Antiviral Drugs Advisory Committee

April 24, 2007

New Drug Application (NDA) 022-128 maraviroc 150 and 300 milligram tablets, Pfizer, Inc., proposed for the treatment of antiretroviral-experienced patients with chemokine (c-c motif) receptor 5 (CCR5) – tropic human immunodeficiency virus (HIV).

ERRATA to the FDA Backgrounder

This document serves as an amendment to section **3.3 Clinical Pharmacology Modeling Results** in the FDA backgrounder

Original on Page 21:

1. Patients with Cmin >75 ng/mL have a better chance of virologic success.
    a. A majority of patients with Cmin <75 ng/mL fail to achieve <400 copies with the sponsor's proposed dosing.
    b. Concomitant drugs or demographic factors were not the source of Cmin values <75 ng/mL.
2. Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose/concentration dependent within the therapeutic concentration range.
3. Virologic success may be improved by doubling the dose for patients with Cmin <75 ng/mL. The proposed dose adjustment does not increase concentrations greater than the range in phase 2b/3 studies.

Correction:

1. Patients with Cmin >50-75 ng/mL have a better chance of virologic success. In addition to Cmin, the probability of success is also influenced by other factors such as baseline CD4+ count, baseline viral load and OSS.
    a. With the sponsor's proposed dosing, ~67% of patients should achieve <400 RNA copies/mL.
    b. Concomitant drugs or demographic factors were not the source of lower Cmin values.
2. Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose or concentration dependent within the observed concentration range.
3. The probability of virologic success (<400 RNA copies/mL) is predicted to be 69% (vs 67% at the proposed dosing) by doubling the dose for patients with Cmin <75 ng/mL.

Original on Page 24

To simulate Cmin, a factor of 2.5 (to account for more than a proportional dose-concentration relationship) was applied to the original values, if the Cmin was below the defined threshold. If the Cmin was above the defined threshold, the original value was retained. **Figure 8** illustrates the predicted virologic success for threshold-based simulation.

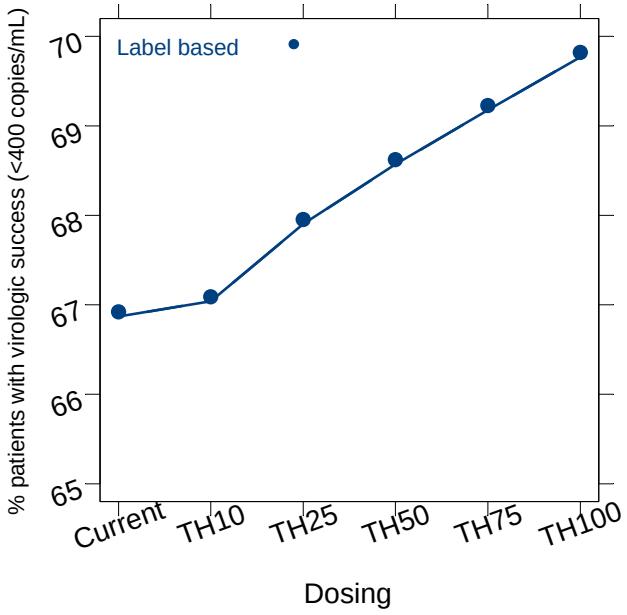
Figure 8: The virologic success can be increased up to 72% (vs. original 64%) by doubling the dose in patients with Cmin <75 ng/mL. THxx represents threshold Cmin (ng/mL) used in simulation

(Original figure not shown)

Correction:

Data from the proposed market doses (150 and 300 mg BID) were used for the simulations. A factor of 2 was applied to the original values, if the Cmin was below the defined threshold. If the Cmin was above the defined threshold, the original value was retained. **Figure 8** illustrates the predicted virologic success for threshold-based simulations.

Figure 8: The probability of virologic success can be increased up to 69% (vs. original 67%) by doubling the dose in patients with Cmin <75 ng/mL. THxx represents threshold Cmin (ng/mL) values used in simulation



Original on page 25:

With the dosing used in phase 2b/3 studies, the virologic success on maraviroc with OBT was shown to be 64%. The virologic success can be increased to 72% by doubling the dose in patients with Cmin <75 ng/mL. Therefore, the virologic success can be increased by 8% (12.5% relative increase) using a threshold of 75 ng/mL. As seen from **Table 8**, 75 ng/mL as a threshold will require 27% (150mg BID group) and 77% (300 mg BID group) to have dosing adjustments post Cmin assessment.-

In conclusion,

1. Patients with Cmin values >75 ng/mL have a better chance of virologic success.
    1. Majority of patients with Cmin <75 ng/mL fail to achieve <400 copies with the sponsor's proposed dosing.
    2. Concomitant drugs or demographic factors were not the source of Cmin <75 ng/mL.
2. Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose/concentration dependent within the therapeutic concentration range.
3. The virologic success may be improved by doubling the dose for patients with Cmin <75 ng/mL. The proposed dose adjustment is not predicted to increase concentrations greater than the range in phase 2b/3 studies.

Correction:

With the proposed market dosing, the probability of virologic success on maraviroc with OBT was shown to be 67%. The probability of virologic success can be increased to 69% by doubling the dose in patients with Cmin <75 ng/mL. As seen from **Table 8**, 75 ng/mL as a threshold will require 27% (150mg BID group) and 77% (300 mg BID group) to have dosing adjustments post Cmin assessment. The population benefit of monitoring therapeutic concentration is 2%. In addition to Cmin, several other patient and virus specific factors are important determinants of the virologic success.

In conclusion,

1. Patients with Cmin >50-75 ng/mL have a better chance of virologic success. In addition to Cmin, the probability of success is also influenced by other patient specific factors such as baseline CD4+ count, baseline viral load and OSS.
    a. With the sponsor's proposed dosing, ~67% of patients should achieve <400 RNA copies/mL.
    b. Concomitant drugs or demographic factors were not the source of lower Cmin values.
2. Toxicity (QT prolongation, ALT/AST elevation, hypotension) was not dose or concentration dependent within the observed concentration range.
3. The probability of virologic success (<400 RNA copies/mL) is predicted to be 69% (vs 67% at the proposed dosing) by doubling the dose for patients with Cmin <75 ng/mL.