

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-187**

**OFFICE DIRECTOR MEMO**

**Acting Deputy Office Director and Office Director Memo**

**Applicant:** Tibotec, Inc.

**NDA #:** 22-187

**Established Name:** etravirine

**Trade Name:** Intelence™

**Dosage Form and Strength:** tablet, 100 mg

**Review Classification:** Priority

**Indication and Usage Section**

INTELENCE™, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral 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 antiretroviral agents.

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 antiretroviral (NNRTI, N[t]RTI, 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 antiretroviral agents 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 [see Clinical Studies (14)].
- The risks and benefits of INTELENCE™ have not been established in pediatric patients or in treatment-naïve adult patients.

**Proposed Dose**

The recommended oral dose of INTELENCE™ tablets is 200 mg (two 100 mg tablets) taken twice daily following a meal.

**Date of Initial Submission:** July 18, 2007 (stamp date)

**PDUFA Goal Date:** January 18, 2008

**Regulatory Action:** Approval (accelerated approval under 21 CFR § 314.500)

### **Background**

Intelence™ (etravirine) is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It acts by inhibiting the action of the HIV reverse transcriptase. There are other approved non-nucleoside reverse transcriptase inhibitors available including nevirapine, efavirenz, and delavirdine. Etravirine retains activity against many HIV isolates that contain the K103N mutation. Hence etravirine addresses an unmet medical need in that it will provide a treatment option for treatment experienced patients with resistance to other NNRTIs in the setting of clinical failure.

Each of the available approved NNRTIs contains information in their product labeling about their respective safety profiles. Nevirapine has a boxed Warning on severe life-threatening hepatic toxicity and severe life-threatening skin reactions and has a Medication Guide. Efavirenz includes Warnings on psychiatric symptoms and nervous system symptoms and includes a Precaution on skin rash that includes Stevens-Johnson syndrome among the listed Grade 4 rashes. The delavirdine label includes a section in the Precautions section on skin rash that includes severe rash including rare cases of erythema multiforme and Stevens-Johnson syndrome.

There is a continued public health need for patients to have additional therapeutic options to treat HIV infection. An addition to the therapeutic armamentarium will allow for the construction of treatment regimens to which treatment experienced patients' HIV is sensitive.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of etravirine for the treatment of HIV infection in antiretroviral experienced adult patients. For a detailed discussion of NDA 22-187, the reader is referred to the individual discipline specific reviews. In addition Dr. Marcus's Team Leader's Memo and Dr. Birnkrant's Division Director's Memo summarize key issues in the NDA submission. This memorandum will focus on selected issues from the application.

### **Chemistry Manufacturing and Controls**

The chemistry manufacturing and controls are summarized in the Chemists' review which recommends approval from the standpoint of CMC for etravirine. Facilities inspections were performed and found to be acceptable. The recommendation regarding CMC is for approval.

### **Pharmacology Toxicology**

The recommendation from Dr. Wu with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. In animals, liver was the primary target organ of toxicity. Several toxicities were noted that were assessed as species specific, including thyroid toxicity in rats and clotting abnormalities and associated cardiac toxicity in rats. Etravirine is categorized as Pregnancy Category B. The completion of the ongoing carcinogenicity studies in rats and mice and submission of study reports are included in the postmarketing commitments.

### **Microbiology**

The microbiologic assessment of etravirine is discussed in Dr. Naeger's microbiologist's review. The microbiologist's recommendation is for approval. As noted in the microbiologist's review, etravirine shows antiviral activity against 55 of 65 HIV-1 strains with single amino acid substitutions at the reverse transcriptase positions associated with NNRTI resistance, including the most commonly found K103N. Mutations associated with etravirine resistance and efavirenz cross-resistance were also identified. In the setting of virologic failure with an etravirine containing regimen, cross-resistance to nevirapine, efavirenz, and delavirdine is expected.

### **Clinical Pharmacology**

The clinical pharmacology of etravirine is discussed in the clinical pharmacology and biopharmaceutics and pharmacometrics review which notes that the information provided by the applicant is acceptable.

The two key formulations used in the etravirine phase 2 and phase 3 trials were TF035 and F060. The exposure produced by TF035 at a dose of 800 mg po bid was somewhat lower than the exposure produced by the F060 formulation at a dose of 200 mg po bid. Also of note is that in the phase 3 trials of the F060 to-be-marketed formulation, all patients received darunavir/ritonavir at a dose of 600/100 mg bid which reduces the exposure of etravirine by approximately 40%. The clinical pharmacology review notes that "As the pivotal efficacy and safety data was collected at these reduced etravirine exposures, the determination of appropriate dosing recommendations to support co-administration of TMC-125 with other ritonavir boosted protease inhibitors or without ritonavir boosted protease inhibitors represented a major omission."

