



NDA 22187/S-010

SUPPLEMENT APPROVAL

Janssen Products, L.P.
Attention: Nancy Nair, Pharm.D., M.B.A.
Associate Director, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Dr. Nair:

Please refer to your Supplemental New Drug Application (sNDA) dated July 13, 2012, received July 13, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Intelence® (etravirine) tablets, 25 mg, 100 mg, 200 mg.

We also refer to our letter dated June 14, 2012, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for antiretroviral products. This information pertains to revised drug-drug interaction information based on additional review of drug-drug interaction data and the risk of the autoimmune disorder as syndromes that can occur in the setting of immune reconstitution with the use of antiretroviral products.

This supplemental new drug application provides for revisions to the labeling for Intelence® (etravirine) tablets, 25 mg, 100 mg, 200 mg, consistent with our June 14, 2012 letter as follows (additions are noted by underline and deletions are noted by ~~strike through~~).

1. The **RECENT MAJOR CHANGES** in the **HIGHLIGHTS** section of the label has been revised as follows:

----- RECENT MAJOR CHANGES -----	
Indications and Usage (1)	3/2012
Dosage and Administration	3/2012
Children and Adolescents (2.2)	
Method of Administration (2.3)	
<u>Warnings and Precautions</u>	
<u>Immune Reconstitution Syndrome (5.3)</u>	<u>XX/2012</u>

2. The revision date has been changed from 03/2012 to XX/2012 at the end of the **HIGHLIGHTS** section of the label.

3. The **WARNINGS AND PRECAUTIONS /Immune Reconstitution Syndrome** subsection has been revised as follows:

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including INTELENCE[®]. During the initial phase of combination antiretroviral treatment, patients whose immune system responds may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium-complex* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia (PCP), and or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable, and can occur many months after initiation of treatment.

4. The Table 3 in the **DRUG INTERACTIONS** section has been revised as follows:

Table 3: Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction [See Clinical Pharmacology (12.3)]		
Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE [®] with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE [®] . INTELENCE [®] and other NNRTIs should not be co-administered.
delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE [®] and delavirdine should not be co-administered.
rilpivirine	↓ rilpivirine ↔ etravirine	<u>Combining two NNRTIs has not been shown to be beneficial. INTELENCE[®] and rilpivirine should not be coadministered.</u>

5. The end section the **Patient Information** has been revised as follows:

Revised ~~March 2012~~ MM2012

We have completed our review of this supplemental application. 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 package insert, text for the Patient Information), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. 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).

If you have any questions, call Kyong Hyon, Safety Regulatory Project Manager, at (301) 796-0734.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Deputy Director for Safety
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

KENDALL A MARCUS
08/10/2012