Tibotec Therapeutics
430 U.S. Highway 22 East
Bridgewater, NJ 08807

www.tibotectherapeutics.com

IMPORTANT DRUG WARNING

August 2009

Dear Healthcare Professional:

Tibotec Therapeutics, in cooperation with the U.S. Food and Drug Administration, would like to inform you of an important safety update to the Severe Skin Reactions WARNINGS AND PRECAUTIONS section (5.1) of the INTELENCE™ (etravirine) tablets prescribing information.

Specifically, the existing Warning and Precaution regarding Severe Skin Reactions has been strengthened to reflect that there have been postmarketing reports of:

- fatality due to toxic epidermal necrolysis
- hypersensitivity reactions, sometimes accompanied by hepatic failure

Additionally, Guidance has been added that INTELENCE should be immediately discontinued when signs and symptoms of severe skin or hypersensitivity reactions develop. Given the clinical relevance of these adverse reactions, the following information regarding severe skin and hypersensitivity reactions has been included in the INTELENCE Prescribing Information:

5 WARNINGS AND PRECAUTIONS

5.1 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme. Hypersensitivity reactions have also been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure. In Phase 3 clinical trials, Grade 3 and 4 rashes were reported in 1.3% of subjects receiving INTELENCE™ compared to 0.2% of placebo subjects. A total of 2% of HIV-1-infected subjects receiving INTELENCE™ discontinued from Phase 3 trials due to rash [*see Adverse Reactions (6)*]. Rash occurred most commonly during the first 6 weeks of therapy.

Discontinue INTELENCE™ immediately if signs or symptoms of severe skin reactions or hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia). Clinical status including liver transaminases should be monitored and appropriate therapy initiated. Delay in stopping INTELENCE™ treatment after the onset of severe rash may result in a life-threatening reaction.

In addition, the following sections of the INTELENCE Prescribing Information have been updated to include this new information: Highlights of Prescribing Information, Adverse Reactions and Patient Counseling. Furthermore the “What are the possible side effects of INTELENCE?” section of the patient Package Insert has also been updated.

Clinical Trials Experience

In Phase 3 studies, the most frequently reported adverse drug reaction of at least Grade 2 in severity was rash (9.0%). Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme were reported in < 0.1% of subjects during clinical development with INTELENCE . In general, in clinical trials, rash was mild to moderate, occurred primarily in the second week of therapy, and was infrequent after Week 4. Rash generally resolved within 1-2 weeks on continued therapy. A total of 2% of HIV-1 infected subjects in Phase 3 trials receiving INTELENCE discontinued due to rash.

Overall, the cases referenced above within clinical and post-marketing experience illustrate the importance of clinical vigilance and familiarity with the signs and symptoms of severe skin rash and hypersensitivity reactions. Additionally they also underscore the importance of immediate discontinuation of INTELENCE in cases where severe rash or hypersensitivity reaction is suspected.

Enclosed, please find the updated Prescribing Information as well as the Patient Package Insert.

Please see INTELENCE Indication and additional Important Safety Information included on page 3 and page 4 of this letter.

Tibotec Therapeutics is committed to ensuring that INTELENCE is used safely and effectively and providing you with the most current information for our products.

Should you have any questions, require further information on product safety, or wish to report adverse patient experiences, please contact Tibotec Therapeutics Medical Information at 1-877-REACH TT (1-877-732-2488).

Alternatively, adverse events may be reported to FDA's MedWatch reporting system

- By phone (1-800-FDA-1088), by facsimile (1-800-FDA-0178),
- Online (https://www.accessdata.fda.gov/scripts/medwatch/) or
- Mailed, using the MedWatch FDA 3500 postage paid form, to the FDA Safety Information and Adverse Event Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787

Sincerely,

Ron Falcon, MD
Vice President, Clinical Affairs

About INTELENCE™ (etravirine) Tablets

INTELENCE, in combination with other antiretroviral agents (ARVs), is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in ARV treatment–experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other ARVs.

This indication is based on Week 24 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE. Both studies were conducted in clinically advanced, 3-class ARV (NNRTI, N(t)RTI, protease inhibitor [PI]) treatment-experienced adults.

The following points should be considered when initiating therapy with INTELENCE:

- Treatment history and, when available, resistance testing, should guide the use of INTELENCE
- The use of other active ARVs with INTELENCE is associated with an increased likelihood of treatment response
- In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE in combination with only N(t)RTIs
- The risks and benefits of INTELENCE have not been established in pediatric patients or in treatment-naïve adult patients

Additional Important Safety Information

Warnings & Precautions

- **Fat Redistribution:** Redistribution and/or accumulation of body fat have been observed in patients receiving antiretroviral (ARV) therapy. The causal relationship, mechanism, and long-term consequences of these events have not been established

- **Immune reconstitution syndrome** has been reported in patients treated with ARV therapy, including INTELENCE

Use in Specific Populations

- **Hepatic Impairment:** INTELENCE should be used with caution in patients with severe hepatic impairment (Child-Pugh Class C) as pharmacokinetics of INTELENCE have not been evaluated in these patients

Adverse Reactions

- The most common adverse events (>10%) of any intensity that occurred at a higher rate than placebo were rash (16.9% vs. 9.3%) and nausea (13.9% vs. 11.1%)

- The most common treatment-emergent adverse reactions (Grade 2-4) that occurred in patients receiving an INTELENCE-containing regimen vs. placebo were rash (9.0% vs. 3.1%), diarrhea (5.2% vs. 9.6%), nausea (4.7% vs. 3.5%), fatigue (3.3% vs. 4.0%), abdominal pain (3.0% vs. 2.5%), peripheral neuropathy (2.8% vs. 1.8%), hypertension (2.8% vs. 2.2%), headache (2.7% vs. 4.1%), and vomiting (2.3% vs. 2.0%)

Drug Interactions

- INTELENCE should not be co-administered with the following ARVs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, full-dose ritonavir (600 mg bid), protease inhibitors administered without ritonavir, and other NNRTIs

- INTELENCE should not be co-administered with carbamazepine, phenobarbital, phenytoin, rifampin, rifapentine, rifabutin (when part of a regimen containing protease inhibitor/ritonavir) or products containing St. John's wort (Hypericum perforatum)

- INTELENCE and lopinavir/ritonavir should be co-administered with caution

- Co-administration of INTELENCE with other agents such as substrates, inhibitors, or inducers of CYP3A4, CYP2C9, and/or CYP2C19 may alter the therapeutic effect or adverse events profile of INTELENCE or the co-administered drug(s). **This is not a complete list of potential drug interactions**

Please see accompanying full Prescribing Information for more details.

28NTL0106