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RESEARCH ARTICLE
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ORAL BIOEQUIVALENCE STUDY OF TEDIZOLID TABLETS 200 MG IN HEALTHY INDIAN SUBJECTS UNDER FASTING CONDITIONS.

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Abstract

Objective: To compare the rate and extent of absorption and also to monitor the safety and tolerability of a single dose of Tedizolid Tablets 200 mg of Test drug with Reference Product SIVEXTRO® (tedizolid phosphate) tablets 200mg

Design: Open label, balanced, randomized single-dose, two-treatment, two-sequence, two-period two-way Crossover design.

Setting: Clinical, Bioanalytical and Quality Assurance Services, Bion Clinicals Pvt. Ltd.

Participants: 24 Healthy, Adult, Human Subjects Under Fasting Conditions.

Method: Twenty-four subjects were dosed with the investigational product [test (T) or reference (R) (as per the randomization schedule)] with approximately 240 ± 02 mL of water at ambient temperature were dosed. Plasma concentrations of Tedizolid were determined using a LC-MS/MS method developed at Bion Clinicals Pvt. Ltd.,Pune,India. Intra-subject variability of the pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ of Tedizolid was estimated using the root mean square error obtained after carrying out an analysis of variance for bioequivalence assessment. Also, the relative bioavailability was evaluated by calculating least squares mean ratios for Cmax, AUC0-t , and AUC0–∞ for tedizolid to tedizolid (reference). The 90% confidence intervals for the ratios of least squares means between drug formulations were calculated for the Ln-transformed data of both $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ of Tedizolid. Additionally, the power of the test to detect a 20% difference between the test product (T) and reference product (R) was computed and reported for Tedizolid.

Results: The mean age, height, weight and BMI (Body Mass Index) of the subjects who were dosed in the study were 28.3 years, 167.5 cms, 68.17 Kgs and 24.28Kg/m2 respectively. The ratios of geometric least squares means of the test product (T) and reference product (R) for the Ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Tedizolid were found to be 92.92%, 96.36% and 96.36% respectively.

The 90% confidence intervals for the ratios of geometric least squares means for the Ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Tedizolid were found to be 88.49% -

97.57%, 93.96% - 98.82% and 94.06% - 98.71% respectively. No adverse event was observed and the changes in lab parameters were clinically non-significant.
Conclusion: The 90% confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Tedizolid were within the bioequivalence acceptance limits of 80.00 - 125.00% and thus the test product (T) Tedizolid Tablets 200 mg and reference product (R) SIVEXTRO® (tedizolid phosphate) tablets 200mg were found bioequivalent with respect to rate and extent of absorption. The 200 mg oral dose of Tedizolid was well tolerated and was found safe.

Introduction

Infections from multidrug resistant gram-positive bacteria continue to be a burden to society and are associated with high morbidity and mortality. Some of the most concerning of these pathogens include methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant enterococci (VRE). In April 2000, linezolid, the first of a new class of antibiotics called oxazolidinones, was approved by the Food and Drug Administration (US FDA) for the treatment of serious gram-positive infections, including MRSA, VRE, and Streptococcus pneumoniae. However, some of the limitations of linezolid include the need for twice-daily dosing, drug interaction potential (with serotonergic agents), and concern for bone marrow suppression with prolonged therapy. In addition, reports of linezolid-resistant strains of S. aureus and enterococci were reported shortly after it became available on the market as reported by Sánchez García *et al.*(2010) (1). Tedizolid phosphate (previously known as torezolid phosphate) is a novel oxazolidinone prodrug antibiotic. (2)Compared with linezolid, tedizolid has greater potency against most methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-resistant Staphylococcus aureus (MRSA) strains, including those resistant to linezolid, as well as vancomycin-resistant enterococci. Spontaneous resistance rates to tedizolid in S. aureus are low(2). tedizolid exhibits its antibacterial effects through the inhibition of protein synthesis, specifically through binding to the 23S ribosomal RNA (rRNA) of the 50S subunit of the ribosome(3). Tedizolid has minimal and predictable accumulation at steady state and an elimination half-life that supports once/day administration(4).