The phase 3 trials were designed to provide for the use of two new investigational agents in order to increase the likelihood of a better response in treatment experienced patients in the setting of resistance to previous antiretroviral therapies. The trials did achieve this goal. However, the use of darunavir/ritonavir in combination with etravirine lowered etravirine exposures. We also have data from the phase 2 program where patients received the TF035 formulation of etravirine (a formulation with lower bioavailability) along with lopinavir/ritonavir, a combination that increases etravirine exposure. The net effect of the lower bioavailability and lopinavir/ritonavir was exposures that were not higher than the exposures in the phase 3 trials. While the number of patients is smaller in the phase 2 program and the TF035 formulation was used in these studies, the phase 2 program also provides some additional data to address the safety profile of etravirine.

The clinical pharmacology team leader review provides an analysis based upon PK and drug interaction data to evaluate a scenario where a patient would experience a high exposure because of co-administration of lopinavir/ritonavir with etravirine. Note that the label cautions clinicians about the use of co-administered lopinavir/ritonavir so this is intended to represent a scenario where drug exposure would be high. Based upon this analysis, 17% of subjects from the phase 3 trial had exposure in the range of an AUC<sub>12</sub> of 10,000-30,000 ng\*hr/mL. In the setting of a high exposure because of co-administration

of lopinavir/ritonavir, approximately 50% of patients would fall into the category of AUC<sub>12</sub> 10,000-30,000 ng\*hr/mL with considerably fewer patients experiencing exposures in the higher AUC categories. (Please see Dr. Reynolds review for the table on AUC.) The data from the AUC comparisons provide information on the extent of safety data available from the phase 3 trials (17% of subjects from the phase 3 trials) to evaluate safety at higher exposures.

Because etravirine had the potential to meet an unmet medical need, the review team in DAVP granted fast track status and provided guidance to the company on their phase 3 clinical trial program that used the new formulation of etravirine (F060). The review teams in DAVP and the Office of Clinical Pharmacology strongly encouraged the applicant to obtain additional pharmacokinetic information during the phase 3 studies. The applicant collected week 4 trough and peak samples and additional random samples for pharmacokinetic analyses from all subjects in the phase 3 studies, in addition to a subset of subjects that received formal pharmacokinetic samplings. This represented a unique opportunity to characterize each individual subject into different exposure categories. The clinical pharmacology and clinical reviewers evaluated the adverse event profiles of the highest quartile of etravirine exposures in order to evaluate AEs in the highest quartile of exposure compared to the rates of AEs with that observed in the other quartiles combined. The purpose of the high quartile analysis is to evaluate whether AEs occurred more frequently in the upper quartile, a quartile with exposures that overlaps with the patients in the AUC 10,000 to 30,000 ng\*hr/mL from the phase 3 data described above. The analyses of adverse events by quartile found the following for the highest quartile compared to the other quartiles combined:

- Discontinuations due to adverse events were 5/145 (3.5%) in the highest quartile vs. 24/431 (5.5%) in the other quartiles combined.
- Discontinuations due to rash were 2/145 (1.4%) in the highest quartile versus 10/431 (2.3%) in the other quartiles combined.
- Grade 3 or 4 rash AEs of 0/145 (0%) in the highest quartile versus 7/431 (1.6%) in the other quartiles combined.
- Under the category of metabolism and nutrition disorders the rates of the following adverse events were slightly higher in the highest quartile (N=145) compared to the other quartiles (N=431) for the following adverse events, hypertriglyceridemia 4.1% vs. 2.8%; hypercholesterolemia 3.4% vs. 2.1%, diabetes mellitus 2.1% vs. 0.7%; dyslipidemia 2.1% vs 0.7%; the rates for these same adverse events in the placebo group (N=604) are 1.7%, 0.7%, 0.3%, 0.8%, respectively.
- There is a higher rate of rash in patients in the highest quartile 11.7% vs 7.9%. (this relationship is also noted in the clinical pharmacology review in an evaluation of exposure and occurrence of rash.) As noted above, the difference is from rash in categories other than grade 3 or 4 rash.
- The number of deaths in the highest quartile group is 1/145 (0.69%) and 6/431 (1.39%) deaths in the other quartiles group. (There were 2 additional deaths for which we do not have PK data.)

