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ORAL BIO-EQUVALENCE STUDY OF FIXED DOSE COMBINATION OF PANTOPRAZOLE 40mg AND CINITAPRIDE 3mg EXTENDED RELEASE CAPSULES IN HEALTHY HUMAN MALE VOLUNTEERS

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ABSTRACT

This present bioequivalence study was designed to determine the bioavailability and bioequivalence of Pantoprazole 40mg+ Cinitapride 3mg Extended Release Capsules in comparison with CINTODAC (Pantoprazole 40mg+ Cinitapride 3mg Extended Release) Capsules after single dose administration under fasting conditions in healthy adult male subjects. Therefore the design of an open label, balanced, randomized, single dose, two-treatment, two-sequence, two-period, crossover study with a wash-out period of at least 7 days was used. The primary pharmacokinetic parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) 90%CI were within the 80 to 125% interval required for bioequivalence as stipulated in the current regulations of the USFDA acceptance criteria. The 90% confidence interval for Pantoprazole log transformed parameters C_{max} and AUC_{0-t} were 97.655% to 98.567% and 96.365% to 99.525% respectively and for Cinitapride were 99.976%-101.918% and 104.957%-111.670%. Fifteen volunteers had completed all treatment periods. There was no significant difference between the two formulations. No serious adverse events related to the study drug were found.

KEYWORDS

Pantoprazole, Cinitapride, Pharmacokinetic parameters and Bio-equivalence.

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INTRODUCTION[1]

A peptic ulcer, also known as peptic ulcer disease (PUD), is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. It is defined as mucosal erosions equal to or greater than 0.5 cm. As many as 70-90% of such ulcers are associated with *Helicobacter pylori*, a helical-shaped bacterium that lives in the acidic environment of the stomach; however, only 40% of those cases go to a doctor.

Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs.

Pantoprazole is an oral proton-pump inhibitor used mainly for gastric ulceritis. Pantoprazole inhibits this proton pump reducing hydrogen ion accumulation in the stomach. Gastric acid secretion is inhibited both during rest and when the stomach is stimulated by food. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

Pantoprazole sodium delayed-release tablets should be swallowed whole, with or without food in the stomach.

Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of Pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric-coated 40 mg Pantoprazole tablet, the peak concentration (C_{max}) is 2.5 µg/mL, the time to reach the peak concentration (t_{max}) is 2.5 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 µg· hr/ mL When Pantoprazole is given with food, its t_{max} is highly variable and may increase significantly. Following intravenous administration of Pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6L.

The absorption of Pantoprazole is rapid, with a C_{max} of 2.5 µg/mL that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%.

The apparent volume of distribution of Pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of Pantoprazole is about 98%, primarily to albumin.

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4.

Pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged Pantoprazole.

Cinitapride (**Cintapro**, **Pemix**)is a gastroprokinetic agent and antiulcer agent of the benzamide class drug. It acts as an agonist of the 5-HT_1 and 5-HT_4 receptors and as an antagonist of the 5-HT_2 receptors.

It is indicated for the treatment of gastrointestinal disorders associated with motility disturbances such as gastro esophageal reflux disease, non-ulcer dyspepsia and delayed gastric emptying.

MATERIAL AND METHODS[2, 3, 4]

STUDY POPULATION

The study was carried out at Clinsync Clinical Research Private Limited, India. The study protocol was approved by the Ethics Committee. In addition, the protocol was performed in accordance with the Declaration of Helsinki Principles as outlined in the ICH-E6 Guidelines for Good Clinical Practice (GCP). All subjects were given a detailed description of the study and written informed consent was obtained prior to the enrollment.

A Total number of 15 Normal, Healthy, Adult, Human Male Subjects will be enrolled in the study between the ages of 18-55 years with a body mass index between 18.5 and 24.9 kg/m^2, with body weight equal to or not less than 45 kgs were assessed to be in good physical condition by a complete medical screening including a medical history, physical examination and laboratory screening test for hematologic and blood biochemistry parameters.

Subjects with normal outcome of the following medical and surgical history: allergy drug sensitives, other diseases, major surgery, micturition,

defecation, sleep, illness, within the last 4 weeks prior to start of the study.

