written response to the inspectional observations, dated February 25, 2019, Dr. Sierra Madero stated that he agreed with the inspectional observation. This issue was also discovered initially during a clinical monitoring visit on January 31, 2018. On February 23, 2018 the study site submitted the request for the annual re-approval to the EC which was granted on February 26, 2019. A subsequent re-approval request was sent to the site EC on November 28, 2018 and was granted with an expiration date of December 10, 2019.

The inspectional observations noted above should not importantly impact overall study outcomes or have placed subjects at undue risk. The inspection revealed no other significant deficiencies. There was no evidence of under-reporting of AEs. The efficacy endpoints were verifiable, and all source data matched with the data listings submitted to the application. The data from Site 222250, associated with Study 205543 appear reliable.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Susan Thompson, M.D., Team Leader
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Kassa Ayalew, M.D., M.P.H., Branch Chief
Good Clinical Practice Assessment Branch
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cc:

Central Doc. Rm. NDA #211994
DAVP /Division Director/Debra Birnkrant, M.D.
DAVP/Deputy Division Director/Jeff Murray
DAVP/Medical Team Leaden/Kim Struble, M.D.
DAVP/Medical Officer/Benjamin Lorenz, M.D.
DAVP/Regulatory Project Manager/Anitra Johnson,
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Susan Thompson
OSI/DCCE/GCP Reviewer/Lauren Iacono-Connors
OSI/ GCP Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters
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/s/

LAUREN C IACONO-CONNORS  
03/14/2019 09:25:00 AM

SUSAN D THOMPSON  
03/14/2019 10:59:41 AM

KASSA AYALEW  
03/14/2019 05:01:54 PM
### LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

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<th>Date of This Review:</th>
<th>March 13, 2019</th>
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<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Antiviral Products (DAVP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 211994</td>
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<tr>
<td>Product Name and Strength:</td>
<td>Dovato (dolutegravir and lamivudine) Tablets, 50 mg/300 mg</td>
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<td>Product Type:</td>
<td>Multi-Ingredient Product</td>
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<td>Rx or OTC:</td>
<td>Prescription (Rx)</td>
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<tr>
<td>Applicant/Sponsor Name:</td>
<td>ViiV Healthcare Company (ViiV)</td>
</tr>
<tr>
<td>FDA Received Date:</td>
<td>October 18, 2018 and March 4, 2019</td>
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<td>OSE RCM #:</td>
<td>2018-2265</td>
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<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Valerie S. Wilson, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Sevan Kolejian, PharmD, MBA</td>
</tr>
</tbody>
</table>
1  REASON FOR REVIEW
As part of the approval process for Dovato (dolutegravir and lamivudine) Tablets 50 mg/300 mg, the Division of Antiviral Products (DAVP) requested that we review the proposed prescribing information, patient package insert, and container label for areas that may lead to medication errors.

2  MATERIALS REVIEWED
We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
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<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
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<tr>
<td>Previous DMEPA Reviews</td>
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<td>Human Factors Study</td>
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<tr>
<td>Other</td>
<td>F (N/A)</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance
3 FINDING AND RECOMMENDATIONS

Tables 2 and 3 below include identified medication error issues with the submitted container label, DMEPA’s rationale for concern, and the proposed recommendations to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Antiviral Products

<table>
<thead>
<tr>
<th>Prescribing Information</th>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Issues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>We note that the primary display panel of the container label does not include an Alert Box to alert end users about a potentially serious drug-drug interaction, contraindication.</td>
<td>The prescribing information includes warning that DOVATO is contraindicated in patients receiving dofetilide due to the risk for serious and/or life-threatening events which may occur with co-administration of these drugs.</td>
<td>Based on communication with the Clinical Team, we defer to the Division to assess and communicate to the Applicant if an “Alert” box should be included on the container label for Dovato.</td>
</tr>
</tbody>
</table>

Table 3: Identified Issues and Recommendations for ViiV Healthcare Company (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>Container Labels, Carton Labeling, and Packaging</th>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Labels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. The number “30” within the net quantity statement competing in prominence with important information (e.g. product strength) on the principal display panel (PDP).</td>
<td>The net quantity shares numeric overlap with the strength (30 vs 300). The net quantity statement should appear away from the product strength statement and should be less prominent than the product strength statement</td>
<td>To mitigate confusion or misinterpretation, we recommend you revise the number ‘30’ within the net quantity statement to appear in the same color as the word ‘tablets’ that follows it. Additionally, we recommend you consider presenting the product strength in a</td>
<td></td>
</tr>
</tbody>
</table>
4 CONCLUSION

Our evaluation of the proposed prescribing information, patient package insert, and container label identified areas of vulnerability that may lead to medication errors. Above, we have provided a recommendation in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

---

Table 4 presents relevant product information for Dovato received on March 4, 2019 from ViiV Healthcare Company.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Dovato</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Approval Date</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>Active Ingredient</td>
</tr>
<tr>
<td>dolutegravir and lamivudine</td>
</tr>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no known substitutions associated with resistance to the individual components of Dovato</td>
</tr>
<tr>
<td>Route of Administration</td>
</tr>
<tr>
<td>Oral</td>
</tr>
<tr>
<td>Dosage Form</td>
</tr>
<tr>
<td>Tablets</td>
</tr>
<tr>
<td>Strength</td>
</tr>
<tr>
<td>50 mg/300 mg</td>
</tr>
<tr>
<td>Dose and Frequency</td>
</tr>
<tr>
<td>1 tablet once daily</td>
</tr>
<tr>
<td>How Supplied</td>
</tr>
<tr>
<td>Bottles of 30 tablets</td>
</tr>
<tr>
<td>Storage</td>
</tr>
<tr>
<td>Store below 30°C (86°F).</td>
</tr>
<tr>
<td>Container Closure</td>
</tr>
<tr>
<td>Bottles with child-resistant closure</td>
</tr>
</tbody>
</table>
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Dovato labels and labeling submitted by ViiV Healthcare Company.

- Container label received on October 18, 2018 and March 4, 2019
- Prescribing Information and Patient Package Insert (Image not shown) received on March 4, 2019 available at: \cdsesub1\evsprod\nda211994\0014\m1\us\114-labeling\1141-draft\draft-annotated.pdf

G.2 Label and Labeling Images

Received March 4, 2019:

\(\text{Reference ID: 4402892}\)

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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VALERIE S WILSON
03/13/2019 08:59:42 AM

SEVAN H KOLEJIAN
03/13/2019 10:47:12 AM