

Guidance on Verapamil Hydrochloride

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Verapamil Hydrochloride

Form/Route: Extended Release Capsules/Oral

Recommended studies: 3 studies

1. Type of study: Fasting, bedtime (PM) dosing
Design: Single-dose, two-way crossover *in-vivo*
Strength: 300 mg
Subjects: Normal healthy males and females, general population.
Additional Comments: Bedtime (PM) dosing.

2. Type of study: Fed, morning (AM) dosing
Design: Single-dose, two-way crossover *in-vivo*
Strength: 300 mg
Subjects: Normal healthy males and females, general population.
Additional comments: Morning (AM) dosing.

3. Type of study: Fasting, Sprinkled over applesauce, morning (AM) dosing
Design: Single-dose, two-way crossover *in-vivo*
Strength: 300 mg
Subjects: Normal healthy males and females, general population.
Additional Comments: Morning (AM) dosing.

Analytes to measure: Verapamil and its metabolite, norverapamil in plasma utilizing a validated LC/MS/MS method.

For norverapamil, 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 C_{max}. The following sampling times are recommended: pre-dose and 2, 3, 4, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post dose.

Bioequivalence based on (90% CI): Verapamil

Waiver request of in-vivo testing: 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 300 mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

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.

For modified release products, dissolution profiles 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 phosphate buffer, water) 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. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for twelve tablets.