Given the findings from analysis of adverse events comparing the highest quartile to the other quartiles, and taking into consideration the types of aforementioned adverse events, the data support that it is reasonable to provide adverse event information for labeling that allows for use of etravirine and accounts for potential safety concerns that might be observed with higher exposures of etravirine. (see Dr. Mulick's review for additional information on the highest quartile analysis performed.)

The clinical pharmacology staff also provided information on the drug interactions section of the product labeling to guide physicians in the use of other antiretroviral medications. Of note is that the labeling recommends that etravirine should not be co-administered with a number of protease inhibitors and boosted protease inhibitors. The information in the label should help to guide healthcare providers to the use of appropriate drugs in combination and should help to address the limitations noted in the clinical pharmacology review regarding the lack of information on appropriate dosing with protease inhibitors with or without ritonavir.

Etravirine exposure increased by 105% when taken with food compared to the fasted state and therefore the label recommends that etravirine should be taken with food. In vitro studies in hepatic microsomes showed that CYP3A and CYP2C (CYP2C and CYP2C19 to a lesser extent) play a major role in the metabolism of etravirine. A study of radiolabeled etravirine found that most of the administered drug was excreted in the feces. Etravirine is also a P-gp substrate and has weak inhibitory properties. The product labeling provides information to guide physicians on the appropriate co-administration of other therapies, as well as other therapies that should not be co-administered with etravirine.

In a thorough QT study, the upper bound for the  $\Delta\Delta QTcF$  90% confidence interval at a dose of etravirine 200 mg po bid was 3.2 ms and the upper bound for the 400 mg and 400 mg bid dose were less than what was seen with 200 mg in the setting of a moxifloxacin positive control with a  $\Delta\Delta QTcF$  of 9.8 ms with a 90% confidence interval of (5.5, 14.1).

Population pharmacokinetic analyses did not identify an influence of gender or race on exposure to etravirine. No dose adjustment is required in HIV positive patients with mild to moderate hepatic impairment.

Dose selection was based upon results from the phase 2 studies TMC125-C203 and TMC125-C223. The finding of an IQ of at least 400 maximized the probability of virologic success that guided dose selection was also supported by results from phase 3.

#### **Clinical Efficacy and Safety**

The results of the clinical trials evaluating the safety and efficacy of etravirine are discussed in detail in the Medical Officer's Review and the Statistical Review, and also in the reviews prepared by Dr. Marcus and Dr. Birnkrant. The statistical review concludes that etravirine 200 mg bid in combination with the background regimen has superior efficacy over placebo in combination with the background regimen for the treatment of HIV treatment-experienced adults who had previously taken or were

retaking enfuvirtide. The statistical reviewer notes that among the non de-novo enfuvirtide subjects, 56% of the etravirine subjects had HIV viral loads < 50 copies/mL at week 24 compared to 34% of the placebo subjects. In the two phase 3 studies, darunavir/ritonavir 600/100 mg was included in the background regimen. Also of note is that darunavir/ritonavir lowers exposure of etravirine by approximately 40%. The Medical Officer, Team Leader and Division Director recommend accelerated approval for etravirine. The reader is referred to their reviews for a detailed discussion of the safety and efficacy findings.

**Efficacy**

For information on dose selection, please see the section on Clinical Pharmacology. Data evaluating the efficacy of etravirine were derived from two phase 3 trials in treatment experienced patients.

These two phase 3 placebo controlled trials in treatment experienced patients compared etravirine with background therapy to placebo with background therapy and found etravirine to be superior to BT based upon suppression of HIV-1 viral load at the 24 week time point. The background therapy regimen in both arms included darunavir/ritonavir. As noted previously, darunavir/ritonavir lowered the exposure to etravirine by approximately 40%. The results for the primary efficacy analysis for viral load <50 copies/mL and the number of deaths are provided for the pooled phase 3 trials in the table below.

