CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-187

SUMMARY REVIEW

Date	January 16, 2008
From	Debra Birnkrant, M.D., Director, Division of Antiviral Products
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 22-187
Proprietary / Established (USAN) names	Intelence™/etravirine
Dosage forms / strength/dose	100 mg tablets/ 200 mg BID with food
Proposed Indication(s)	For 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
Action	Approval

1. **Introduction to Review:** This Division Director's memorandum summarizes salient features of NDA 22-187, Tibotec, Inc.'s New Drug Application (NDA) for etravirine, a new molecular entity in the class of NNRTIs. This review will cover safety and efficacy in detail; brief comments will cover pharmacology/toxicology, clinical pharmacology and clinical microbiology.

2. **Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status:** Currently, there are six antiretroviral drug classes and almost 25 marketed antiretroviral products for HIV treatment. They fall into the following distinct categories: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors, fusion inhibitors, CCR5 receptor antagonists, and integrase inhibitors. As there are an estimated 40,000 new cases of HIV per year in the United States and tens of millions infected worldwide with the virus, there continues to be a need for novel drugs to overcome significant treatment issues related to drug resistance, toxicity and adherence.

   Etravirine is an NNRTI developed by Tibotec, Inc. Regarding mechanism of action, etravirine binds directly to reverse transcriptase and blocks both RNA- and DNA-dependent DNA polymerase by disruption of the enzyme's catalytic site. It has potent in vitro activity and is also active against NNRTI resistant HIV-1 strains containing the K103N mutation.

   This NDA was submitted in July, 2007 and received a priority review because it meets an unmet medical need. This application was not presented at the Antiviral Products Advisory Committee because etravirine is the fourth member of the NNRTI

class of antiretrovirals, drug interactions are well described and no new safety signals emerged for this class of drugs.

3. **Chemistry, Manufacturing and Controls (CMC):** All CMC issues have been adequately addressed. The stability of the drug product has been demonstrated under ICH conditions. Further, CGMP inspections were satisfactory. Please see CMC reviews by Drs. Sharmista Chatterjee and Mark Seggel.

4. **Nonclinical Pharmacology/Toxicology:** The toxicity profile of etravirine was explored in multiple non-clinical studies. A thorough pharmacology/toxicology review was performed by Dr. K-M Wu. Per Dr. Wu's review, toxicity targets included: liver, kidney, thyroid, heart, clotting and hematologic parameters.

   - Hepatotoxicity was examined in rodents and dogs. In rodents, liver organ weight increases were seen as were enzyme elevations without bilirubin elevations. In the dog, liver enzyme elevations were accompanied by bilirubin elevations. Liver toxicity occurred at much higher drug exposures in the dog than in the rat or mouse. The margin of safety is around 7 using the dog as a model and < 1 for rodents.
   - Renal toxicities were not observed in the dog. In a 3-month rat study, focal renal tubular basophilia and high urinary excretion of electrolytes and protein were seen.
   - Thyroid toxicities in the rat appeared to be secondary to enhanced T4 clearance. No thyroid toxicity was reported in dogs or mice studied.
   - Hemorrhagic cardiomyopathy occurred in male mice. It appeared to be related to etravirine-induced clotting abnormalities in this species. Clotting abnormalities without cardiomyopathy were also seen primarily in male rats. The Applicant and FDA reviewers concluded that hemorrhagic cardiomyopathy is a mouse-specific entity.
   - Hematotologic toxicity was limited in animal studies. Increases in platelet counts were reported in mice. In the rat, one study showed increases in neutrophil counts. Bone marrow atrophy was seen in a one-month dog study that was felt to be secondary to weight loss in high-dose animals.