As per study conducted by Prokocimer P *et al.* (2011), after oral administration, absorption occurs in an average of 45 minutes and tedizolid enters into the central compartment(5). Flanagan SD *et al.* (2014) demonstrated that, First-order intercompartmental distribution to the peripheral compartment occurs at an elimination rate of 12.7 hour(1) and redistributes to the central compartment at 12.8 hour(2).In 2014, Flanagan *et al*. determined the absolute bioavailability of tedizolid in eight healthy human subjects who received 200 mg of tedizolid phosphate intravenously and orally in a two-way crossover design. The mean area under the concentration-time curve from zero to infinity (AUC0–inf) after oral administration was 26.67 ± 6.03 mgh/L, while the AUC0–inf after intravenous administration was 29.02 ± 6.14 mgh/L with an absolute bioavailability of 91.4 ± 6.8 %.(4).

A population pharmacokinetic study of oral tedizolid phosphate in 188 patients with complicated skin and skin structure infections was carried out by Flanagan *et al. in* 2014. The data described a two-compartment model with linear pharmacokinetics for doses of 200, 300, and 400 mg once daily for 5–7 days. Bien *et al.* (2010)also reported linear pharmacokinetics for tedizolid phosphate with single doses ranging from 200 to 1200 mg orally and from 100 to 400 mg intravenously(6)

Flanagan *et al.* (2014) also conducted pharmacokinetics of a single 200-mg oral dose of tedizolid phosphate in subjects with hepatic impairment. Study groups included moderate (Child-Pugh 7–9) or severe (Child-Pugh 10–15) hepatic impairment and matched controls for age, weight and sex. Tedizolid pharmacokinetics were reported to be minimally altered in hepatic impairment (AUC0–24h of 34.82 ± 20.87 mgh/L in those with the severe hepatic impairment compared with 24.38 ± 8.03 mgh/L in controls).(7)

According to the results of studies by Prokocimer P *et al.* (2013) and Moran GJ *et al.* (2014), phase III trials in adult patients with acute bacterial skin and skin structure infections (ABSSSI) demonstrated the noninferior efficacy of tedizolid 200 mg daily for 6 days to linezolid 600 mg twice daily for 10 days(8)(9). Due to its higher in vitro activity against S. aureus than linezolid, tedizolid

was examined and found to be effective at a relatively lower dose and for a shorter treatment duration, as reported by McKee EE et al. (2006) and Moran GJ et al. (2014). Lower overall drug exposure was associated with decreased hematologic toxicity (10)(9)

According to Hall RG *et al.* (2018), while Tedizolid offers potential advantages over linezolid, such as once-daily dosing, shorter therapy duration, and increased tolerability, its cost is likely to restrict its adoption for MRSA-associated ABSSSIs due to the availability of more cost-effective generic oxazolidinone antibiotics. Therefore, it is essential to introduce a generic version of Tedizolid to mitigate this limitation, under these circumstances, the rigorous scientific assessment of the pharmacokinetic properties of generic drug products becomes imperative.(11)

The objective of this study was to investigate the pharmacokinetics and bioavailability of two different oral Tedizolid formulations following single dosing in healthy adult subjects in order to prove the bioequivalence between both preparations.

Materials and Methods

Study Drugs:

Tedizolid Tablets were supplied and manufactured by Exemed Pharmaceuticals (Vapi, Gujarat, 396195, India) for oral administration (200 mg). Reference Product SIVEXTRO® (tedizolid phosphate) tablets 200mg were manufactured and marketed by Patheon Inc. (Whitby, Ontario, L1N 5Z5, Canada), MSD Pharma (Singapore) Pte Ltd. (#31-00 Gateway West, Singapore), respectively. The study drugs were stored at 22 °C and a relative humidity of 60±5%.

Study Designs:

The study was an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period two-way crossover at a single site in India (Bion Clinicals Pvt. Ltd., Pune). The study investigated the safety, tolerability, and Pharmacokinetics of tedizolid after oral dosing in fasting, healthy human adults.

