Responses to Comments of Reviewer No. 2 on the Application of Etravirine to the WHO Essential Medicines List
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RESPONSES TO QUESTIONS

Checklist item 1

Have all important studies that you are aware of been included? Answer reviewer 2: NO

Reviewers comment:

Although the basic efficacy and safety data from the pivotal DUET-1 and DUET-2 trials was presented in the application, no mention was made of other studies or clinical experience with this agent\textsuperscript{1-6}, or of emerging safety data\textsuperscript{7-10}. There was also inadequate coverage of the issue of resistance to ETV\textsuperscript{11-15}.

\textit{Tibotec’s response}

To date, the DUET studies remain the strongest data set for etravirine (ETR). The studies cited by the reviewer were not included in the application because these studies were done in different patient populations outside of the licensed indication for ETR.

Consistent with subgroup analyses from the DUET studies, the ETR safety and efficacy profile is well established irrespective of patient demographics and disease characteristics. In addition, a study focusing on women, particularly women of color (i.e., GRACE) has been completed (see answer to Checklist item 3). Studies in pregnant women (TMC114HIV3015, ClinicalTrials.gov Identifier NCT00855335) and in children between 6-18 years of age (study TMC125-TiDP35-C213, see Appendix 1) are currently ongoing. A list of additional studies is provided in Appendix 1. No new safety concerns arose from these other completed or ongoing studies. Recent data has shown that ETR was equally effective in suppressing viral replication in patients infected with HIV-1 subtype B or various HIV-1 non-B subtypes.\textsuperscript{16}

ETR was shown in the DUET studies to be the first NNRTI with activity against NNRTI-resistant virus, even if reduced susceptibility to the used PI (DRV) was observed or no active background ARVs were included in the treatment regimen\textsuperscript{17-19}. ETR can thus play an important role as second-line NNRTI in the selection of treatment regimens, taking into account that the level of NNRTI-resistance determines the level of virological response. Several methods exist for predicting the virologic response to ETR based on a genotypic resistance test and mostly show good concordance in the prediction of outcome, confirming that these scoring systems are a reliable tool for prediction of response to ETR\textsuperscript{20-26}. Resistance testing, when available, should guide the use of ETR. Clinical study TMC125-C227 showed that in patients who have experienced virological failure on an NNRTI and N(t)RTI containing regimen, ETR is not recommended for use in combination with N(t)RTIs only, but must be used in combination with a BPI.

\footnote{Although it is clear that the reviewer refers to etravirine, we would like to clarify that etravirine is commonly abbreviated as ETR while ETV is commonly used for entecavir, an anti HBV drug.}

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Checklist item 2
Is there adequate evidence of efficacy for the proposed use? Answer reviewer 2: YES

Reviewers comment:
The two pivotal studies have provided adequate evidence of the efficacy of a combined ETV and boosted-darunavir (DRV/r) 3rd-line option.

Tibotec’s comment
In treatment-experienced subjects, particularly those in need of a 3rd line regimen, it is often difficult for the treating physician to construct an ARV with at least 2 ARVs to which the virus is susceptible. The availability of ETR provides the physician another valuable agent to help design an efficacious regimen in this population. In the DUET studies, ETR combined with DRV/rtv and other ARVs demonstrated efficacy, in a patient population with varying baseline PI and NNRTI resistance, and showed superior efficacy over placebo. Additional virological activity of ETR was seen regardless of the activity of the underlying PI.

Checklist item 3
Is there evidence of efficacy in diverse settings and/or populations? Answer reviewer 2: NO

Reviewers comment:
Given the paucity of data from resource-constrained settings, in which the use of NNRTI based 1st-line regimens is more prevalent, the concerns about ETV plus boosted darunavir (DRV/r) use in patients requiring concomitant treatment for tuberculosis, and the lack of data in children, this cannot be considered evidence in meaningfully “diverse settings”.

Tibotec’s response
We acknowledge that there is limited data from ETR use in resource-limited settings. However, ETR has been studied in otherwise diverse patient populations:

ETR was co-administered with ritonavir boosted darunavir (DRV/r) in 207 patients in clinical trial TMC114-HIV3004, known as the GRACE trial, where GRACE stands for Gender, Race, And Clinical Experience. The trial was specifically designed to enroll women and people of color. The objective of the trial was to evaluate if there were differences in drug efficacy and safety between men and women.

In this trial, antiretroviral treatment-experienced subjects received DRV/rtv 600/100 mg bid with an optimized background regimen for up to 48 weeks. A subanalysis of all subjects who took ETR as part of their optimized background regimen was performed.

Of the subjects receiving both ETR and DRV/rtv, 57.5% were female, 64.3% were Black, 17.4% were Hispanic, 17.4% were Caucasian and 1% were Asian. Subjects in the ETR sub analysis had a wide range of baseline disease characteristics regarding CDC disease category, viral load, and CD4 cell count.