<b>Outcomes of Treatment at Week 24 of the TMC125-C206 and TMC125-C216 Trials (Pooled Analysis)</b>		
	<b>Pooled TMC125-C206 and TMC125-C216 Trials</b>	
	<b>INTELENCE™ + BR N=599</b>	<b>Placebo + BR N=604</b>
Virologic Responders at Week 24 Viral Load < 50 HIV-1 RNA copies/mL	358 (59.8%)	243 (40.2%)
Virologic Failures (VF) at Week 24 Viral Load ≥ 50 HIV-1 RNA copies/mL	190 (31.7%)	320 (53.0%)
Death*	9 (1.5%)	16 (2.6%)
Discontinuations before Week 24†:		
due to VF	2 (0.3%)	3 (0.5%)
due to Adverse Events	28 (4.7%)	11 (1.8%)
due to other reasons	12 (2.0%)	11 (1.8%)

\* all deaths, including the follow-up period  
† all discontinuations up to and including day 154 of the treatment period  
BR=background regimen

The statistical reviewer also evaluated the robustness of the data by evaluating the data using different approaches to imputing missing data and TLOVR; the sensitivity analyses did not change the conclusion that etravirine is superior to placebo.

### **Safety**

The overall safety database for etravirine is comprised of data from approximately 1200 HIV infected patients and approximately 1100 healthy subjects who received etravirine in clinical studies from phase 1 to phase 3. In the two phase 3 trials, there are 599 patients in the etravirine arms and 604 patients in the placebo arms. In the phase 3 trials, all patients received darunavir/ritonavir. Co-administration of darunavir/ritonavir with etravirine results in an approximately 40% reduction of exposure to etravirine. In addition to the data from the phase 1 to phase 3 trials, as of July 2007 there were also over 2900 subjects enrolled in the expanded access program.

In the phase 3 trials, deaths occurred in 1.5% of subjects randomized to receive etravirine compared to 2.6% of subjects randomized to receive placebo.

Rash was a common adverse event that occurred in greater than 10% of subjects. In the pooled safety analyses from studies C206 and C216, rash occurred in 16.9% of subjects that received etravirine and 9.3% of subjects that received placebo. In general the rash appeared within 4 weeks of initiation of etravirine, was mild to moderate in severity, and resolved on continued therapy. As mentioned in the Clinical Pharmacology section, there appears to be a positive correlation between etravirine exposure categories and the incidence of mild or moderate rash. Approximately 2% of subjects discontinued therapy because of rash in the group that received etravirine, and 1.2% were characterized as Grade 3 or Grade 4 adverse events. A rash associated with hypersensitivity was observed in one subject that received etravirine in the phase 3 trials. Stevens-Johnson syndrome was observed in one subject from the phase 3 trials that received placebo; the syndrome was attributed to trimethoprim-sulfamethoxazole in this subject. Rash was observed in approximately 26% of subjects receiving etravirine in phase 2 studies receiving the TF035 formulation using combinations other than darunavir/ritonavir. Erythema multiforme minor occurred in two healthy adult subjects that received etravirine in phase 1 studies. In the expanded access program (over 2900 subjects enrolled as of July 2007), Stevens-Johnson syndrome occurred in three subjects that received etravirine. Two of the three subjects were also receiving darunavir/ritonavir, which has been associated with Stevens Johnson syndrome, and the other subject was not receiving darunavir/ritonavir as part of the combination antiretroviral regimen.

The product labeling includes a Warning and Precaution on Severe Skin Reactions that is also included in the Highlights of Prescribing Information. The Patient Package Insert also includes a section on the possible side effects of etravirine that informs patients about rash and serious rash and advises patients to call their doctor right away if the patient gets a rash.

Hepatic adverse events, most of which were Grade 1 and 2 events, were seen in 7.8% (47/599) of etravirine subjects compared to 7.1% (41/604) on the placebo arm. The frequency of Grade 3 or 4 hepatic AEs was the same (2.2%) across the treatment arms of the phase 3 trials. There were no Hy's Law cases in phase 3 trials. Evaluation of Grade 3/4 laboratory transaminases in phase 3 trials revealed a higher frequency in etravirine-

treated subjects compared to placebo. The rate of elevations for ALT was 2.7% versus 1.8% and for AST it was also 2.7% versus 1.8%. In the etravirine arm 0.3% of subjects were discontinued from treatment due to elevated transaminases.

Lipid abnormalities and initiation of lipid-lowering agents were observed more frequently in subjects that were randomized to receive etravirine (16.5%) in comparison to placebo (12.9%). Gastrointestinal, renal, and endocrine adverse events were observed with equal frequencies between the treatment groups.

Although the pre-clinical toxicology finding of hemorrhagic cardiomyopathy was felt to be a species-specific finding, deaths and adverse events due to any cardiovascular etiology were examined and found to be similar between treatment groups in the phase 3 studies (1.9% for etravirine and 1.5% for placebo). As noted in the Clinical Pharmacology section, a thorough QT study was performed and did not reveal significant prolongation of the QT interval.