5. **Clinical Pharmacology/Biopharmaceutics:**
   Tibotec, Inc. conducted 36 trials to characterize the biopharmaceutics of etravirine. Important points from the primary clinical pharmacology reviewers, Drs. Vikram Arya and Pravin Jadhav include the following:

   - Metabolism is mediated through CYP 3A and CYP 2C; etravirine is mostly eliminated in the feces and renal excretion is a minor pathway.
   - Etravirine is a substrate of CYP3A and CYP2C (2C9 and 2C19). Therefore, co-administration with drugs that are inducers/inhibitors of these enzymes may alter plasma concentrations of etravirine with the potential for altered therapeutic effects and adverse reactions. It is also an inducer of CYP3A4 and

an inhibitor of CYP2C9 and CYP2C19. Therefore, co-administration with substrates of these enzymes may alter effects of the co-administered drugs.

- Etravirine is a P-gp substrate and a weak P-gp inhibitor.
- Food effect is significant and it is recommended that etravirine be given with food.
- Dose-finding studies were adequate. The dose selection was agreed upon at the end-of-phase 2 meeting. The dose selection for the registrational phase 3 efficacy and safety trials in HIV-1 infected subjects, TMC-125-206 (DUET-1) and TMC-125-216 (DUET 2) was based on the antiviral activity (change in $\log_{10}$ plasma viral load from Baseline at Week 24), safety (incidence and severity of adverse events and laboratory parameters), pharmacokinetics, and pharmacokinetic/pharmacodynamic assessments that were obtained from the primary analysis of the Phase 2b dose-escalating trial TMC125-C203 and the Phase 2b dose-finding trial TMC125-C223, both conducted in HIV-1 infected subjects with previous NNRTI experience and/or resistance. These earlier trials were conducted using TMC125 administered as a tablet formulation TF035 (TMC125 in HPMC, _ ——— , and therefore a second stage of the dose selection process investigated the correspondence of TMC125 dosing between formulation TF035 and the final, selected formulation F060 (TMC125 in HPMC, spray-dried) to be used in the phase 3 efficacy and safety trials and intended for commercialization.

- In phase 3 studies, etravirine was co-administered with darunavir/ritonavir. This combination resulted in a 37% decrease in the mean systemic exposure (AUC) of etravirene compared to those not receiving darunavir/ritonavir; clinical data from these trials support concurrent use despite the lower AUC. Dosing etravirine without concurrent darunavir/ritonavir could lead to higher exposures of etravirine. For example, dosing with lopinavir/ritonavir without boosted darunavir will lead to increased exposures of etravirene (mean AUC increased by 85% compared to etravirene exposures in phase 3 trials). FDA conducted an analysis comparing etravirine exposures across a population who receives etravirine with lopinavir/ritonavir compared to the distribution of exposures seen in phase 3 trials. Almost 50% of patients who receive etravirine with lopinavir/ritonavir may have an etravirine AUC between 10,000-30,000 ng *hr/ml while AUCs in this range were observed in only 17% of patients in phase 3 trials. It is concluded that the etravirine exposure in most patients who receive etravirine with lopinavir/ritonavir will not be higher than that observed in at least a small percentage of subjects in phase 3 trials, due to variability in etravirine pharmacokinetics. Labeling states that this combination should be co-administered with caution.

- A multitude of drug-drug interaction studies (DDIs) were performed. Selected drugs included other antiretrovirals and non-antiretroviral agents frequently taken by HIV infected patients. Based on DDIs, **etravirine should not be co-administered with the following drugs: tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, protease inhibitors**

administered without ritonavir, and other NNRTIs. Specifically, boosted tipranavir reduces etravirine plasma concentrations. Due to a significant increase in the systemic exposure of amprenavir (increased by 69%), the appropriate dose of etravirine with ritonavir-boosted fosamprenavir has not been established. The results of the DDI between etravirine and atazanavir/ritonavir showed that etravirine decreased the mean Cmin of atazanavir by 38%; this decrease is greater than the decrease in the mean Cmin of atazanavir in the presence of tenofovir which represents the lowest mean Cmin for which efficacy data are available. Therefore, the division does not support concomitant dosing of etravirine with ritonavir-boosted atazanavir.