The results of this trial demonstrated that ETR when co-administered with DRV/rtv and other ARVs was safe and effective in all groups. There were no differences in efficacy results between racial groups except for the incidence of achieving a viral load of
<50 HIV-1 copies/mL at Week 48, which was somewhat lower in Black subjects (55.6%) compared to subjects of Caucasian (61.8%) and Hispanic (69.4%) origin. The evaluation of safety in this sub analysis demonstrated no remarkable differences between racial groups except for rate of SAEs (Black 24.8%, Caucasian 29.4% and Hispanic 11.1%) and of AEs leading to permanent discontinuation (Caucasian 14.7%, Black 7.5%, and Hispanic 8.3%).

ETR/DRV is used in patients failing third line treatments in the public sector. The majority of patients with concomitant TB are ARV naïve or first line patients, where ETR is not recommended. For patients requiring TB treatment rifabutin can be used.

Due to concerns about the teratogenecity of efavirenz, it has been listed as a Category D drug by the FDA. Data on the safety and efficacy of ETR in pregnant women and in pediatric populations (2 months-18 years) are being generated. Results of the first analysis of our currently ongoing pediatric clinical trial are expected by the end of 2011.

Checklist item 5
Are there special requirements or training needed for safe/effective use? Answer reviewer 2: YES

Reviewers comment:
Appropriate use of 3rd-line or rescue regimens in resource-constrained settings will be hampered by lack of access to viral load measurements as well as genetic typing and interpretation of such results. As yet, no “public health” approach to third line options has been developed, although the clinical need has been identified.

Tibotec’s response
ETR, in combination with other antiretrovirals, is indicated for the treatment of HIV in antiretroviral experienced adults. Patients who have virologically failed previous ARV regimens, most often require treatment with medications with unique resistance profiles. The availability of ETR provides the physician with another valuable agent to help design an efficacious regimen in this population. As seen from the results of the DUET trials, ETR, in combination with DRV/rtv and other ARVs, demonstrated superior efficacy in a patient population with varying degrees of baseline PI and NNRTI resistance. Additional virological activity of ETR was seen regardless of the activity of the underlying PI.

The use of ETR should be guided by treatment history, and when available, resistance testing. In patients who have experienced virological failure on a regimen containing NNRTIs and N(t)RTIs, ETR is not recommended for use in combination with N(t)RTIs only.

Checklist item 6
Is this product needed to meet the majority health needs of the population? Answer reviewer 2: NO

Tibotec’s response
An application for the use of ETR (100 mg tablets) in adult patients has been submitted to the health authorities of more than 15 countries of sub-Saharan Africa. For Burkina Faso and Ivory Coast the application was approved and additional approvals e.g., in South-Africa are expected in the course of 2011.
In treatment-experienced subjects, particularly those in need of a 3rd line regimen, it is often difficult for the treating physician to construct an ARV with at least 2 ARVs to which the virus is susceptible. The availability of ETR provides the physician another valuable agent to help design an efficacious regimen in this population.
REFERENCES**


** Publicly available guidelines (e.g. ICH, WHO, FDA, EMEA, NIH, ...) are not routinely submitted, but can be made available upon request.

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23. Stanford HIVdb version 6.0.9 (n=41; updated August 2010; /http://hivdb.stanford.edu
25. ANRS version 19 (n=27; updated July 2010; http://www.hivfrenchresistance.org/)
# APPENDICES

