World Journal of Pharmaceutical ReseaRch
SJIF Impact Factor 5.045
Volume 3, Issue 8, 511-523. Research Article ISSN 2277 – 7105

BIOEQUIVALENCE STUDY OF DOFETILIDE IN HEALTHY HUMAN VOLUNTEERS UNDER FASTING AND FED CONDITIONS

R Arunkumar[1]*, A Ruckmani[2], Lakshmipathy Prabhu R[3], Pradeep G Nayar[4], M Chokkalingam[4], D Rajasekaran[5], O Arjun Arumugam[6]

[1]Associate Professor, Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu – 603103. India.
[2]Professor and Head, Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu – 603103.
[3]Dept. of Clinical Research and Experimental Medicine, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu – 603103
[4]Department of Cardiology, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu – 603103
[5]Professor and Head, Department of Medicine, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu – 603103
[6]Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu – 603103

Article Received on
28 July 2014,

Revised on 21 August 2014,
Accepted on 16 Sept 2014

***Correspondence for Author**
Dr. R Arunkumar
Associate Professor, Department of Pharmacology, Chettinad Hospital and Research Institute, Kelambakkam, Tamilnadu India.

ABSTRACT

Dofetilide is an antiarrhythmic agent belonging to class III. It is indicated for the conversion and maintenance of sinus rhythm in atrial fibrillation and atrial flutter. The objective of this study is to investigate the bioequivalence of generic dofetilide 0.5 mg in comparison with Tikosyn ® (dofetilide) 0.5 mg under fasting and fed conditions in healthy human volunteers. The study was designed as a "two period, two treatment, two way, cross over, open label" study. 12 healthy, adult, male subjects were enrolled after obtaining written informed consent. Six of them received the medications under fasting conditions and the remaining six under fed conditions, both generic and innovator drugs with the wash out period of 5 days in between. Blood samples were collected for dofetilide estimation in K3EDTA blood collection tubes. QTc interval was recorded at scheduled time points to assess the effect of the drug on ECG. There was no adverse effect observed during the study. The generic and innovator products were well tolerated. Both the formulations produced an increase in the QTc interval, which returned pre-dose level within 8 to 12 hours.

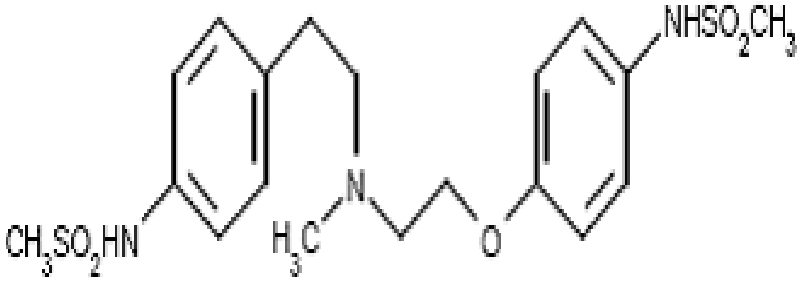
The drug concentration was measured using LCMSMS with the validated bioanalytical method. Pharmacokinetic and statistical analysis were done using WinNonlin® and SAS®. The results indicate that the generic dofetilide produced pharmacokinetic parameters cmax, AUC0-t and AUC0-inf that met bioequivalence limits of 80-125 under fasting conditions but failed to meet the BE limits under fed conditions for cmax whereas it met the limits for AUC0-t and AUC0-inf.

KEY WORDS: Dofetilide, bioequivalence, generic drug, pharmacokinetics

INTRODUCTION AND OBJECTIVE

Dofetilide is an antiarrhythmic agent belonging to class III. It is indicated for the conversion and maintenance of sinus rhythm in atrial fibrillation and atrial flutter.[1]

The molecular formula of dofetilide is $C_{19}H_{27}N_3O_5S_2$ and its molecular weight is 441.6. The structural formula is



The chemical name of dofetilide is: N-[4-[2-[methyl[2-[4-[(methylsulfonyl)amino]phenoxy]ethyl]amino]ethyl]phenyl]-methanesulfonamide. It is a white to off-white powder, slightly soluble in water and propanol and soluble in 0.1M aqueous sodium hydroxide, acetone, and aqueous 0.1M hydrochloric acid. Its antiarrhythmic activity is due to the blockade of the cardiac ion channel carrying the rapid component of the delayed rectifier potassium current. It has highly selective action against this potassium current and does not block calcium channels in cardiac myocytes. [2] It does not block the other repolarizing potassium currents and has no effect on sodium channels, alpha and beta adrenergic receptors [3].

