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Review Article

DRONEDARONE: A NEW MOLECULE FOR ATRIAL FIBRILLATION

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ABSTRACT
Atrial fibrillation is one of the most common serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality. Efficacy and safety of currently employed antiarrhythmic drugs continue to be less optimal in atrial fibrillation. Development of newer antiarrhythmic drugs has recently been made possible through a greater understanding of electro-pathophysiology of atrial fibrillation. Amiodarone is currently one of the most widely used and most effective antiarrhythmic agents for atrial fibrillation. But during chronic usage amiodarone can cause some serious extra cardiac adverse effects, including effects on the thyroid. Dronedarone is a newer therapeutic agent with a structural resemblance to amiodarone with two molecular changes, and with a better safety profile. Dronedarone is a multichannel blocker and like amiodarone, possesses both a rhythm and a rate control property in atrial fibrillation. The US Food and Drug Administration approved dronedarone for atrial fibrillation on July 2, 2009.
KEYWORDS: Dronedarone, Amiodarone, Atrial fibrillation, Cardiac.

INTRODUCTION

Atrial fibrillation is a growing epidemic in Western countries with an estimated prevalence of 3.8% of the population over 60 years of age and 9% over 80 years.[1] The prevalence of AF is almost 1% and it is estimated that by the year 2050[2], approximately 5 million subjects will have AF in the United States.[3] Atrial fibrillation (AF) is the most common of the serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality and requiring hospitalization.[4] Efficacy and safety of currently employed antiarrhythmic drugs (AADs) continue to be less optimal in AF. Development of newer AADs has recently been made possible through a greater understanding of electro-pathophysiology of AF.[5] Currently; there are two major treatment strategies for AF: rate control and rhythm control. Sustained sinus rhythm is associated with an improved quality of life and improved exercise performance.[3] Inadequacies in current therapies for atrial fibrillation have made new drug development crucial.[5] Conventional antiarrhythmic drugs increase the risk of ventricular proarrhythmia. Molecular modification of the highly effective multichannel blocker, amiodarone, to improve safety and tolerability has produced promising analogues such as dronedarone.[5] Although arrhythmia-related symptoms and thromboembolic strokes are significantly reduced by anticoagulation therapy and rate control, sinus rhythm is often associated with improvement in exercise capacity and quality of life.[4] Despite advances in nonpharmacological treatment of atrial fibrillation, notably catheter ablation, pharmacological therapy continues to be the mainstay of treatment. Because catheter ablation is an invasive, time-consuming procedure which carries a significant risk, particularly in elderly patients with or without concomitant structural heart disease, most elderly and older patients with atrial fibrillation are not suitable for this procedure.[1] On the other hand, currently available, parmacologic agents are used in the management of atrial fibrillation for prevention of embolic stroke, control of ventricular rate, and restoration and maintenance of normal sinus rhythm [6] but, available antiarrhythmic drugs are limited by lack of efficacy or by adverse effects in many instances. For instance, class I antiarrhythmic drugs are suitable for treatment of atrial fibrillation in patients with minimal or no structural heart disease. However, in individuals with significant underlying heart disease, particularly coronary disease, these drugs are not allowed due to potential proarrhythmic drug effects.[1] Amiodarone is one of the most widely used and most effective antiarrhythmic agents with little proarrhythmic potential. But during chronic usage amiodarone and its active

metabolite desethyl amiodarone can cause some serious extra cardiac adverse effects, including effects on the thyroid. Amiodarone is an iodinated benzofuran derivative and contains 37% of organic iodine by weight. Amiodarone itself and its high iodine content can cause subclinical to overt thyroid dysfunction, manifesting either amiodarone-induced hypothyroidism or amiodarone-induced thyrotoxicosis. About 15% to 28% of patients develop thyroid dysfunction after 2 to 3 years of therapy, a risk that increases with higher doses. Moreover, amiodarone is lipophilic because of its iodine content, thus accumulates in adipose tissue and highly perfused organs like the liver, lung, cornea, and skin. In addition, because of its long half-life of up to 100 days, high iodine levels persist for >6 months after discontinuation of the drug.[3] The US Food and Drug Administration approved dronedarone for atrial fibrillation on July 2, 2009. Dronedarone is new compounds developed for treatment of atrial fibrillation. Dronedarone is a benzofuran derivative structurally related to amiodarone but free of iodine and with a sulfonamide group placed on the benzofuran ring. So, with structural differences intended to eliminate the effects of amiodarone on thyroid and pulmonary functions.