Subjects with a normal cardiovascular, respiratory, neurological, psychiatric, gastrointestinal, hepatic, Biliary, Urogenital, Musculoskeletal, Endocrine and Metabolic system.

Study drugs

Test Drug: Pantoprazole 40mg E.C + Cinitapride 3mg Extended Release Capsule

Reference Drug: CINTODAC (Pantoprazole 40mg+ Cinitapride 3mg Extended Release) Capsule.

Study design

An Open label, Balanced, Randomized, Single Dose, Two-Treatment, Two-sequence, Two- period, crossover comparative Oral Bioequivalence study in 15 Normal, Healthy, Adult, Human Male Subjects under fasting conditions.

The Subjects will be admitted and housed in the clinical facility from not less than 11.00 hours pre-dose till at least 24.00 hours post-dose in each period. They have to report to the clinical facility for 36^{th} hour's ambulatory sampling time point.

Subjects will be fasted for at least 10hours prior to scheduled time for dosing. Meals or snacks will be provided at 4^{th} hr lunch, 8^{th} hr snacks, 12^{th} hr dinner and 24^{th} hour breakfast, after dosing in each period. During housing, the meal menu will be same for both the periods. During housing, the meal menu will be same for all the periods. In case, meal and blood sample collection timings coincide, samples will be collected before meal. Drinking water will be restricted from one hour pre-dose till one hour post-dose (except during the administration of the dose) in each period. At all other times, drinking water will be provided ad libitum.

Sample collection

Twenty five samples will be collected from each subject during each period. The venous blood samples (5ml) each will be withdrawn at pre-dose (with in 1 hr prior to dosing) 0.50, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.33, 4.66, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00, 36.00 hours after dosing.

At each time point, the blood samples will be collected in pre-labeled(Project No., Subject No, Period, sampling time point and Sample ID) vacuettes® / vacutainers® containing K_2 EDTA as anticoagulant.

After collecting the blood samples within 5 minutes at each sampling time point, samples will be centrifuged under refrigeration with machine set at 3000 rpm, 10 minutes and 4^oC. After centrifugation, the plasma samples will be separated and transferred into respective pre-labeled Ria vials in duplicate double aliquot tubes. These polypropylene tubes will be stored below -20°C for a maximum period of 12 hours and then transferred to analytical department in an appropriate container containing dry ice and stored at or below -70°C until transferred to Clinse Lab Ltd for analysis.

Analysis by HPLC[5, 6, 7]

A simple, selective, accurate high Performance Liquid Chromatographic (HPLC) method was developed and validated for the analysis of Cinitapride and Pantoprazole. Chromatographic separation achieved isocratically on a C18 column [Use Inertsil C18, 5µ , 250 mm x 4.6 mm] utilizing a mobile phase of acetonitrile: phosphate buffer (80:20 v/v, pH 6.8) at a flow rate of 1.0 ml/min with UV detection at 278 nm. The retention time of Cinitapride and Pantoprazole was 3.18 min and 4.725 min respectively. The method is accurate (98.22-101.66% and 98.5- 101.40% for cinitapride and Pantoprazole respectively), precise (method precision 0.44% and intermediate precision 0.78%) and linear within range 1.5-12µg/ml and 20-160 µg/ml for cinitapride and Pantoprazole respectively. The correlation coefficient was found to be r2=0.9991 for both the drugs. The detection limit of Cinitapride and Pantoprazole was 0.064 µg/ml and 0.78 µg/ml while quantification limit was 0.205 µg/ml and 2.38 µg/ml respectively.

Statistical Analysis

Statistical analysis will be performed on the pharmacokinetic parameters using Phoenix Version 6.3 software. The confidence intervals are expressed as a percentage relative to the GLM of the reference treatments. 90% confidence intervals for log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ will be reported. Point estimates

(T/R) of log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ will be calculated and reported. To established BE, the calculated 90% confidence interval for The test Capsule should fall within the acceptance range, 0.80-1.25 (80% -125%) for log transformed pharmacokinetic parameter C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Conclusion will be made on the basis of bioequivalence criteria.

RESULTS AND DISCUSSION

The present Bioequivalence study was conducted in 15 healthy male volunteers with age between 19 to 43 years and BMI with range 18.9-24.7 $kg/m^{2.}$ The final evaluation was carried out on data obtained from 15 volunteers who completed the study according to protocol. The mean plasma concentrations of Pantoprazole and Cinitapride for test and reference products on linear and logarithmic scales. The demographic details of the subjects shown in table no.1.