Dofetilide has no effect on cardiac output, cardiac index, stroke volume index and systemic vascular resistance. It does not produce negative inotropic effect and there is no increase in heart failure in patients with significant left ventricular dysfunction. It does not affect blood

pressure and reduces heart rate only by 4–6 beats per minute[3]. The Cmax of dofetilide 0.5 mg capsule under fasting and fed conditions was 2.22 ng/ml and 2.01 ng/ml respectively.[3] The oral bioavailability of dofetilide is more than 90%, with Cmax occurring at about 2–3 hours in the fasting state. Oral bioavailability is unaffected by food or antacid. The terminal half-life of dofetilide is approximately 10 hours. It reaches steady state plasma concentration in 2–3 days, with an accumulation index of 1.5 to 2.0 [3].

80% of dofetilide is excreted in urine, of which approximately 80% is excreted unchanged and the remaining 20% as metabolites. It is eliminated through both glomerular filtration and active tubular secretion [3].

The recommended dose of dofetilide is 0.5 mg administered twice a day. The most frequent adverse events reported are headache, chest pain, and dizziness. Dofetilide increases QTc interval and may lead to Long QTc syndrome. The common reason for discontinuation of therapy with dofetilide is ventricular tachycardia. Other adverse effects include angina, anxiety, arthralgia, asthenia, atrial fibrillation, hypertension, pain, palpitation, peripheral edema, supraventricular tachycardia, sweating, urinary tract infection and ventricular tachycardia. [4]

The innovator brand is Tikosyn® and the innovator company of dofetilide is Pfizer. US FDA approved Dofetilide on Oct 1, 1999 and it has patent protection till Oct 9, 2018.[5] The primary objective of the present study is to assess the bioequivalence of generic dofetilide capsules 0.5 mg and TIKOSYN (Dofetilide) capsule 0.5 mg of Pfizer Pharmaceuticals LLC, USA in healthy, adult, human subjects, under fasting and fed conditions. The secondary objective is to investigate dofetilide induced changes in QTc interval. It is important to study the bioequivalence of generic dofetilide before approval of generic version as it is a narrow therapeutic drug[1] and if the pharmacokinetics is not similar to the innovator drug it may lead to significant toxicities or therapeutic failure.

MATERIALS AND METHODS

The study was initiated after obtaining approval from the Institutional Human Ethics Committee and Office of the Drugs Controller General, India. The clinical phase of the study was conducted in Chettiand Hospital and Research Institute and the bioanalytical phase in Azidus laboratories Ltd. The study was conducted in compliance to schedule Y of drugs and

cosmetics act and Indian Good Clinical Practice guidelines. Informed written consent was obtained from all the study subjects prior to their participation.

The study was designed as an open label, randomized, two treatment, two sequence, two period, single dose, cross over, bioequivalence study. The study design was based on the US FDA recommendation on bioequivalence of dofetilide.[6] The randomization schedule was generated by using the software application SAS®. Wash out period was 5 days between period 1 and period 2.

12 healthy adult male subjects participated in the study. Dosing was done in fasting conditions in 6 subjects and in the remaining 6, fed conditions. The inclusion and exclusion criteria for selecting the volunteers are listed in table 1 and 2. The subjects were admitted, on the previous day of drug administration and the drug was administered after 10 hours of overnight fasting. The subjects, who received dofetilide under fed condition, had high fat high calorie breakfast as recommended by US FDA [7], 30 minutes prior to dosing. The meal component is given in table 3. After dosing, standard food and snacks were provided to the subjects at 4, 8, 12 hours (on dosing day) and 24, 28, 32 and 36 hours (day after the dosing day). Subjects were discharged 48 hours after dosing after ensuring that their ECG and vital parameters were normal.