- Information on DDIs will be adequately described in the package insert. A post-marketing commitment will be requested to examine pharmacokinetics and safety in 200 subjects who receive etravirine without darunavir/ritonavir due to the concern of higher exposures in the absence of darunavir/ritonavir.

6. **Clinical Microbiology:** The following points are excerpted from Dr. Lisa Naeger's extensive microbiology review.

- Etravirine is an NNRTI with antiviral activity against a broad panel of HIV-1 isolates with EC_{50} values ranging from 0.29-1.65 nM.
- Development of reduced susceptibility to etravirine required more than one substitution in reverse transcriptase and the following were observed most frequently: L100I, E138K, E138G, V179I, Y181C and M230I.
- In phase 3 trials, substitutions that developed most frequently in subjects who failed therapy at week 24 were: V179F, V170I, Y181C and Y181I.
- Etravirine shows antiviral activity against 85% of HIV-1 strains with single amino acid substitutions at RT positions associated with NNRTI resistance, including K103N.
- The following mutant strains exhibited cross-resistance between etravirine and efavirenz: K101P, K101Q, E138Q, or M230L.
- The highest levels of resistance to etravirine were observed for HIV-1 strains with the following combination of substitutions: V179F plus Y181C (187-fold change), V179F plusY181I (123 fold change) and V179F plus Y181C plus F227C (888 fold change).
- In phase 3 studies, response rates to etravirine decreased as the number of baseline NNRTI mutations increased. Response rates also decreased in the setting of baseline etravirine susceptibility > 3-fold.
- Treatment history and resistance should guide the use of etravirene.

7. **Efficacy/Statistical:** Please see reviews by Drs. Charu Mullick and Fraser Smith.

Efficacy and safety were based primarily on phase 3 trials, TMC-125-206 (DUET-1) and TMC-125-216 (DUET 2), identically designed trials that were implemented in different geographic regions. Briefly, etravirine was shown to be safe and effective in phase 3 trials.

More specifically, both 206 and 216 were randomized, double-blind, placebo-controlled phase 3 trials that compared etravirine 200 mg BID plus an optimized background regimen to an optimized background alone in triple-class resistant HIV-1 infected subjects; darunavir/ritonavir was included in the optimized background regimens in both arms. Select criteria for inclusion were antiretroviral therapy failure with plasma HIV RNA > 5000 copies/ml, at least 1 NNRTI mutation and at least 3 primary protease mutations at baseline. The primary efficacy endpoint was HIV RNA < 50 copies/ml at week 24. Analyses were pooled as the trials were identically designed.

Pooled efficacy analyses were based on the intention-to-treat population that included a total of 1203 subjects who received at least one study dose where 599 patients received etravirine plus background therapy and 604 subjects received placebo plus background therapy. The majority of subjects were male and Caucasian. With regard to HIV status, this was an advanced population with 36% of subjects having a CD4 count < 50 cells/mm3 and almost 60% having Stage C HIV. More than 50% of subjects did not have any NRTIs to which their virus was sensitive. Approximately half of randomized subjects had a PSS of 0-1. Subjects were also stratified by enfuvirtide use into the following categories: de novo (26%), re-used/not used (74%).

Results were highly statistically significant for the integrated analysis of efficacy as determined by the primary endpoint, HIV RNA < 50 copies/ml at week 24 comparing etravirine plus OBT compared to OBT alone, 60% versus 40% respectively; an additional 16% achieved a viral load > 50 and < 400 copies/ml on the etravirine arm. Change from baseline in CD4 count was also highly statistically significant with subjects receiving etravirine experiencing a change from baseline in CD4 count of 85.6 cells/mm3 compared to 66.8 cells/mm3 for OBT alone at week 24.

In subgroup analyses, when examining the primary endpoint based on enfuvirtide use, there was a greater treatment difference between etravirine and placebo (60% versus 34%) when re-used or not used enfuvirtide was considered; when de novo enfuvirtide was used, the treatment difference was not as great between the arms (70% versus 62%). This is likely explained by having more active drugs in the background regimen in both arms. Similarly, response rates were comparable between arms as the PSS increased. A PSS between 0-1 yielded the following results for the primary endpoint: 54% versus 22% etravirine versus placebo for HIV < 50 copies/ml whereas

a PSS > 2 yielded a response rate of 75% versus 65% for etravirine versus placebo for the endpoint of HIV RNA < 50 copies/ml.