The present Bioequivalence study was conducted in 15 healthy male volunteers with age between 19 to 43 years and BMI with range 18.9-24.7 kg/m^2. A complete medical examination of volunteers is performed before their check-in into the study facility and no aberrant laboratory values are observed in any of the subjects. All the subjects were tested as negative in alcohol breath test and in urine examination for the drugs of abuse. ECG performed was found to be normal in all subjects participated in the study. The final evaluation was carried out on data obtained from 15 volunteers who completed the study according to protocol and was found to be Ethical, acceptable and does not have any impact on the pharmacokinetic parameters i.e., C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, K_{el} and $t_{1/2}$. The results are shown in Table No. 1-5.

Tolerability

Total fifteen volunteers were dosed. All the volunteers were included in the safety evaluation. Of the 15 subjects enrolled, 15 volunteers received both the test and reference products during the study. Total five adverse events were reported in the study when a test drug is administered in subject-02, 09, 16 and 19 in period-I and in subject-14 in period-II, which included head ache, myalgia and dizziness . The adverse events were mild in nature and were possibly related to the Pantoprazole 40mg + Cinitapride 3mg. But they were resolved completely before discharge of volunteers. There were no trends towards clinically significant changes in laboratory safety parameters in Figure No.3 and 4.

Table No.1: Demographic Details

MINIMUM	19	54.94	163	18.9
MAXIMUM	43	75.4	177	24.7
RANGE	19-43	54.94-75.4	163-177	18.9-24.7
MEAN	30.13	64.40	168.87	22.57
SD	8.17	5.76	4.44	2.10
%CV	27.12	8.94	2.63	9.30

Table No.2: Summary statistics for PK parameters for Bioequivalence of Pantoprazole

Parameter	**C_{max}**	**AUC_{0-t}**	**$AUC_{0-\alpha}$**
Lsm-A	0.8225	2.8352	2.9981
Lsm-B	0.8527	2.8217	2.9973

Difference (Lcm-A, Lcm-B)	-0.0302	0.0135	-0.0008
T / R Ratio	103.07	98.66	99.91
Variation (A & B)	0.000448 0.003227632	0.004861	0.005291
Mean Standard Error (A & B)	0.000895	0.009721	0.010581
Standard Error (A & B)	0.002351	0.007746	0.008082
ISCV	74.44	60.21	72.90
Lower CL (A & B)	87.77	81.28	84.80
Upper CL (A & B)	121.04	119.75	117.72

Table No.3: Summary statistics for PK parameters of Pantoprazole

Treatment	**Statistics**	**T_{max} (hr)**	**C_{max} (ng/mL)**	**AUC_{0-t} (ng.hr/mL)**	**AUC_{inf} (ng.hr/mL)**
R	N	15	15	15	15
	Mean	4.104	3540.793	8751.896	9002.325
	SD	1.257	1236.671	4772.397	4899.394
	Min	3.5	1936.46	3995.42	4098.17
	Median	4.0	3424	6648.2	6723.88
	Max	4.5	6325.2	23002.78	23370.92
	Geo mean	2.202	3346.314	7705.573	7925.254
	%CV	49.5	34.9	54.5	54.4
T	N	15	15	15	15

	Mean	2.705	3409.145	8699.665	8907.449
	SD	1.056	1179.233	3984.03	4068.456
	Min	3.33	1576.2	3545.48	4475.45
	Median	4.0	2901.41	9137.18	7605.14
	Max	4.33	4608.82	16447.32	16631.2
	Geo mean	2.499	3212.147	7850.398	8040.473
	%CV	39	34.6	45.8	45.7

Table No.4: Summary statistics for PK parameters for Bioequivalence of Cinitapride

Parameter	**C_{max}**	**AUC_{0-t}**	**$AUC_{0-\alpha}$**
Lsm-A	0.19663025	0.71819368	1.5006947
Lsm-B	0.200091	0.78613588	1.5033519
Difference (Lcm-A, Lcm-B)	-0.00346075	-0.0679422	-0.0026572
T / R Ratio	99.654523	107.03034	100.26608
Variation (A & B)	0.002459 0.003227632	0.02554	0.028411
Mean Standard Error (A & B)	0.004917	0.05108	0.056822
Standard Error (A & B)	0.005509	0.017757	0.018728
ISCV	100.00	99.99	91.01
Lower CL (A & B)	96.47	101.37	88.59
Upper CL (A & B)	102.94	113.00	113.47