Vital signs measurement and subject well-being assessment were done at the time of admission and at 00.00 hours (pre dose), 01.00, 02.00, 03.00, 04.00, 06.00, 08.00, 10.00, 12.00, 24.00 hours and during subject discharge (48.00 hours). All the subjects were under continuous cardiac monitoring during the study. Serum Potassium levels were measured at 12.00, 24.00, 36.00 and 48.00 hours post dose. 12 lead ECG was recorded while the subjects were admitted and at 0 hr (predose) and 01, 02, 03, 04, 05, 06, 07, 08, 12, 24, 36 & 48 hours postdose to assess the QTc interval. A total of 21 blood samples for drug concentration measurement were drawn at 0.00 hours (predose) and 0.50, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 12.00, 24.00, 36.00 and 48.00 hours after dosing in K3EDTA blood collection tubes. The samples were centrifuged at 4000 rpm for 10 minutes at 4 ± 2°C. Plasma was separated into a single aliquot and stored at about -20°C or below till analysis.

Assessment of plasma samples for dofetilide was done by a validated bioanalytical method using LC-MS/MS. The method was validated as per the regulatory requirements and the

parameters such as precision, accuracy, specificity, recovery, stability and sensitivity were well established for dofetilide in plasma.

During bioanalysis of subject samples, distribution of quality control samples throughout each batch was ensured. All samples from one subject were analyzed with the same standard curve. The sample concentration above the upper limit of the standard curve from validated range was analyzed by diluting the sample with drug free biological matrix and assayed.
The drug concentration data was subjected to pharmacokinetic analysis. The following Pharmacokinetic parameters were calculated using non-compartmental model of WinNonlin®: "Cmax: Maximum drug concentration achieved in systemic circulation following drug administration.

AUC0-t: Area under the plasma concentration - time curve from 0 h to the last quantifiable concentration to be calculated using the trapezoidal rule.

AUC0-∞: Area under the plasma concentration - time curve, from zero to infinity to be calculated as the sum of AUC0-t plus the ratio of the last measurable concentration to the elimination rate constant.

Tmax: Time required to achieve maximum drug concentration in systemic circulation.

Kel: Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve.

T1/2: Elimination half life of a drug is the time necessary to reduce the drug concentration in the blood, plasma, or serum to one-half after equilibrium is reached." [8]
Statistical analysis was performed on the pharmacokinetic parameters using SAS®. Summary Statistics, ANOVA, Ratio Analysis, power, intrasubject CV and 90% Confidence Interval were calculated. To establish bioequivalence, 90% Confidence Interval (CI) for the ratio (Test/Reference) of Least Square Means of the log transformed PK parameters (AUC0-t, AUC0-∞ and Cmax) should be between 80%-125% for Dofetilide[9].

RESULTS AND DISCUSSION

In this study, 12 male subjects participated. Their mean age was 28.5±2.7 yrs in the fasting study and 30.76±3.5 yrs in the fed study. The mean weight and Body Mass Index (BMI) of the subjects was 61.75±5.4 kg and 23.76±1.3 kg/m2 respectively in the fasting study and they

were 65.56±4.6 kg and 22.43±2.34 kg/m2 in the fed study. There were no adverse events reported by the subjects or observed by the study team.

The individual and mean pharmacokinetic data of the fasting and fed studies are tabulated in tables 4 and 5. The bioequivalence evaluation of the log transformed pharmacokinetic parameters is provided in table 6. The results indicate that the generic dofetilide is bioequivalent to the innovator product under fasting conditions for Cmax, AUC0-t and AUC0-inf. However the generic drug did not meet the bioequivalent criteria of 80-125 under fed conditions for cmax, though it met the criteria for AUC0-t and AUC0-inf. Cmax fails to meet the bioequivalence (BE) criteria under fed conditions as its upper limit of 90% confidence interval is 127.38 and not within 80 to 125.

