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Evaluation of bio-equivalence and bio availability of levetiracetam 1000 mg tablet with reference to standard 1000 mg tablet in normal male in human healthy volunteers

Bhukya Ramesh*[1], Santhosh Pawar V*

Department Of Pharmacology, Nova College of Pharmaceutical Education And Research, Jaffergud, Hayath Nagar, R.R Dist, Telangana.

Corresponding Author: Bhukya Ramesh

ABSTRACT

This present study was designed on a treatise on open labeled randomized double blinded two period crossover evaluations of bio-equivalence and bioavailability of levetiracetam 1000 mg tablet with reference to standard 1000mg tablet in normal male healthy volunteers under fasting conditions. From the clinical data it can be concluded that the study objectives like the safety and efficacy of the test product has been achieved. Based on clinical, pharmacokinetic and statistical data obtained from 22 healthy, adult, male, human subjects under fasting conditions, it was concluded that a single dose of test formulation 't' containing drug levetiracetam 1000mg was found to be safe and bioequivalent to the reference formulation 'r' (keppra 1000mg) containing levetiracetam 1000mg as 90 % confidence interval for the ratios of means of test and reference parameters such as ln-transformed c_{max}, auc_{0-t} and $auc_{0-\infty}$ of drug levetiractam fell within the bioequivalence acceptance range of 80.00% – 125.00 %. This study gave us insight that a levetiractam 1000mg tablet was bioequivalent to keppra 1000mg in terms of rate and extent of absorption under fasting conditions.

Keywords: Levetiracetam, Antiepileptic.

INTRODUCTION [1-2]

Levetiracetam, an antiepileptic drug (AED), was first approved as an adjunctive therapy for the treatment of partial epilepsy in adults. It is currently being used in the treatment of multiple seizure disorders, including generalized tonic-clonic; absence; myoclonic, especially juvenile myoclonic; Lennox-Gastaut syndrome; and refractory epilepsy in children and adults. Data are emerging on possible uses of levetiracetam outside the realm of epilepsy because of its unique mechanisms of action. There is preliminary evidence about the efficacy of levetiracetam in the treatment of different psychiatric disorders, including anxiety, panic, stress, mood and bipolar, autism, and Tourette's syndrome. The most serious adverse effects associated with levetiracetam use are behavioral in nature and might be more common in patients with a history of psychiatric and neurobehavioral problems.

EXPERIMENTAL SECTION[3]

According to the USFDA A treatise on open labeled randomized double blinded two period crossover evaluations of Bio-equivalence and Bioavailability of Levetiracetam 1000 mg tablet with reference to

Standard 1000mg tablet in normal male healthy volunteers under fasting conditions The study will be carried out in accordance with the provisions of the current versions of the ICH Guidance for good clinical practices ICMR guidance for biomedical research on human subjects.

Study design [5-15]

Open, Labeled, Balanced, Randomized, Blinded, Two period, Single dose, Crossover study in normal male healthy volunteers under fasting conditions.

Duration

Screening procedure done no earlier than 21 days before the first day of dosing. Upon entering the study, subjects will be housed in the clinical facility from at least 10.50 hours before dosing to 24.00 hours post-dose.

Sample collection

Total of 22 samples (2 pre-dose & 20 post-dose) each of 6 ml were collected for each period of study. The total of 20 venous blood samples each of 6 ml were taken after giving drug at different times as in protocol like 10th minute post dose, after 15th min, 20th min, 30th min, 40th min, 50th min, 1sthour, 75th min (1.25th hour), 1.5 hours, 2 hours, 2.5 hours, 3 hours, 4 hours, 6 hours, 8 hours, 10 hours, 12 hours, 16 hours, 24th hour and at 36th hour (ambulatory sample, 36+/- 2hours which is collected separately). The mid-point time of collection of blood sample will be recorded on appropriate CRFSamples collected at each sampling time point and transferred to pre-labeled (Project No., Subject No. and Sampling time point) vacuettes containing K2EDTA as anticoagulant. After every blood sample collection 0.5 ml of Period heparinized saline (1 ml of 5 IU/ml of heparin in normal saline as an Anticoagulant) will be injected to the I.V. cannula to maintain solution the cannula patent. Also before every blood sample collection 0.5ml of blood present in the I.V. cannula will be discarded (except for pre- ml dose). While sampling through the cannula, blood samples will be collected discarding the first 0.5 ml of blood from the tube of the cannula. Samples were then centrifuged at 4000 RPM for 10 minutes below100C. Now the plasma was separated and transferred to pre-labelled Ria vials which were stored after at 250c and are to be transferred to bio-analytical department within 12 hours

