Active ingredient: Trandolapril; Verapamil Hydrochloride

Form/Route: Extended Release Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way crossover in-vivo
   Strength: 4 mg/240 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study.

2. Type of study: Fed
   Design: Single-dose, two-way crossover in-vivo
   Strength: 4 mg/240 mg
   Subjects: Normal healthy males and females, general population.
   Additional Comments: Please see comment above.

Analytes to measure (in appropriate biological fluid): Trandolapril, Verapamil and their respective active metabolites, trandolaprilat and norverapamil in plasma

Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Bioequivalence based on (90% CI): Trandolapril and Verapamil

Waiver request of in-vivo testing: 2 mg/180 mg, 1 mg/240 mg and 2 mg/240 mg based on (i) acceptable bioequivalence studies on the 4/240 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Recommended Dec 2008
Please note that a Dissolution Methods Database is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.