The semilog plots comparing the plasma concentration in log scale (Y axis) and time points (X axis) of fasting and fed studies are provided in Figure 1 and 2. The estimated mean QTc interval of the subjects in both fasting and fed studies is tabulated in table 7 and 8. The QTc results indicate that both test and reference products produced significant increase in the QTc interval from the time of dosing till 6 to 8 hours and then the interval falls gradually reaching the pre-dose QTc interval. However the QTc was never beyond 440 ms and never more than 50 ms higher than the pre-dose QTc in any of the subjects. There was no intervention made to revert the QTc to baseline level. None of the subjects had hemodynamic instability because of QTc prolongation. The potassium levels estimated did not show any significant change in period 1 and period 2. There are number of reasons for a bioequivalence study to fail. There could be formulation differences between the generic and innovator products, high variability of the drug pharmacokinetics, variable characteristics of participating subjects, protocol noncompliance and erratic blood collection schedule for drug estimation [10]. In this study, failure to meet the acceptable BE limits under fed conditions could be due to the small number of subjects or the formulation difference. Since the drug is not highly variable and there is no significant food effect reported [4], failure could be most likely due to small sample size. If the study is done in a larger sample size, the molecule might meet BE limits in both fasting and fed conditions.

DECLARATIONS

Funding: The study was funded by Azidus Laboratories Ltd., Chennai

Competing interests: None

Ethical approval: The study was approved by the Institutional Human Ethics Committee at Chettinad Hospital and Research Institute.

Table 1: Inclusion Criteria
Healthy male volunteers of 20 to 45 yrs
Body Mass Index (BMI) between 18.50 – 24.99 Kg/m^2 and body weight not less than 50 kg.
Healthy individual as evaluated by personal history, medical history and general clinical examination.
Normal biochemical, hematological and urinary parameters.
Normal Chest X - ray PA view & ECG in 12 leads.
Negative for HIV 1 & 2, Hepatitis B, Hepatitis C, and Syphilis tests.
Negative urine test for drugs of abuse for morphine, barbiturates, benzodiazepines, amphetamine, THC & cocaine
Negative alcohol breath analysis

Table 2: Exclusion Criteria
Subjects incapable of understanding the informed consent.
History of diabetes mellitus, tuberculosis and systemic hypertension.
History suggestive of cardiac, gastrointestinal, respiratory, hepatic, renal, endocrine, neurological, metabolic, psychiatric or hematological systems, judged to be clinically significant.
Subjects with congenital or acquired long QT syndromes.
Chronic alcohol intake of more than 2 units (approximately 50 ml of spirits such as whiskey/brandy, 100 ml of wine, 540 ml of beer) per day for the past 6 months.
History of smoking 9 or more cigarettes or beedies per day and / or inability to withhold smoking or consumption of tobacco containing products during the study.
History of any drug abuse in the past 12 months.
History of any incidence of arrhythmia or cardiac rhythm abnormalities.
History of hypersensitivity to Dofetilide and related drugs or excipients in the formulation
History of allergy to vegetables and / or food substances and / or any other manifestations suggestive of hypersensitivity reactions.
Present or past history of intake of drugs which potentially modify kinetics / dynamics of Dofetilide or any other medication judged to be clinically significant by the investigator.
Present or past history of intake of cimetidine, verapamil, ketoconazole, trimethoprim, sulphamethoxazole, hydrochlorothiazide, triamterene, metformin, amiloride, macrolide antibiotics, azole antifungal agents, protease inhibitors, serotonin reuptake inhibitors, amiodarone, cannabinoids, diltiazem, nefazadone, norfloxacin, quinine, zafirlukast,
Consumption of grapefruit / its products within 10 days prior to the start of study.
Intake of any prescription drug or over-the counter (OTC) drugs within 7 days prior to study and / or intake of any drug in the past that could

affect the kinetics or dynamics of Dofetilide in view of investigator.
Subjects with QTc interval of > 440 ms at the time of screening.
Subjects with Creatinine clearance of < 60 mL/min.
Subject who had participated in any other clinical study during the last 3 months.
Subject who had bled in the past 3 months from the date of start of study either for blood donation or for any other reason.