Sampling Schedule

Twenty two (22) blood samples will be collected from each subject during each period. The venous blood samples (2 x 6 ml) will be withdrawn at pre- dose (before dosing, in the morning of the day of dosing). The venous blood samples (1 x 6 ml each) will be withdrawn at 00.17, 00.25, 00.33, 00.50, 00.67, 00.83, 01.00, 01.25, 01.50, 02.00, 02.50, 03.00, 04.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00 and 36.00 hours post dose. The sample collected at 36.00 hour sample will on an ambulatory basis (i.e. on separate visit).

Tolerability assessment

Physical examination and measurement of vital signs (Blood Pressure, Pulse Rate and Oral Temperature) were examined at the time of Check-in, prior to administration of the each study drug (0.00 hr), 1.00, 3.00, 6.00, 12.00, 24.00 and 36.00hours post dose and during the entire study period. Adverse events were monitored throughout the study and recorded by physicians

RESULTS

Pharmacokinetic parameters: Treatment-A (TEST)

Table: 1 Pharmacokinetic parameter of treatment A (Test)

S.no	PERIOD	SEQUENCE	Cmax	AUC(0-t)	Tmax	Kel	AUC
1	2	BA	24306.62	242000.39	2.00	0.09	253153.79
2	1	AB	18837.02	206291.82	4.50	0.09	239892.40
3	1	AB	28321.92	251668.95	2.00	0.11	274770.78
4	2	BA	27178.23	265051.26	2.00	0.08	277739.96
5	1	AB	22563.25	161847.90	2.00	0.12	171210.78
6	2	BA	29731.57	227749.69	4.00	0.08	269639.81
7	2	BA	24106.62	213722.33	2.00	0.09	243907.69
8	1	AB	18687.02	202804.32	4.50	0.09	234083.08

9	1	AB	28021.92	244543.95	2.00	0.11	264071.49
10	2	BA	27428.23	273988.76	2.00	0.08	291147.49
11	1	AB	22723.25	165647.90	2.00	0.12	176747.78
12	2	BA	29766.57	228580.94	4.00	0.08	271186.17

Summary table: Test Product (Treatment A)

Table: 2 Summary tablet of test product (Treatment A)

N	**12**	**12**	**12**	**12**	**12**	**12**
Mean	25139.352	223658.182	2.750	0.095	7.487	247295.934
SD	3883.758	35503.755	1.118	0.017	1.278	38135.232
Variance	15083576.469	1260516599.280	1.250	0.000	1.632	1454295910.109
Median	25742.43	228165.32	2.00	0.09	7.64	258612.64
CV%	15.4	15.9	40.7	18.0	17.1	15.4
GeometricMean	24846.923	220896.462	2.570	0.094	7.384	244220.085
CV%Geometric Mean	16.367	16.908	38.522	17.716	17.716	17.44

Pharmacokinetic parameters: Treatment-B (Reference)

