

Draft Guidance on Dronedarone Hydrochloride

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Dronedarone Hydrochloride

Form/Route: Tablet/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
Design: Single-dose, two-way crossover in vivo
Strength: 400 mg
Subjects: Healthy males aged ≥ 18 years, general population.
Additional Comments: Specific recommendations are provided below.

2. Type of study: Fed
Design: Single-dose, two-way crossover in vivo
Strength: 400 mg
Subjects: Healthy males, general population.
Additional Comments: Specific recommendations are provided below. Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Additional comments regarding the BE studies with pharmacokinetic (PK) endpoints:

1. Inclusion Criteria:
 - Healthy males ≥ 18 years.
 - No clinically relevant renal, liver, hematologic or electrolyte abnormality in screening blood chemistry testing.
 - No significant abnormality on 12-lead electrocardiogram (ECG), i.e., $120 \text{ ms} < \text{pulse rate (PR)} < 200 \text{ ms}$, $\text{QRS} < 120 \text{ ms}$, $\text{QTc (Bazett's formula)} \leq 200 \text{ ms}$.
 - No significant abnormality on 24-hour Holter, i.e., sinus pauses $< 2.5 \text{ sec}$, minimum HR $> 45 \text{ bpm}$, isolated supraventricular premature beats (SVPB) $< 1000/24 \text{ h}$ and or $< 2 \text{ SV tachycardia}/24 \text{ h}$ (defined as > 10 consecutive SVPBs with HR $> 140 \text{ bpm}$), and no ventricular tachycardia (VT) ($< 3 \text{ PVCs}$ with HR $> 100 \text{ bpm}$).

Consider adding to Inclusion Criteria:

- No significant abnormality on echocardiography.

2. Exclusion Criteria:

- Exposure prior to enrollment within 7 half-lives of any drug product known to interact with dronedarone.
- Any history risk factors for torsade de pointes e.g., hypokalemia, hypomagnesemia or family history of long QT Syndrome.

3. Prohibited Concomitant Medications and Foods:

- Any medication known to interact with dronedarone or listed in the “Drug Interactions” section of the latest approved labeling for the Reference Listed Drug (RLD), e.g., any drug prolonging the QT interval (including certain phenothiazines, tricyclic antidepressants, certain macrolide antibiotics and Class I and III antiarrhythmics), digoxin, calcium channel blockers (including verapamil, diltiazem and nifedipine), CYP2D6 substrates (including beta-blockers, such as propranolol and metoprolol, tricyclic antidepressants and selective serotonin reuptake inhibitors), potent CYP3A inhibitors (including ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin and nefazodone), CYP3A inducers (including rifampin, phenobarbital, carbamazepine, phenytoin and St John’s wort), simvastatin and other statins, CYP3A substrates with narrow therapeutic range (including sirolimus and tacrolimus), dabigatran and warfarin.
- Grapefruit juice

4. Study Procedures:

- Continuous cardiac monitoring beginning prior to dosing and continuing through the study period.

5. Dronedarone Hydrochloride Tablet is under a Risk Evaluation and Mitigation Strategy (REMS) program (1) to prevent use in patients with: (a) symptomatic heart failure with recent decompensation requiring hospitalization or NYHA Class IV heart failure, (b) permanent atrial fibrillation (AF) that will not or cannot be cardioverted into normal sinus rhythm, and (2) to reduce serious risks including increased risk of cardiovascular death, heart failure, stroke, liver injury, and hepatic failure. All pertinent elements of the REMS are to be incorporated into the protocols and informed consents for the bioequivalence studies.

Analytes to measure (in appropriate biological fluid): Dronedarone and its active metabolite, N-debutyl dronedarone in plasma

Bioequivalence based on (90% CI): Dronedarone

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 C_{max}.

Waiver request of in vivo testing: Not Applicable

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.accessdata.fda.gov/scripts/cder/dissolution/>. 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.