Table 3: Components of High fat High calorie breakfast

S. No	Food Item	Quantity (grams)	Protein (g)	Carbohydrate (g)	Fat (g)	Caloric value (Kcal)
1	Toasted Bread + butter	2 slices + 20g butter	3.8	24.6	20.7	299.9
2	Fried Egg	2 No.s (70g)	10.64	1.0	16.9	198.66
3	French Potato fries	75 g	1.07	11.75	2.8	76.48
4	Milk with Sugar 1 tsp	240 ml	10.32	22	15.6	269.68
5	Fried Chicken	100g	15.76	3.73	6.4	135.56
Total Caloric values (Kcal)			166.36	252.32	561.6	980.28
Percentage of calories			16.97	25.74	57.29	100

Table 4: PK data - Dofetilide under fasting conditions

	Tikosyn data (Reference product)						
Subject	Cmax (ng/ml)	AUClast (ng.hr/ml)	AUCINF_obs (ng.hr/ml)	Tmax (hr)	Lambda_z	HL_Lambda_z (hr)	AUC_% Extrap_obs
1	2.5529	26.9377	28.0241	1.50	0.0881	7.8684	3.8765
2	1.7899	20.4641	21.2952	1.00	0.0961	7.2107	3.9031
3	2.0158	26.0026	27.2399	3.33	0.0883	7.8469	4.5424
4	2.1185	24.2598	25.2362	3.33	0.0959	7.2307	3.8691
5	2.3155	26.6790	27.9057	2.33	0.0881	7.8655	4.3958
6	2.0822	27.2746	28.0163	3.00	0.0797	8.6991	2.6474
N	6	6	6	6	6	6	6
Mean	2.146	25.270	26.286	2.415	0.089	7.787	3.872
SD	0.262	2.586	2.667	0.986	0.006	0.546	0.667
SE	0.107	1.056	1.089	0.403	0.002	0.223	0.272
Variance	0.069	6.688	7.112	0.973	0.000	0.298	0.445
Min	1.79	20.46	21.30	1.00	0.08	7.21	2.65
Median	2.10	26.34	27.57	2.67	0.09	7.86	3.89
Max	2.55	27.27	28.02	3.33	0.10	8.70	4.54
Range	0.76	6.81	6.73	2.33	0.02	1.49	1.89
CV%	12.2	10.2	10.1	40.8	6.8	7.0	17.2
Geometric Mean	2.133	25.150	26.163	2.209	0.089	7.771	3.817
	Generic Dofetilide data (Test product)						
Subject	Cmax (ng/ml)	AUClast (ng.hr/ml)	AUCINF_obs (ng.hr/ml)	Tmax (hr)	Lambda_z	HL_Lambda_z (hr)	AUC_% Extrap_obs
1	2.3511	26.2241	27.2287	3.00	0.0926	7.4871	3.6893
2	1.8477	20.4042	21.1467	1.00	0.0967	7.1679	3.5112

3	2.0423	26.0990	27.0586	3.67	0.0935	7.4147	3.5462
4	2.0759	25.4594	26.4260	2.67	0.0965	7.1811	3.6577
5	2.1622	28.0363	28.7473	2.00	0.0795	8.7231	2.4734
6	2.0361	30.5663	31.5224	1.00	0.0664	10.4371	3.0333
N	6	6	6	6	6	6	6
Mean	2.086	26.132	27.022	2.223	0.088	8.069	3.319
SD	0.166	3.363	3.410	1.090	0.012	1.296	0.477
SE	0.068	1.373	1.392	0.445	0.005	0.529	0.195
Variance	0.027	11.312	11.630	1.188	0.000	1.681	0.227
Min	1.85	20.40	21.15	1.00	0.07	7.17	2.47
Median	2.06	26.16	27.14	2.34	0.09	7.45	3.53
Max	2.35	30.57	31.52	3.67	0.10	10.44	3.69
Range	0.50	10.16	10.38	2.67	0.03	3.27	1.22
CV%	7.9	12.9	12.6	49.0	13.9	16.1	14.4
Geometric Mean	2.080	25.940	26.831	1.972	0.087	7.990	3.287