Consistent treatment effects favored etravirine regardless of race or gender, though numbers of females and non-Caucasians were more limited as compared to males and Caucasians. To address this issue, the applicant has agreed to a post-marketing commitment to further examine the safety of etravirine in women.

It is also noteworthy that a trial in first NNRTI treatment failures that compared etravirine to lopinavir/ritonavir or boosted atazanavir, study TMC-125-227, was stopped early because suboptimal virologic response was seen in the etravirene group compared to the boosted PI group; fewer subjects achieved a viral load < 50 copies/ml on the etravirene arm (25%) compared to the boosted PI control (52.8%). The package insert will reflect this information by stating that patients who have experienced virologic failure on an NNRTI-containing regimen should not use etravirine in combination with only N(t)RTIs.

8. **Safety:** With regard to extent of population exposure, a total of 719 HIV infected subjects received 6 months of therapy, 161 received 12 months of therapy and 28 received more than 36 months of therapy at the to-be-marketed dose. The total number of subjects, both healthy and HIV infected who received at least one dose was 2328 by the time of the safety update report. In addition there were 2915 subjects enrolled in the expanded access program as of July 2007.

   Rash: The safety assessment in the package insert is based on 1203 subjects enrolled in studies 206 and 216 where 599 subjects received etravirine plus an optimized background and 604 received an optimized background regimen. The most commonly reported adverse reactions (incidence > 10%) in the adult treatment-experienced population in studies 206 and 216 were rash and nausea. Regardless of causality, rash of any type occurred in 16.9% of etravirine subjects compared to 9.3% of placebo subjects. The most frequently reported treatment-emergent adverse reaction of at least grade 2 intensity was also rash occurring at a rate of 9% in etravirine-treated subjects compared to 3.1% of placebo subjects.

   A total of 2% (n=12) of subjects receiving etravirine in phase 3 trials discontinued due to rash. Of those who discontinued, 5 subjects had a grade 3 rash and 7 subjects had a grade 2 rash. Pharmacokinetic data was only obtained on two subjects who discontinued for rash; etravirene exposures were not at the highest quartile of plasma concentrations. Among those continuing with rash in clinical trials, rash was described as mild-to-moderate, occurring primarily in the second week of treatment and was infrequent after week 4. In general, rash resolved on continued therapy. The incidence of rash was higher in women than men. More serious rash occurred at a rate of <0.1% during clinical development of etravirine. Serious rash included presumed Stevens-Johnson Syndrome (SJS), hypersensitivity reactions and erythema multiforme minor. Erythema multiforme minor occurred in a phase 1 trial in two

healthy women who received a different formulation (F035) than the to-be-marketed formulation (F060); a single site and a single investigator were involved. Of note, based on the chemistry review, there were some differences in excipients between F035 and F060, but all are widely used at comparable or higher exposures. Three presumed cases of SJS occurred in the expanded access program; no biopsies were obtained. Only two of the cases had oral lesions. SJS-associated fatalities were not seen in the data base.

Of note, our pharmacometrics reviewers performed analyses examining predictors of rash. They noted that rash other than severe rash appeared to increase with increasing etravirine exposures. As etravirine belongs to the same class as nevirapine a comparison was made between the 2 NNRTIs. Compared to nevirapine, skin reactions related to etravirine appear to be less severe. Similar to nevirapine, rash was more common in women. Etravirine-associated rash was also less likely to be associated with elevated liver enzymes.

In the package insert, a description of serious and potentially life-threatening skin reactions appears in the warnings and precautions section.