Dronedarone

Amiodarone is an especially potent atrial antifibrillatory agent, but it induces potentially serious side effects in some patients.[4] Amiodarone-induced thyroid disorders are common and often present as a management challenge for endocrinologists. The pathogenesis of amiodarone-induced thyroid dysfunction is complex but the inherent effects of the drug itself as well as its high iodine content appear to play a central role.[7] Dronedarone is one of these new compounds developed for treatment of atrial fibrillation. The drug is a benzofuran derivative structurally related to amiodarone but free of iodine and with a sulfonamide group placed on the benzofuran ring.[1] Thus, with structural differences intended to eliminate the effects of amiodarone on thyroid and pulmonary functions.[4] The absence of iodine substituents and a less lipophilic character should be associated with a better tolerability.[8] The electrophysiological properties of dronedarone are very similar to those of amiodarone,[1, 4] which is presently the most effective drug to maintain sinus rhythm (SR) in patients with atrial fibrillation. Similar to amiodarone, dronedarone demonstrates electrophysiologic characteristics belonging to all 4 Vaughan-Williams classes.[9] Dronedarone is a potent blocker of multiple ion currents, including the rapidly activating delayed-rectifier potassium current, the slowly activating delayed-rectifier potassium current, the inward rectifier potassium current, the acetylcholine activated potassium current, peak sodium current, and L-type calcium current, and exhibits antiadrenergic effects.[3, 5, 10]

In vitro the amiodarone metabolite N-desethylamiodarone strongly inhibited T3 binding to thyroid hormone receptor, both TRα1 and TRb1, within the same order of magnitude, whereas the active metabolite of dronedarone N-debutlydronadarone was shown to inhibit T3 binding to TRα1 but much less so to TRb1. This isoform selectivity may explain the effects of dronedarone on the heart (a mainly TRα1 organ) and the lack of effect on the liver (a mainly TRb1 organ) with little effect on plasma thyroid hormone.[3]

CHEMISTRY, SYNTHESIS AND SAR

Dronedarone HCl is a benzofuran derivative with chemical name: N-{2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]benzofuran-5-yl} methanesulfonamide, hydrochloride. Dronedarone HCl is a white fine powder that is practically insoluble in water and freely soluble in methylene chloride and methanol. Its empirical formula is $C_{31}H_{44}N_2O_5$ S, HCl with a relative molecular mass of 593.2. It's structural formula[11] is provided in figure 1.

Dronedarone is a newer benzofuran derivative with a structural resemblance to amiodarone, with two molecular changes: it lacks the iodine moiety[6] and it has methane sulfonyl group that decreases lipophilicity, resulting in a shorter half-life and lower tissue accumulation.[3]

PHARMACOKINETICS

Dronedarone inhibits outward and inward Na^+/Ca^{2+} exchange current a concentration-dependent manner with IC50 values of 33 and 28 μM, respectively, and Hill coefficients of 1. The inhibitory effect of dronedarone on Na^+/Ca^{2+} exchange current is not changed by trypsin in the pipette solution, suggesting that dronedarone inhibits Na^+/Ca exchanger from the external side and /or in the membrane. Therefore, dronedarone may inhibit Na^+/Ca^{2+} exchange current modestly in a therapeutic concentration range in a similar manner to aprindine.[12]