Table 5: PK data - Dofetilide under fed conditions

	Tikosyn data (Reference product)						
Subject	Cmax (ng/ml)	AUClast (ng.hr/ml)	AUCINF_obs (ng.hr/ml)	Tmax (hr)	Lambda_z	HL_Lambda_z (hr)	AUC_% Extrap_obs
1	2.0102	24.4478	25.2639	3.33	0.0785	8.8252	3.2304
2	1.8375	20.4253	21.3946	2.67	0.0820	8.4510	4.5305
3	1.9354	25.2962	26.1592	4.50	0.0970	7.1467	3.2990
4	2.2846	28.4648	29.1569	4.50	0.0825	8.4012	2.3736
5	1.7509	21.3426	22.0734	5.00	0.0991	6.9972	3.3110
6	3.1481	25.1720	25.7343	1.50	0.1031	6.7200	2.1850
N	6	6	6	6	6	6	6
Mean	2.161	24.191	24.964	3.583	0.090	7.757	3.155
SD	0.517	2.926	2.856	1.336	0.011	0.901	0.836
SE	0.211	1.195	1.166	0.545	0.004	0.368	0.341
Variance	0.267	8.562	8.158	1.785	0.000	0.813	0.699
Min	1.75	20.43	21.39	1.50	0.08	6.72	2.19
Median	1.97	24.81	25.50	3.92	0.09	7.77	3.26
Max	3.15	28.46	29.16	5.00	0.10	8.83	4.53
Range	1.40	8.04	7.76	3.50	0.02	2.11	2.35
CV%	23.9	12.1	11.4	37.3	11.6	11.6	26.5
Geometric Mean	2.117	24.043	24.827	3.325	0.090	7.713	3.065
	Generic Dofetilide data (Test product)						
Subject	Cmax (ng/ml)	AUClast (ng.hr/ml)	AUCINF_obs (ng.hr/ml)	Tmax (hr)	Lambda_z	HL_Lambda_z (hr)	AUC_% Extrap_obs
1	1.8398	21.9385	23.1303	3.67	0.0842	8.2278	5.1524
2	2.8189	21.9975	24.0364	1.00	0.1028	6.7426	8.4825
3	2.2601	26.5145	26.9993	3.67	0.1163	5.9578	1.7955
4	2.4749	25.9738	27.4330	3.33	0.0820	8.4501	5.3193

5	2.2702	22.0721	22.9450	2.00	0.0938	7.3880	3.8045
6	3.2098	28.0487	28.8073	2.67	0.1055	6.5730	2.6335
N	6	6	6	6	6	6	6
Mean	2.479	24.424	25.559	2.723	0.097	7.223	4.531
SD	0.480	2.739	2.498	1.064	0.013	0.979	2.376
SE	0.196	1.118	1.020	0.434	0.005	0.400	0.970
Variance	0.230	7.502	6.238	1.131	0.000	0.959	5.647
Min	1.84	21.94	22.95	1.00	0.08	5.96	1.80
Median	2.37	24.02	25.52	3.00	0.10	7.07	4.48
Max	3.21	28.05	28.81	3.67	0.12	8.45	8.48
Range	1.37	6.11	5.86	2.67	0.03	2.49	6.69
CV%	19.3	11.2	9.8	39.1	13.6	13.6	52.4
Geometric Mean	2.441	24.297	25.457	2.492	0.097	7.168	4.014