Cardiac: Hemorrhagic cardiomyopathy was seen in nonclinical studies. Based on this finding, the clinical database was searched for similar findings. Cardiac events of interest occurred in 1.9% of etravirine subjects compared to 1.5% of placebo subjects. In general, subjects who developed cardiac events had risk factors for coronary artery disease or pre-existing conditions. Based on a formal QT study, etravirene is not associated with the risk of QT prolongation.

Hepatic: Hepatic events were seen in 7.8% of etravirine subjects compared to 7.1% on the placebo arm. The majority of hepatic events were Grade 1 and 2. No increase in frequency in Grade 3 and 4 hepatic events was seen in subjects receiving etravirine compared to placebo. Further 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. For ALT it was 2.7% versus 1.8% and for AST it was also 2.7% versus 1.8%. Treatment discontinuation due to elevated transaminases occurred in 0.3% of subjects in the etravirine arm. Co-infected subjects had more abnormalities in both treatment groups.

Other adverse drug reactions:

- The frequency of renal adverse events was balanced between treatment groups; concomitant tenofovir use was the most common risk factor for renal failure. The package insert contains information about this adverse event in the section pertaining to less frequently seen adverse drug reactions.

- Cases of pancreatitis were reported in Phase 2b studies. In phase 3 studies, more subjects experienced pancreatitis in the etravirine arm compared to placebo, 0.7% (n=4) versus 0.3% (n=2). Pancreatitis events were associated

with known risk factors. The package insert contains information about pancreatitis in the section pertaining to less frequently seen adverse drug reactions.

- Thyroid adverse events were balanced between etravirine and placebo.

- Cases of —— and cases of anemia appear in the package insert in the section pertaining to less frequently seen adverse drug reactions.

- Lipid abnormalities were observed more frequently in etravirine subjects compared to placebo. A greater proportion of subjects receiving etravirine required initiation of lipid-lowering agents compared to placebo subjects.

9. Mortality/AIDS-Defining Illness (ADI): A decrease in mortality was observed in the etravirine arm compared to placebo in phase 3 trials. Death occurred at a rate of 1.8% in the etravirine group compared to 3.3 % in the placebo group. Causes of death were consistent with an advanced population and there was no specific clustering of causes, although the majority was related to infection. No deaths in the phase 3 studies were attributable to etravirine per our clinical review.

AIDS-defining illness was seen less frequently in the subjects who received etravirene compared to placebo. Numerically there were 18 subjects (3%) with an ADI on the etravirene arm compared to 36 subjects (5.9%) on placebo.

10. Risk Minimization Considerations: A pre-approval safety meeting was held with the Office of Surveillance and Epidemiology. It was determined that routine pharmacovigilance activities will serve as tools to identify potential etravirine-associated risks.

Conclusions and Recommendations: I am in agreement with the multidisciplinary review team that etravirine should be approved under the accelerated approval regulations based on the totality of the data contained in NDA 22-187. It has been demonstrated that the benefits of using etravirine in the indicated population exceed the risks of using etravirene. A greater treatment effect was seen with regard to viral load response, a mortality benefit was seen and there were fewer ADIs when etravirene was part of a treatment regimen. Labeling and post-marketing commitments address concerns identified during the review process. In particular, mild-to-moderate rash was seen more frequently in the etravirene arm compared to control, but most subjects were able to continue etravirene treatment. SJS occurred at a rate of 0.038% (3/7836 subjects exposed to etravirene in all clinical trials and the EAP as of January 7, 2008) and no fatalities were seen. The Highlights section and the Warnings and Precautions section contain adequate wording to describe these findings. Although etravirine was dosed with darunavir/ritonavir in phase 3 trials, our review team concluded that the etravirine exposure in most patients who receive etravirine with lopinavir/ritonavir will not be higher than that observed in at least a

small number of subjects (n=97) in phase 3 trials, due to variability in etravirine pharmacokinetics.

With the approval of a second-generation NNRTI, we can provide new options for constructing viable treatment regimens for patients with HIV-1/AIDS. Treatment regimens with three new drugs for treatment-experienced patients will translate into more advanced patients becoming undetectable and mortality benefits.

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Debra Birnkrant
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