

PK/PD in Medicine: Amiodarone

Amiodarone is an antiarrhythmic drug indicated for treatment and prophylaxis of ventricular fibrillation (VF)* and hemodynamically unstable congestive ventricular tachycardia (VT)*

Pharmacology: Amiodarone is a class III antiarrhythmic drug.

Mechanism: Inhibition of potassium rectifier currents responsible for repolarizing the heart during phase 3 of cardiac action potential.

K⁺ channel-blocking effect results in increased action potential duration and a prolonged effective refractory period in cardiac myocytes.

Amiodarone Human ADMEPK snapshot

LogP
7.2 -7.9

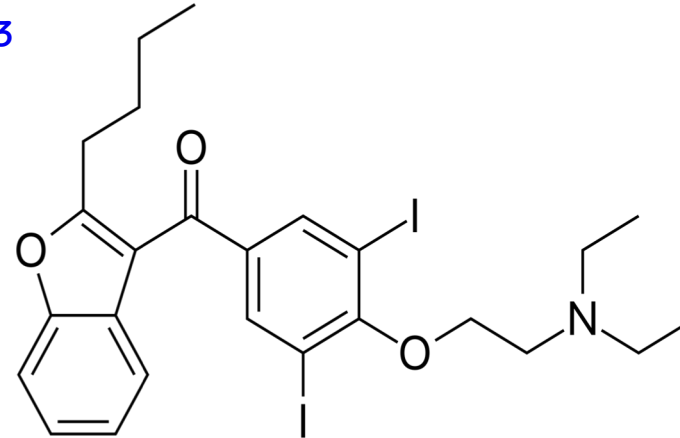
Solubility
5 µg/ml

pKa
9.06

MW 645.3

V_{ss}
40-84
l/kg

CL_p
0.09-0.16
l/h/kg



Elimination
Hepatic, Biliary

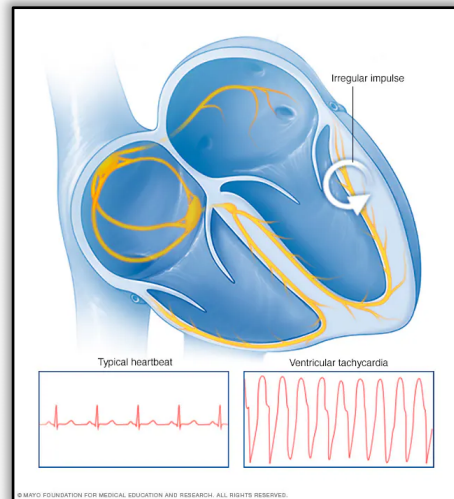
Metabolism
CYP3A, CYP2C

DDI
PgP, CYP1A2
2C9, 2D6, 3A

T_{1/2}
20-47
days

PPB
>96%

F
20-80 %



*Ventricular fibrillation (VF) is a type of irregular heartbeat rhythm (arrhythmia). During VF, the lower heart chambers (ventricles) contract in a very rapid and uncoordinated manner. As a result, the heart doesn't pump blood to the rest of the body. It's the most frequent cause of sudden cardiac death.

*VT: Ventricular tachycardia is a type of irregular heartbeat arrhythmia. It starts in the ventricles. A healthy heart typically beats about 60 -100 times a minute at rest. In VT, the heart beats faster -100 or more beats a minute. Sometimes the rapid heartbeat stops the heart chambers from properly filling with blood. The heart may not be able to pump enough blood to the body.

Ref: <https://www.mayoclinic.org/diseases-conditions/ventricular-fibrillation/symptoms-causes/s>

Amiodarone is administered intravenously (infusions) & orally in humans. The recommended starting dose is about 1000 mg over the first 24 hours of therapy given as a sequence of infusions.

Amiodarone displays 4 compartment behaviour, with very high V_{ss} (because of high LogP), very low systemic clearance (due to low intrinsic clearance & high PPB), a long terminal elimination half-life (t_{1/2} = 0.693 * V_{ss} / CL). The long t_{1/2} of 47 days means it will take 235 days to reach steady state & 235 days for it to be completely eliminated from the body post cessation of therapy. Its pharmacological effect will persist post therapy and also has drug-drug interaction potential if other medications are taken during this period.

Chow MS. 1996. Intravenous amiodarone: pharmacology, pharmacokinetics, and clinical use. *Ann Pharmacother.* 30(6):637-43.
<https://pubchem.ncbi.nlm.nih.gov/compound/Amiodarone#section=Dissociation-Constants;> <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=022325>
<https://www.ncbi.nlm.nih.gov/books/NBK482154/>