Table 6: Bioequivalence data – Fasting and fed conditions

Bioequivalecne criteria - Fasting conditions							
PK parameter	Ref GeoLSM	Test GeoLSM	Ratio [%Ref]	CI_90_Lower	CI_90_Upper	Power	Intra CV
Ln(Cmax)	2.13	2.08	97.55	94.02	101.22	1.00	0.03
Ln(AUClast)	25.15	25.94	103.14	98.79	107.69	1.00	0.04
Ln(AUCINF_obs)	26.16	26.83	102.55	98.27	107.02	1.00	0.03
Bioequivalecne criteria - Fed conditions							
PK parameter	Ref GeoLSM	Test GeoLSM	Ratio [%Ref]	CI_90_Lower	CI_90_Upper	Power	Intra CV
Ln(Cmax)	2.12	2.44	115.29	104.35	127.38	0.97	0.08
Ln(AUClast)	24.04	24.30	101.06	93.73	108.95	0.99	0.06
Ln(AUCINF_obs)	24.83	25.46	102.54	95.31	110.32	0.99	0.06

Table 7: QTc Interval data, Fasting study

Time point	**Test product (period I)**		**Test product (period II)**		**Reference product (period I)**		**Reference product (period II)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
CHECK IN	372.33	6.43	385.33	5.03	381.67	23.25	378.00	11.14
0.00	374.33	14.29	391.00	7.00	378.00	8.19	390.33	4.16
1.00	397.67	15.95	410.00	10.44	414.00	6.56	398.33	5.13
2.00	417.33	10.07	416.67	8.39	420.00	11.00	419.67	4.73
3.00	412.00	20.66	424.33	5.13	414.00	6.24	424.00	5.29
4.00	407.33	12.86	426.00	5.29	420.00	7.00	431.33	4.73
5.00	408.00	21.00	427.00	6.24	421.33	10.02	426.67	5.51
6.00	401.00	11.79	419.33	4.04	406.00	10.82	417.67	5.69
7.00	400.67	5.13	417.67	6.66	399.00	11.00	416.33	9.61
8.00	404.67	13.43	414.00	2.65	395.67	15.95	406.67	8.33
12.00	394.00	5.00	398.67	11.24	397.00	25.36	402.67	6.51

24.00	371.00	15.13	383.67	9.07	375.33	23.59	393.33	3.06
36.00	376.33	16.20	388.33	4.73	380.67	14.57	394.00	2.65
48.00	363.00	8.72	387.67	11.72	389.00	13.89	393.00	19.31

Table 8: QTc Interval data, Fed study

Time point	Test product (period I)		Test product (period II)		Reference product (period I)		Reference product (period II)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
CHECK IN	385.33	14.19	381.33	3.06	383.33	16.04	370.67	11.37
0.00	373.33	6.66	376.67	18.15	395.33	7.02	389.00	11.53
1.00	402.33	25.15	409.67	19.35	396.33	5.13	399.00	13.89
2.00	405.00	13.00	407.33	11.50	418.33	11.72	416.00	8.66
3.00	411.67	4.16	414.67	23.63	409.00	5.29	422.67	11.55
4.00	409.33	15.04	417.00	24.06	422.33	8.39	431.67	7.02
5.00	405.33	18.50	414.00	9.85	426.67	14.84	426.67	10.12
6.00	402.33	13.65	408.33	27.61	424.33	6.66	421.33	2.08
7.00	402.00	12.17	412.67	28.04	416.00	5.29	424.67	7.02
8.00	406.00	10.44	403.00	21.17	411.67	10.50	417.67	4.16
12.00	394.67	10.97	399.67	24.01	394.00	6.93	411.00	8.72
24.00	380.00	19.00	363.33	2.52	393.67	2.08	387.67	11.37
36.00	385.33	9.24	380.67	18.15	392.33	3.51	390.33	5.13
48.00	375.00	14.11	391.00	12.12	389.00	7.00	398.33	5.69