Dronedarone is extensively metabolized, mainly by CYP3A.[2] Initial metabolic pathway includes N-debutylation to form the active N-debutyl metabolite, oxidative deamination to form the inactive propanoic acid metabolite, and direct oxidation.[11] The steady-state serum level of dronedarone is achieved in 5 to 7 days. The elimination half-life of dronedarone is 24 hours. It is cleared by nonrenal mechanism. Like amiodarone, oral bioavailability is increased 2- to 3-fold when taken with food. It is well absorbed after oral administration (70% to 100%). The bioavailability is relatively low (15%)

because of extensive hepatic first-pass metabolism by Cytochrome P4503A4 and CYP2D6, thus requiring twice-daily dosing to achieve steady-state serum levels. Dronedarone has been shown to exhibit even less reverse use-dependency of repolarization than that found with amiodarone, which may provide better cardiac safety. In patch-clamp experiments in canine ventricular myocytes, 10 μM dronedarone markedly reduced the rapid component of the delayed rectifier potassium current (97%, $P < 0.05$) and the L-type calcium current (76.5%, $P < 0.05$). In the same experimental study on dog myocytes, acute superfusion of dronedarone shortened the action potential duration in Purkinje fibres (at 1 Hz from 309.6 ± 11.8 to 287.1 ± 10.8 ms, $P < 0.05$) and reduced the incidence of early and delayed after depolarizations induced by dofetilide and strophantidine in Purkinje fibers. Chronic treatment with dronedarone for 4 weeks, unlike chronic administration of amiodarone, did not lengthen significantly the QTc interval of the electrocardiogram.[3]

PRE-CLINICAL DEVELOPMENT

The effect of the antiarrhythmic drug dronedarone on the Acetylcholine-activated K+ current (IK[Ach]) was investigated in single cells isolated from sinoatrial node tissue of rabbit hearts. In a study of effects of dronedarone on Acetylcholine-activated current in rabbit were dronedarone externally perfused (0.001 ± 1 mM) caused a potent, voltage independent block of IK(ACh). Fitting of the dose response curve of IK(ACh) block yielded an IC50 value of 63 nM, a value over one order of magnitude lower than those reported for dronedarone block of other cardiac currents. IK(ACh) block was not due to an inhibitory action of dronedarone on the muscarinic M2 receptor activation, since the drug was effective on IK(ACh) constitutively activated by intracellular perfusion with GTP-gS. External cell perfusion with dronedarone inhibited the activity of IK(ACh) channels recorded from cell-attached patches by reducing the channel open probability (from 0.56 to 0.11) without modification of the single-channel conductance.[13]

These data suggest that dronedarone blocks IK(ACh) channels either by disrupting the G-protein- mediated activation or by a direct inhibitory interaction with the channel protein.[13]

CLINICAL DEVELOPMENT

Clinical efficacy of dronedarone in various therapeutic conditions such as atrial fibrillation and heart failure is demonstrated by various clinical trials as summarised below.[14]

ATHENA: A placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter.

EURIDIS: European trial in atrial fibrillation patients receiving dronedarone for the maintenance of sinus rhythm.

ADONIS: American-australian-african trial with dronedarone in atrial fibrillation patients for the maintenance of sinus rhythm.

ANDROMEDA: A placebo-controlled, double-blind, multicentre parallel arm trial to evaluate the efficacy of dronedarone 400mg bid on the mortality rate after dronedarone therapy for severe heart failure.

DAFNE: A placebo-controlled, double-blind, parallel arm trial to assess the effect of dronedarone various doses (800, 1200, 1600 mg/d) in patients with persistent atrial fibrillation: a dose ranging study.

ERATO: A placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg bid for the control of ventricular rate in permanent atrial fibrillation: the efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation (erato) study.

Atrial Fibrillation

ATHENA

The effect of dronedarone 400 mg twice daily on hospitalization for cardiovascular (CV) events or death in 4628 patients with AF were compared to placebo in ATHENA. The mean follow-up was 21 months. Treatment with dronedarone reduced the primary endpoint of composite first hospitalization for CV events or death compared to the placebo group (hazard ratio [HR] 0.76; 95% CI 0.69 to 0.84; $P < 0.001$) which was driven by the secondary endpoint of CV hospitalizations. There was no significant difference in the secondary endpoint of all-cause mortality.

Trial summary: Treatment with dronedarone reduced first hospitalization for CV events or death by 24% compared to placebo in patients with paroxysmal or persistent AF/AFL.[6]

Results summary is displayed in Table 1.