## Appendix 1: List of Additional Studies with ETR

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Title</th>
<th>Phase</th>
<th>Status</th>
<th>Sponsor</th>
<th># Required Subjects</th>
<th>First Subject Consented - Expected</th>
<th>First Subject Consented - Actual</th>
<th>Last Subject Last Visit - Expected</th>
<th>Last Subject Last Visit - Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC125-C214</td>
<td>Early access of TMC125 in combination with other antiretrovirals in treatment-experienced HIV-1 infected subjects with limited treatment options.</td>
<td>3</td>
<td>In Progress</td>
<td>Company</td>
<td>5,179</td>
<td>28-Jul-06</td>
<td>06-Feb-06</td>
<td>11-Dec-13</td>
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<tr>
<td>TMC125-C217</td>
<td>An open-label trial with TMC125 as part of an ART including TMC114/rtv and an investigator-selected OBR in HIV-1 infected subjects who participated in a DUET trial (TMC125-C206 or TMC125-C216).</td>
<td>3</td>
<td>In Progress</td>
<td>Company</td>
<td>300</td>
<td>07-Jun-06</td>
<td>07-Jun-06</td>
<td>31-Aug-11</td>
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<tr>
<td>TMC125-TIDP2-C238</td>
<td>Evaluate safety and efficacy of ERT in combination with ATV/r at two different doses and 1 NRTI, in term of the proportion of subjects with plasma viral load &lt;50 HIV-1 RNA copies/ml, at Week 24.</td>
<td>2</td>
<td>In Progress</td>
<td>Company</td>
<td>46</td>
<td>25-Jun-09</td>
<td>25-Jun-09</td>
<td>30-Apr-12</td>
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<tr>
<td>TMC125-TIDP35-C213</td>
<td>A Phase II, open-label trial, to evaluate the safety, tolerability and antiviral activity of TMC125 in antiretroviral experienced HIV-1 infected children and adolescents</td>
<td>2</td>
<td>In Progress</td>
<td>Company</td>
<td>100</td>
<td>06-Aug-08</td>
<td>06-Aug-08</td>
<td>09-Dec-11</td>
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<tr>
<td>TMC125-TIDP35-C234</td>
<td>Pediatric trial in patients &lt; 6 years old.</td>
<td>2</td>
<td>In Preparation</td>
<td>Company</td>
<td>60</td>
<td>15-Apr-11</td>
<td></td>
<td>29-Dec-14</td>
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<tr>
<td>TMC125-TIDP35-C239</td>
<td>Continued access to etravirine (ETR) in treatment experienced HIV-1 infected children and adolescents.</td>
<td>3</td>
<td>In Progress</td>
<td>Company</td>
<td>67</td>
<td>09-Dec-09</td>
<td>09-Dec-09</td>
<td>09-Dec-13</td>
<td></td>
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</tbody>
</table>
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<thead>
<tr>
<th>Protocol ID</th>
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<th>Sponsor Type</th>
<th># Required Subjects</th>
<th>First Subject Consented - Expected</th>
<th>First Subject Consented - Actual</th>
<th>Last Subject Last Visit - Expected</th>
<th>Last Subject Last Visit - Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC125HIV4005</td>
<td>Spencer IIS: A Pilot Study to Measure the levels of Antiretroviral Drug Concentrations and HIV-1 viral load in breast milk and plasma in HIV+ women receiving HAART Therapy</td>
<td>4</td>
<td>In Progress</td>
<td>Investigator</td>
<td>10</td>
<td>30-Jun-10</td>
<td>12-May-10</td>
<td>30-Jun-11</td>
<td></td>
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<tr>
<td>TMC125HIV4008</td>
<td>Estimation of average costs of patients with HIV-1 infection in antiretrovirals treatment-experienced adult patient, including those with NNRTI resistance in Mexico</td>
<td>4</td>
<td>Closed</td>
<td>Company</td>
<td>180</td>
<td>01-Oct-08</td>
<td>01-Oct-08</td>
<td>30-Nov-08</td>
<td>30-Nov-08</td>
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<tr>
<td>TMC125IFD3002</td>
<td>Phase IIIb Open label, single arm, Post-approval commitment trial (n=200)</td>
<td>3</td>
<td>In Preparation</td>
<td>Company</td>
<td>200</td>
<td>13-Jun-11</td>
<td></td>
<td>19-Dec-13</td>
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<tr>
<td>TMC125VIR1001</td>
<td>A Phase I, randomized, open label, two-way, two period cross-over trial to investigate the pharmacokinetic interaction between etravirine or darunavir/rtv and artemether/lumefantrine (Coartem) at steady-state in healthy HIV-negative subjects</td>
<td>1</td>
<td>In Preparation</td>
<td>Company</td>
<td>32</td>
<td>07-Mar-11</td>
<td></td>
<td>21-Jul-11</td>
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<tr>
<td>TMC114HIV3020</td>
<td>2LADY - Evaluation of three second-line antiretroviral treatment regimens in Africa (Dakar, Bobo-Dioulasso, Yaoundé)</td>
<td>3</td>
<td>In Progress</td>
<td>Investigator</td>
<td>450</td>
<td>02-Dec-09</td>
<td>02-Dec-09</td>
<td>31-Dec-12</td>
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<tr>
<td>TMC125HIV2031</td>
<td>TRIO - A prospective, open label, single arm clinical trial to assess the safety of DRV/r + ETR + RAL in addition to OBR in HIV-1+ patients with limited to no treatment options</td>
<td>4</td>
<td>Completed</td>
<td>Investigator</td>
<td>105</td>
<td>09-May-07</td>
<td>09-May-07</td>
<td>18-Aug-09</td>
<td>18-Aug-09</td>
</tr>
<tr>
<td>INT-PMS-JPN-2</td>
<td>Drug Use Results Survey on Pregnancy Cases of Intenence 100mg tablets</td>
<td>4</td>
<td>In Preparation</td>
<td>Company</td>
<td></td>
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</table>