Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Antiviral Drugs Advisory Committee

May 19, 2005

FINAL QUESTIONS TO THE COMMITTEE

Question 1:

- Do the data demonstrate that tipranavir/ritonavir (TPV/r) is safe and effective for the multi-drug resistant HIV-1 infected population?

    - If no, what additional data are needed to provide evidence of safety and efficacy?

    - If yes, please address the appropriate population for TPV/r use considering the following:
        - limited inclusion criteria of the RESIST trials
        - drug-drug interactions
        - resistance information and patterns associated with optimal use
        - safety considerations

Question 2:

- Given the data on transaminase elevations, please provide your recommendations for:
    - TPV/r use in patients with underlying liver disease
    - Monitoring and management of hepatotoxicity during clinical use
    - Future studies

Question 3:

- The limited amount of data in females with HIV infection in the TPV program shows an increased incidence of rash in females. Please provide your recommendations for:
    - Investigation of this safety signal in future studies with TPV

Question 4:

- Current information indicates the net effect of TPV/r on substrates of CYP1A2, CYP2C9, CYP2C19 and CYP2D6 is not known, and there are competing effects of TPV/r on CYP3A (inhibition) and P-glycoprotein (induction). Please comment on additional post-marketing drug interaction studies.

Question 5:

- Given the high inter-patient variability in TPV exposures following fixed doses and exposure (blood levels)-virologic response relationships, could a biomarker such as Cmin/IC50 be used for the individualization of TPV/r therapy? Please discuss the studies that would supplement the data presented today.

Question 6

- Please provide your recommendations regarding the display of TPV/r resistance data/analyses in the TPV package insert that would be useful to clinicians.

Background referring to Question 6 on next page

(Question 6 Continued: Background)

Slide 1:

Examples

- **Baseline Outcome Analyses**
  - Baseline Number of PI Mutations
  - Type of PI Mutation
  - Baseline Phenotype
  - TPV score
  - Key mutations
- **Endpoints**
  - Primary endpoint (proportion of responders)
  - Change from Baseline (e.g. median, average)
- **+/-T20 use**

Slide 2:

Response by Baseline Number of PI Mutations

Proportion of Responders
(confirmed ≥1 log decrease at Week 24)

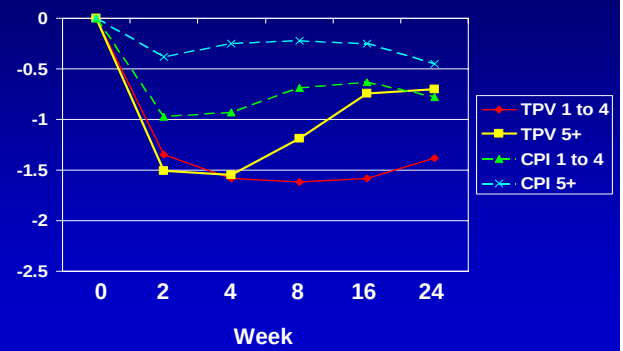
# Baseline FDA PI Mutations	TPV/r N=531			CPI/r N=502		
	All	No T20	+ T20	All	No T20	+ T20
Overall	47% (241/531)	40% (148/369)	65% (93/144)	22% (110/502)	20% (76/389)	30% (34/113)
1 - 2	70% (30/43)	69% (27/39)	75% (3/4)	44% (19/43)	41% (17/41)	100% (2/2)
3 - 4	50% (117/236)	44% (78/176)	65% (39/60)	27% (60/221)	23% (39/169)	40% (21/52)
5+	41% (94/231)	28% (43/151)	64% (51/80)	13% (31/236)	11% (20/178)	19% (11/58)

 # Any change at positions 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88 and 90

Slide 3:

Response by Baseline PI Mutations

Median Change from Baseline - Overall



Question 7:

- Please discuss and recommend future study designs /data acquisition for the heavily pretreated population.