SINUS RHYTHM

EURIDIS and ADONIS

The efficacy of dronedarone 400 mg twice daily on the primary endpoint of time to first recurrence of AF/AFL was compared to placebo in two randomized, multicenter trials of patients with a history of AF (at least one episode of AF within the past 3 months and in sinus rhythm for at least 1 hour prior to randomization). Patients with New York Heart Association (NYHA) Class III or IV HF were excluded from the trial. Mean left ventricular ejection fraction (LVEF) at baseline was

59%. The results of the two trials (ADONIS: 625 patients enrolled in the U.S., Canada, Australia, South Africa, and Australia; EURIDIS: 612 patients enrolled in 12 countries in Europe) are presented separately and combined in the table below. In ADONIS, the median time to first recurrence of AF/AFL was 158 days with dronedarone compared to 59 days in the placebo group; for EURIDIS, the results were 96 days with dronedarone and 41 days in patients receiving placebo. When results of the trials were combined, the median time to AF recurrence was 116 days with dronedarone and 53 days in patients on placebo. The secondary endpoint of ventricular rate at first recurrence of AF was 103 with dronedarone compared to 117 on placebo (P<0.001). According to an evaluation of another secondary endpoint, the rates of symptomatic recurrence AF occurred in 38% of patients on dronedarone and 46% on placebo (P<0.001). The only reported adverse event that occurred more frequently in the dronedarone group was an increase in sCr (2.4% of patients vs. 0.2% on placebo; P=0.004). One patient receiving dronedarone was reported to have interstitial lung disease, and another with pulmonary fibrosis that was also found at baseline.[6]

Trial summary: Treatment with dronedarone increased median time to first recurrence AF/AFL by 63 days compared to placebo; the rate of AF recurrence at 12 months was reduced by 25% with dronedarone compared to placebo.

Results summary is displayed in Table 2.

Heart Failure

ANDROMEDA

The effect of dronedarone 400 mg twice daily on the primary endpoint of all-cause mortality or hospitalization for worsening HF was to be evaluated in a randomized, double-blind, placebo-controlled, multicenter trial conducted in Europe. Patients hospitalized with new or worsening HF (with NYHA Class III or IV HF or paroxysmal nocturnal dyspnea within the last month), were included in the trial. Entry criteria also included a LVEF equivalent to no more than 35%. Approximately 40% of patients had a history of AF; 56% were in NYHA Class III HF and approximately 40% in Class II HF. The trial was planned to include at least 12 months of treatment for each patient, and was to be conducted over a period of 2 years. The trial was discontinued prematurely after 627 patients were enrolled and after a median follow-up of 2 months due to an increase in mortality in the treatment group: 25 deaths (8.1%) in patients treated with dronedarone compared to 12 deaths (3.8%) in patients on placebo (HR 2.13; 95% CI 1.07 to 4.25; P=0.03). It was reported that the increased mortality was primarily due to an increase in death due to worsening HF (10 deaths with dronedarone compared to 2 deaths on placebo). There was no difference in the primary endpoint reported at study termination. According to subgroup analysis, the risk of death was greater in patients with a lower LVEF (approximately < 35%) compared to a higher LVEF. The only reported serious adverse event that occurred significantly more frequently in the dronedarone group was an increase in sCr (2.6% of patients vs. 0% on placebo; P=0.01).

Trial summary: The risk of all-cause mortality was doubled in patients with moderate to severe HF and reduced LVEF who were treated with dronedarone compared to placebo.[14]

Results summary is displayed in Table 3.

Additional Efficacy Trials

DAFNE

Patients with persistent AF scheduled for cardioversion (n=270; 199 analyzed) were randomized to treatment with dronedarone 400 mg twice daily, 600 mg twice daily, 800 mg twice daily, or placebo. The primary efficacy endpoint of median time to AF relapse during the 6 month evaluation period was 60 days with dronedarone 400 mg twice daily vs. 5.3 days with placebo (RRR 55%; 95% CI 72 to 28%; P=0.001). A significant benefit was not found at the higher doses of dronedarone; although, there was an increase in the discontinuation rate due to adverse events with 800 mg twice daily (22.6%) and 600 mg twice daily (7.6%) compared to the 400 mg twice daily treatment group (3.9%) or placebo (0%). The most frequent reason for drug discontinuation was due to diarrhea, nausea, or vomiting.[3]