Table: 3: Pharmacokinetic parameters of Treatment B (Reference)

s.no	**PERIOD**	**SEQUENCE**	**Cmax**	**$AUC_{(0-t)}$**	**Tmax**	**K_{el}**	**$AUC_{(0-inf)}$**
1	1	BA	27946.21	266230.02	4.00	0.08	281823.50
2	2	AB	19268.25	231092.98	4.00	0.09	241856.31
3	2	AB	33016.96	245244.15	3.00	0.09	276635.97
4	1	BA	25512.15	258381.34	3.50	0.08	272640.29
5	2	AB	27911.01	187409.07	1.50	0.09	209227.37
6	1	BA	31316.97	252743.98	4.50	0.10	279782.07
7	1	BA	27746.21	259180.02	4.00	0.09	270789.83
8	2	AB	19118.25	207507.66	4.00	0.10	229339.44
9	2	AB	32716.96	237710.31	3.00	0.09	264078.28
10	1	BA	25762.15	267788.12	3.50	0.07	286507.41
11	2	AB	28071.01	191129.07	1.50	0.08	215790.23
12	1	BA	31351.97	253557.73	4.50	0.10	281096.06

Summary table: Reference Product (Treatment B)

Table: 4 Summary tables: Reference Product (Treatment B)

N	**12**	**12**	**12**	**12**	**12**	**12**
Mean	27478.175	238164.537	3.417	0.090	7.791	259130.563
SD	4600.361	28274.205	1.019	0.009	0.810	27596.812
Variance	21163320.097	799430669.295	1.038	0.00	0.656	761584017.418
Median	27928.61	248994.06	3.75	0.09	7.75	271715.06
CV%	16.7	11.9	29.8	10.3	10.4	10.6
Geometric Mean	27087.018	236512.700	3.229	0.089	7.753	257698.261
CV% Geometric Mean	18.356	12.606	39.611	10.396	10.396	11.209

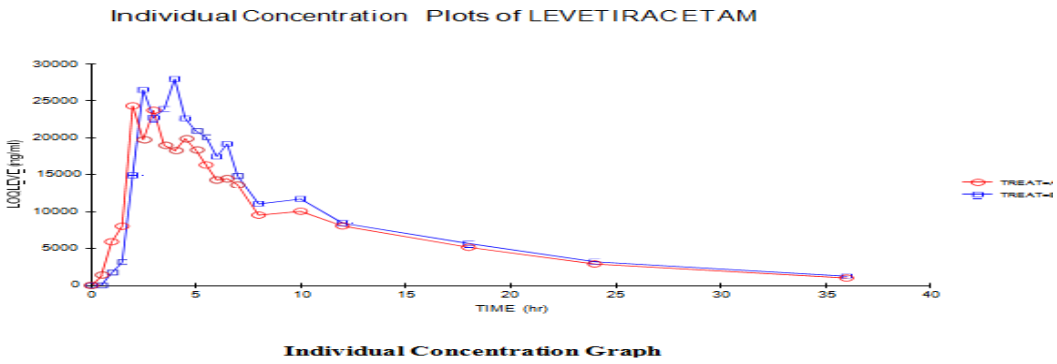

Fig: 1 Individual concentration plots of levetircetam

SUMMARY & CONCLUSION

All the study procedures followed were in compliance with the protocol and the ICH-GCP guidelines, Declaration of Helsinki and Schedule Y. From the analyses of pharmacokinetic and statistical results it was inferred that, for the ln-transformed data, the 90 % confidence interval about the test to reference ratio of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of drug Levetiracetam were falling within the bioequivalence acceptance range of 80.00 % - 125.00 %, which demonstrates the bioequivalence of test formulation 'T' with reference formulation 'R' under fasting conditions. From the clinical data it can be concluded that the study objectives like the safety and efficacy of the test product has been achieved. Based on clinical, pharmacokinetic and statistical data obtained from 22 healthy, adult, male, human subjects under fasting conditions, it was concluded that a single dose of test formulation 'T' containing drug Levetiracetam 1000mg was found to be safe and bioequivalent to the reference formulation 'R' (keppra 1000mg) containing levetiracetam 1000mg as 90 % confidence interval for the ratios of means of test and reference parameters such as ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of drug levetiractam fell within the bioequivalence acceptance range of 80.00% – 125.00 %. This study gave us insight that a levetiractam 1000mg tablet was bioequivalent to keppra 1000mg in terms of rate and extent of absorption under fasting conditions.

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