Table No.5: Summary statistics for PK parameters of Cinitapride

Treatment	Statistics	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (ng.hr/mL)	AUC_{inf} (ng.hr/mL)
R	N	15	15	15	15
	Mean	3.984	1.332	3.19	6.56
	SD	1.401	1.259	2.821	4.737
	Min	2.33	0.319	0.010	0.262
	Median	4.0	1.238	0.932	1.915
	Max	4.5	1.435	2.323	2.568
	Geo mean	3.681	0.821	2.051	3.681
	%CV	35.2	94.5	88.4	72.2
T	N	15	15	15	15
	Mean	3.998	1.343	3.444	6.405
	SD	2.042	1.257	2.993	5.437
	Min	3.33	0.839	0.062	0.344
	Median	4.0	0.892	0.948	1.399
	Max	4.33	1.897	2.358	2.902
	Geo mean	3.476	0.819	2.195	4.544
	%CV	51.1	93.5	86.9	84.9

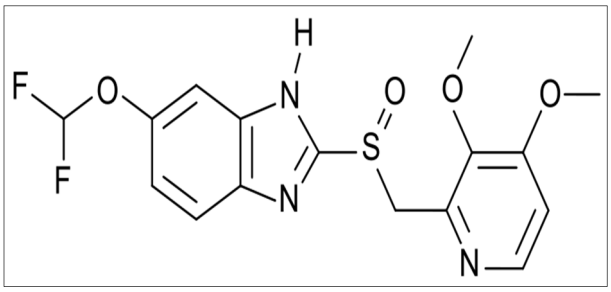

Figure No.1: Chemical structure of Pantoprazole

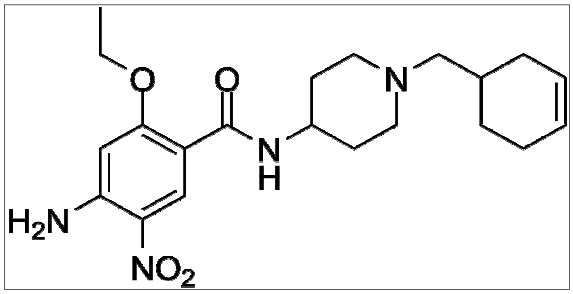

Figure No.2: Chemical structure of Cinitapride

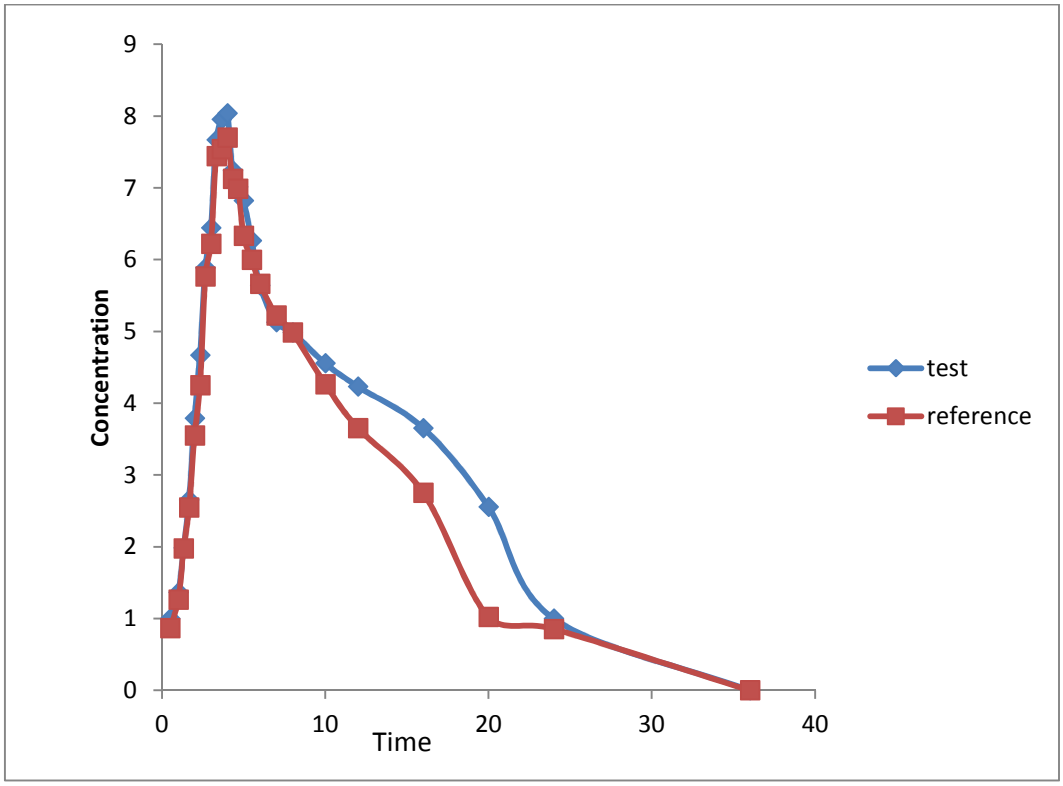

Figure No.3: Mean Concentration graph for Pantoprazole

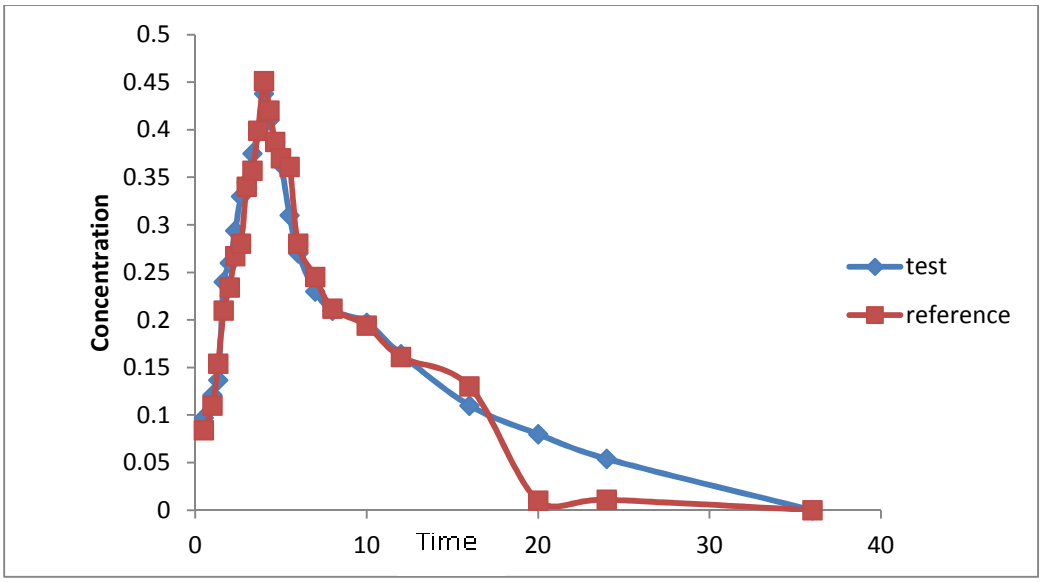

Figure No.4: Mean Concentration graph of Cinitapride

CONCLUSION

The bioavailability and bioequivalence of Pantoprazole 40mg + Cinitapride 3mg Extended Release Capsules was carried out in 15 healthy volunteers in Clinsync clinical research pvt. Ltd, Hyderabad, the blood samples were collected from the volunteers after single oral dose of test formulation i.e., Pantoprazole 40mg + Cinitapride 3mg Extended Release Capsules (T) and reference formulation i.e., Cintodac ® (Pantoprazole 40mg + Cinitapride 3mg Extended Release Capsules) at scheduled time period and the blood samples are analyzed.

Hence it is concluded that single dose bioéquivalence study of test drug of Pantoprazole 40mg + Cinitapride 3mg Extended Release Capsule is bioequivalent with reference drug of Cintodac ® (Pantoprazole 40mg + Cinitapride 3mg Extended Release Capsules) in terms of rate and extent of absorption after administration of single dose as set in the protocol.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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