ERATO

The effect of dronedarone 400 mg twice daily on the primary endpoint of change in mean ventricular rate from baseline to day 14 compared to placebo was evaluated in 174 patients with symptomatic permanent AF. Treatment was continued for 6 months to evaluate tolerability. Mean 24-hour ventricular rate was reduced by 11 beats per minute (bpm) compared to an increase of 0.7 bpm with placebo (P<0.0001). Although the effect of dronedarone on resting heart rate appeared to achieve clinical significance, the reduction in exercise heart rate (dronedarone 27.4 bpm vs. placebo 2.9 bpm; P<0.0001) did not improve to clinically recommended levels.3 Results from the per protocol analysis showed that dronedarone reduced mean ventricular rate by 12.3 bpm (from 88.8 to 76.5 bpm) compared to a reduction of 0.4 bpm with placebo (from 92.3 to 91.1 bpm). There was no significant difference in mean increase in maximal exercise duration (P=0.514). There was an increase in treatment emergent adverse events (TEAEs) with

dronedarone compared to placebo (77% vs. 60%) and a slight increase in serious TEAEs with dronedarone (17%) vs. placebo (14%). The rates of any infection (31% vs. 25%), gastrointestinal disorder (20% vs. 14%), respiratory-related (19% vs. 7%), or nervous system disorder (17% vs. 12%), were all increased with dronedarone compared to placebo. There was one report of sudden death in a patient treated with dronedarone (reported to have a history of congenital heart disease and a family history of sudden death and Steinert's disease (myotonic dystrophy). It was reported that this patient's ECG abnormalities were not detected upon enrollment which would have resulted in exclusion from the study. There was a 41.4% increase in digoxin levels that was reported not to result in a significant difference in levels outside the therapeutic range compared to placebo.

TOLERABILITY AND SIDE EFFECTS

Clinical trials of dronederone have produced highly satisfactory data in terms of improving atrial fibrillation parameters, together with a good safety profile and good tolerability over a period of up to maximum 30 months both as monotherapy and in combination with other antiarrythmia drugs. In drug-naïve patients with atrial fibrillation, dronedarone 400 mg monotherapy once daily showed a similar tolerability profile to the placebo. The clinical trial studies revealed similarity in the overall incidence of side effects between dronedarone (400mg) and placebo. The most common events reported with dronedarone 400mg (more commonly than placebo) were diarrhea (9% vs. 6%), nausea (5% vs. 3%, respectively), abdominal pain (4% vs. 3%, respectively), vomiting (2% vs. 1%, respectively), dyspepsia (2% vs. 1%, respectively), asthenia (7% vs. 5%, respectively), bradycardia (3% vs. 1%, respectively), rash, pruritus, eczema, dermatitis, allergic dermatitis (5% vs. 3%, respectively), photosensitivity (< 1% vs. not reported, respectively), dysgeusia (< 1% vs. not reported, respectively). In one of the pivotal trial with dronedarone (ATHENA), there was no statistically significant difference in serious adverse events (e.g., cardiac, respiratory, gastrointestinal, endocrine, neurologic, skin-related, or increase serum Creatinine) with dronedarone compared to placebo. There was one reported case of torsades de pointes in a patient receiving dronedarone.[9,13,14]

A randomized, cross-over, placebo-controlled, double-blind study in twelve healthy volunteers was carried out for effect of dronedarone on renal function. Dronedarone reduces renal creatinine and N-methylnicotinamide clearance by about 18%, without evidence of an effect on GFR, renal plasma flow or electrolyte exchanges. A specific partial inhibition of tubular organic cation transporters, limited increase in serum creatinine is therefore expected with dronedarone treatment, but not mean there is a decline in renal function.[9]