The product labeling includes class labeling Warnings and Precautions on Fat Redistribution and also on Immune Reconstitution Syndrome.

Please also see the Clinical Pharmacology section of this review (and Dr. Mullick's review) for a discussion of analyses of adverse events in the subset of patients in the highest quartile of exposure compared to patients in the other quartiles.

The product labeling adequately describes findings from the safety evaluation to date. Additional data from ongoing studies, postmarketing commitments, and postmarketing surveillance will provide additional data to further characterize the safety profile of etravirine. A postmarketing commitment is also included in the approval letter (PMC #5) for the sponsor to provide data from a 48-week clinical study of etravirine in patients not receiving darunavir/ritonavir. The sponsor will also provide an interim analysis of the study including analysis of 12-week safety data.

**DSI Inspections / DDMAC / DMETS / DSRCS consults**

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name Intelence.

The Division of Scientific Investigations performed inspections of four sites and did not identify any significant observations that would compromise the integrity of the data.

Pediatric studies required under PREA for patients between 8 weeks and 18 years of age have been deferred as noted in the approval letter. This requirement was waived for patients less than 8 weeks of age because the indication for etravirine is for treatment-experienced patients, and patients less than 8 weeks of age would not be considered treatment-experienced.

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### **Advisory Committee**

The application was not referred to the Antiviral Drugs Advisory Committee because there are previously approved agents in the non-nucleoside class of drugs, evaluation of safety data did not reveal particular safety issues that were unexpected for this class of drugs, and the design and results of the safety and efficacy trials did not pose particular concerns.

### **Risk Benefit Summary**

The data support a favorable overall risk benefit profile for etravirine for its indication of use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to an NNRTI, and other antiretroviral agents. The results of the phase 3 studies provide evidence of efficacy based on a HIV-RNA response at 24 weeks that was statistically superior to placebo among groups randomized to receive etravirine. The increase in CD4 cell counts was greater among recipients of etravirine. The observations of a lower frequency of AIDS-defining illnesses and AIDS defining illnesses or death also supports the benefits of etravirine.

The phase 3 studies used the combination of darunavir/ritonavir, which lowers exposure to etravirine by approximately 40%. Efficacy would not be expected to be altered with higher pharmacokinetic exposures that might occur with the administration of etravirine in therapeutic antiretroviral combinations that did not include darunavir/ritonavir. Analyses evaluating adverse events in patients in the highest quartile of exposure reveal the expected finding of higher rash rates (based upon the exposure response analysis for rash) and other adverse event findings do not alter the risk benefit profile. Product labeling carefully describes the drug-drug interactions that guide prescribing practices for etravirine.

An adverse event of concern for etravirine is rash. The non-nucleoside agent nevirapine has a black box warning of severe skin reactions include Stevens Johnson syndrome and toxic epidermal necrolysis, and etravirine is in the same non-nucleoside class. Although severe skin reactions appeared to be rare in the safety database of the application, rash of any grade was a common adverse event that occurred in approximately in approximately 17% of subjects in phase 3 studies. Rash is described throughout appropriate sections of product labeling, and severe and potentially life-threatening skin reactions are placed in the Warnings And Precautions section, in the Highlights of Prescribing Information, and in the Patient Package Insert.

### **Postmarketing Study Commitments**

The postmarketing study commitments including commitments for accelerated approval under Subpart H and Pediatric studies are enumerated in the action letter. There is also a postmarketing commitment to perform a study designed to get additional information on

etravirine in the absence of darunavir/ritonavir in order to gain additional safety and antiviral activity data in the setting of higher exposures to etravirine.

**Summary**

I concur with the assessment of the review team that adequate safety and efficacy information have been provided for etravirine in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication of HIV-1 strains resistant to an NNRTI and other antiretroviral agents, under the subpart H accelerated approval regulations for serious or life-threatening illnesses (21CFR §314.510). The clinical studies show a clear beneficial effect on viral load and CD4 cell count and the safety profile is acceptable. The product labeling adequately describes the available information. Approval under Subpart H is appropriate for etravirine given that it can be used to construct antiretroviral treatment regimens in treatment-experienced patients with clinical isolates resistant to other classes of antiretroviral drugs, including resistance to other NNRTIs. As part of approval under Subpart H, the applicant will study the drug further to verify and describe its clinical benefit as described in the postmarketing study commitments under Subpart H listed above.

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/s/

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