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

Cardiovascular and Renal Drugs Advisory Committee

Questions to the Committee

May 29, 2003

1. The alfuzosin and vardenafil studies evaluated the effects of a single dose on QT/QTc. Were the studies for alfuzosin, a drug that will be dosed daily, adequate to evaluate the drug's effect on QT? Yes___ No___ Please explain. Were the studies for vardenafil, a drug that will be dosed intermittently, adequate to evaluate the drug's effect on QT? Yes ___ No___ Please explain.

2. The patients enrolled in these studies were healthy male volunteers (mean age 27, range: 19 to 45, in the alfuzosin study and mean age 53, range: 45-60, in the vardenafil study) with normal electrolytes and baseline cardiac function. Was the effect of alfuzosin on QT for the population intended for actual treatment adequately studied? Yes___ No___. Was the effect of vardenafil on QT for the population intended for actual treatment adequately studied? Yes___ No___

3. Is it appropriate to use pooled baseline and placebo exposure data for calculating linear and non-linear regression correction formulae? Explain.

4. Because of uncertainty about an optimal correction methodology for determining QTc, it is likely that sponsors will submit the results of multiple correction methodologies.
    a. Should trials specify and adhere to a primary endpoint (i.e. primary correction methodology)?
    b. Should FDA require and adhere to a formal statistical analysis plan (including confidence intervals) for assessing multiple correction methodologies?
    c. Explain how the totality of the data obtained from a comprehensive panel of QT/RR correction methodologies should be evaluated to assure valid conclusions.

5. The table below summarizes the mean change of QT from baseline, both uncorrected and corrected, of alfuzosin (10 mg and 40 mg) and moxifloxacin relative to placebo, as observed in Study PDY 5105.

Table 1. Mean QTc change (95% CI) from baseline at Tmax (relative to placebo)

	QT	**Bazett's (QTcB)**	**Fridericia (QTcF)**	**Population (QTcN)**	**Individual (QTcNi)**	**Holter Monitor** (Largest sample RR bins)
Alfuzosin 10 mg	-5.8 (-10.2,-1.4)	10.2 (3.9,16.6)	4.9 (0.9,8.8)	1.8 (-1.4,5.0)	1.8 (-1.3,5.0)	0.4 (-1.8,2.6)
Alfuzosin 40 mg	-4.2 (-8.5.0.2)	13.9 (5.8,22.0)	7.7 (1.9,13.5)	4.2 (-0.6,9.0)	4.3 (-0.5,9.2)	2.5 (0.4,4.7)
Moxifloxacin 400 mg	6.9 (2.3,11.5)	15.7 (10.8,20.6)	12.7 (8.6,16.8)	11.0 (7.0,15.0)	11.1 (7.2,15.0)	6.9 (4.8,9.1)

a. Are the results of any one correction methodology more valid than the others? Yes ___ No ___ If yes, please state which one and why it is more valid.

b. Do these data demonstrate a clinically relevant QT prolongation associated with alfuzosin? Yes___ No___ If yes, how might this risk be managed?

6. The table below summarizes the mean change of QT from baseline, both uncorrected and corrected, of vardenifil (10 mg and 80 mg) and moxifloxacin relative to placebo, as observed in Study 10929.

Table 2. Mean QTc change (90% CI) from baseline at 1 hour relative to placebo.

	QT	Fridericia QTcF	Individual QTcI	FDA Individual Analysis QTcI.2
Vardenafil 10 mg	-2.3 (-4.1, -0.5)	7.7 (6.3,9.1)	4.1 (2.7,5.6)	4.1 (2.5,5.6)
Vardenafil 80 mg	-2.1 (-4.2, 0.1)	9.8 (8.4,11.1)	5.8 (4.4,7.2)	5.7 (4.1,7.3)
Moxifloxacin 400 mg	3.5 (1.6, 5.5)	7.7 (6.3,9.0)	6.6 (5.3,7.9)	6.7 (5.4,8.1)

a. Are the results observed from any one correction methodology more valid than the others?
Yes ___ No ___ If yes, please state which one and why it is more valid.

b. Do these data demonstrate a clinically relevant QT prolongation associated with vardenafil? Yes___ No___ If yes, how might this risk be managed?

7. a. Do the QT prolongation results from the alfuzosin clinical trial warrant study of QT effects of other drugs in its class? Yes____ No___

b. Do the QT prolongation results from the vardenafil clinical trial warrant study of QT effects of other drugs in its class? Yes___No___