DRUG INTERACTIONS

Pharmacokinetic interaction between dronedarone and a range of commonly-prescribed therapeutic agent was investigated by conducting series of studies in healthy individuals dronedarone is metabolized primarily by CYP 3A and is a moderate inhibitor of CYP 3A and CYP 2D6. Ketoconazole is a broad spetrum antifungal agent and being a strong CYP 3A4/5 inhibitor, resulted in a 17-fold increase in dronedarone exposure and a 9-fold increase in Cmax due to repeated dose of ketoconazole. Therefore, the dose of dronedarone should be limited when co-administered with a strong CYP3A/5 inhibitor. Simvastatin, (HMG CoA) reductase inhibitor prescribed to control hypercholesterolemia and prevent cardiovascular disease, which shares the CYP3A4 metabolic pathway with dronedarone. Coadministration of simvastatin with dronedarone increased simvastatin and simvastatin acid exposure by 4- and 2- fold, respectively. Dronedarone administration did not meaningfully alter the pharmacokinetics of simvastatin. Diltiazem is a calcium-channel blocker used in the treatment of hypertension; it is a moderate inhibitor of CYP3A4/5 and would be expected to alter the pharmacokinetics of dronedarone. Coadministration of calcium channel blocker (verapamil, dialtiazam or nifedipine) with dronedarone increases the exposure of calcium channel blocker by 1.4- to 1.5- fold.Therefore, dosage adjustment of saxagliptin may be required when coadministered with calcium channel blocker. Digoxin is a cardiac glycoside widely used in the treatment of various cardiac conditions and is a P-glycoprotein substrate. Dronedarone increased digoxin exposure by 2.5-fold by inhibiting the P-gP transporter. Other P-gP substrates are expected to have increased exposure when coadministered with dronedarone. So, if digoxin treatment is continued, the doses of digoxin, monitor serum levels closely, and observe for toxicity.[2,11,14]

CONCLUSION

Dronedarone is a newer benzofuran derivative structurally similar to amiodarone except it lacks the iodine moiety and there is an addition of a methane sulfonyl group. It does not significantly prolong the QTc and no significant pulmonary, hepatic, ocular, or neurologic toxic effects have been observed in the studies done to date. Dronedarone, in addition to its benefits for rate and rhythm control, may reduce all-cause hospitalization or death in patients with AF.

Dronedarone may be a viable, uniformly effective, and safer treatment option for patients with AF.

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Table 1: Primary results of ATHENA

Outcomes	Dronedarone (n=2301)	Placebo (n=2327)	HR (95% CI)	P value
Composite first hospitalization for CV event or death*	734 (31.9%)	917 (39.4%)	0.76 (0.69-0.84)	<0.001
All-cause mortality	116 (5.0%)	139 (6.0%)	0.84 (0.66-1.08)	0.18
First hospitalization due to CV event	675 (29.3%)	859 (36.9%)	0.74 (0.67-0.82)	<0.001

* Primary endpoint

CI= confidence interval, CV= cardio vascular, HR= hazard ratio.

Table 2: Primary results of Adonis and Euridis

Outcomes	Dronedarone (n=417)	Placebo (n=208)	HR (95% CI)	P value
ADONIS				
Recurrence AF (median days)	158	59	-	-
Recurrence AF at 12 months (% patients)	61.1%	72.8%	0.73 (0.59-0.89)	0.002
EURIDIS				
Outcomes	**Dronedarone (n=411)**	**Placebo (n=201)**	**HR (95% CI)**	**P value**
Recurrence AF (median days)	96	41	-	-
Recurrence AF at 12 months (% patients)	67.1%	77.5%	0.78 (0.64-0.96)	0.01
Combined trials				
Outcomes	**Dronedarone (n=828)**	**Placebo (n=409)**	**HR (95% CI)**	**P value**
Recurrence AF (median days)	116	53	-	-
Recurrence AF at 12 months (% patients)	64.1%	75.2%	0.75 (0.65-0.87)	<0.001

AF=atrial fibrillation, CI= confidence interval, CV= cardio vascular, HR= hazard ratio.

TABLE 3: PRIMARY RESULTS OF ANDROMEDA

Outcomes	Dronedarone (n=310)	Placebo (n=317)	HR (95% CI)	P value
Composite all-cause mortality and hospitalization for worsening HF*	53 (17.1%)	40 (12.6%)	1.38 (0.92-2.09)	0.12
All-cause mortality	25 (8.1%)	12 (3.8%)	2.13 (1.07-4.25)	0.03

* Primary endpoint

HF=heart failure, HR= hazard ratio.

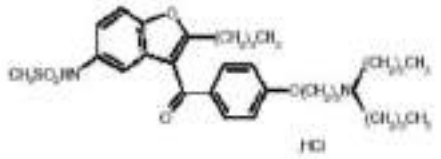

Figure 1: Structural formula