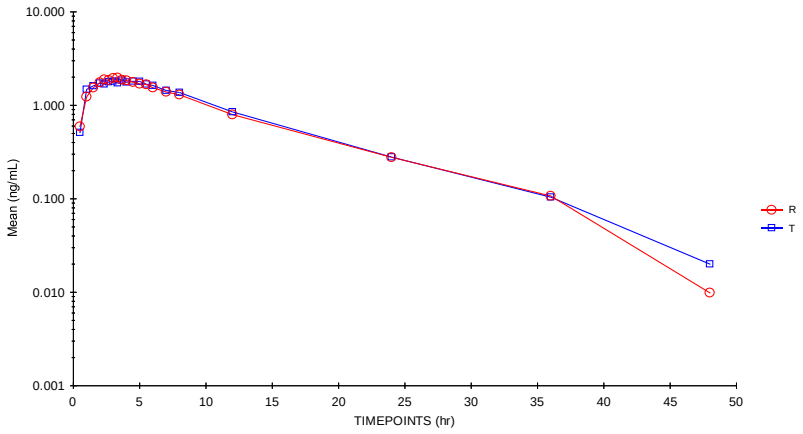


Figure 1: Semilog plot of mean dofetilide concentrations Vs time under fasting conditions.

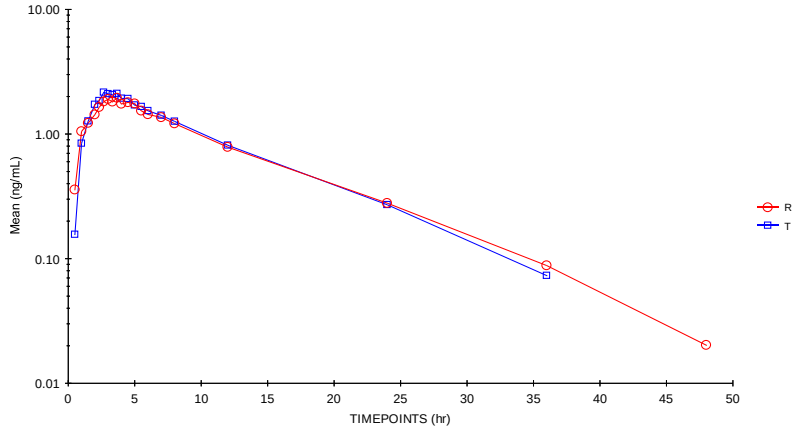


Figure 2: Semilog plot of mean dofetilide concentrations Vs time under fed conditions.

CONCLUSION

In this study conducted to evaluate the bioequivalence of dofetilide under fasting and fed conditions in 6 subjects each, the generic drug meets the BE limits under fasting conditions and fails to meet the limits under fed conditions. However, to confirm the results obtained in this study under fasting and fed conditions, another study with larger sample size may be required.

ACKNOWLEDGEMENT

The authors express their sincere thanks and gratitude to management of Chettinad Hospital and Research Institute and Azidus Laboratories Ltd., Chennai for their support in conducting the study.

REFERENCES

1. J. Paul Mounsey and John P. DiMarco. Dofetilide. Circulation. 2000; 102: 2665-2670.
2. Paul AA1, Leishman DJ, Witchel HJ, Hancox JC. Effects of the class III antiarrhythmic agent dofetilide (UK-68,798) on L-type calcium current from rabbit ventricular myocytes. J Pharm Pharmacol. 2001; 53(12):1671-8.
3. FDA Accessdata, Clinical Pharmacology and Biopharmaceutics Review, NDA Application no. 20931, Tykosyn (Dofetilide) Capsules
4. Prescribing Information. Tikosyn®. Pfizer. 2011.
5. www.accessdata.fda.gov
6. Guidance on Dofetilide. US FDA guidance document. May 2008.

7. Food-Effect Bioavailability and Fed Bioequivalence Studies, Guidance for Industry. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). December 2002.
8. Guidelines for bioavailability & bioequivalence studies. Central Drugs Standard Control Organization, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, New Delhi. (March 2005)
9. Shein-Chung Chow, Laszlo Endrenyi, Eric Chi, Lan-Yan Yang and Laszlo Tothfalusi. Statistical Issues in Bioavailability/Bioequivalence Studies. J Bioequiv Availab 2011, S1
10. Nilesh Wagh, Gayakwad NJ, Christina AJM, Amit Bhople and Anup Thakre. A Bioequivalence Study of Two Finofibrate Tablet Formulations in Indian Healthy Subjects J Bioequiv Availab 2013; 5(1): 016-02.1