The single-dose oral bioequivalence study has been divided into two periods:

In period 01, twelve (12) subjects were given a single dose of test drug Tedizolid Tablets 200 mg of Exemed Pharmaceuticals in Gujarat, India, and twelve (12) subjects were given a single dose of reference drug SIVEXTRO® (tedizolid phosphate) tablets 200mg of MSD Pharma (Singapore) Pte Ltd. The subjects fasted for 24 hours following the administration of the study drug.

In a period 02, Following a 07-day washout period, the subjects received the alternate formulation to that they were given in period 01 (12 received the test product and 12 received the reference product) under identical conditions.

The subjects fasted overnight for at least 10.00 hours prior to drug administration. All safety and tolerability data and available PK data at the TPD dose were reviewed by the clinical investigator.

Ethical Considerations

The study was approved by the Pulse Multispeciality Hospital's ethics committee on November 30, 2022. Written informed consent was given by all participants. The study was carried out in accordance with the EC approved protocol and clinical research guidelines established by the basic principles defined in the ICH-GCP guidelines, the ICMR Ethical Guidelines for Biomedical Research on Human Subjects (2017), the Declaration of Helsinki (Fortaleza, Brazil, October 2013), G.S.R. 227(E) New Drugs and Clinical Trials Rules, 2019, and Guidelines for Bioavailability and Bioequivalence Studies, Central Drugs Standard Control Organization, March 2005.

Study Populations:

In the study, all subjects eligible for enrollment were in good health based on medical history, clinical examination, along with vital signs, recording of electrocardiogram and laboratory test results, tested negative for drugs of abuse and for pregnancy, and were able to provide written informed consent (pg no 28). Subjects who were aged between 18 -45 years with a body mass index (BMI) between 18.50-

30.00 kg/m^2 (inclusive of both) and body weight not less than 50.00 kg and agreeing to use appropriate contraceptive measures.

Randomization
Subjects were assigned to either of the treatments using computer generated randomization schedules.

Study Procedures:
Subjects were checked in on 30JUL2023 for period 01 and on 06AUG2023 for period 02. The total duration of the study was 11 days from the day of check-in of the first period till the end of the second period. Extra subjects E1 and E2 were enrolled in the study on the day of period 01 check-in. Subject E1 and E2 checked-out from the facility after dosing of the required number of subjects.
The study was conducted in two periods, after overnight fasting of at least 10.00 hours, A single dose of either test product (T) or reference product (R) was administered orally to the subjects in sitting posture with approximately 240 ± 02 mL of water at ambient temperature in period 01, whereas in period 02, Following a washout period of 07 days, a single dose of the alternate product to that of used in period 01 was dosed to each subject.
Serial blood samples (01 pre-dose (0.00 hour) sample and 21 post-dose samples in each period up to 48.00 hours) were taken during each study period.
Blood samples were collected through an indwelling cannula placed in a forearm vein using a disposable syringe or alternatively through venipuncture with disposable syringes and needles in the case of cannula blockage. An intravenous indwelling cannula was kept *in situ* as long as possible during the 24.00 hours post-dose in-house stay in each period. Normal saline solution was injected to keep the cannula patent, and blood samples were drawn after discarding the first 0.5 mL of normal saline mixed blood from the cannula (except ambulatory samples). Ambulatory samples were collected by fresh venipuncture. Five (05) mL of blood was collected in pre-labelled (Study No., Subject No., Period No., Time Point) polypropylene tubes (initially stored at -70 ± 10°C) containing K_2EDTA anticoagulant at each sampling time point.
Blood samples were collected at the following time points during treatment periods in Studies.
0 hour (pre dose) 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00- and 48.00-hours post-dose. The blood samples at 36.00- and 48.00-hours post-dose were collected on ambulatory basis (i.e., on separate visit).
After collection of blood samples from all subjects at a particular time point, the centrifugation under refrigeration was commenced within 01 hour of blood sample collection.
The subjects received a standard meal on the day of check-in and at approximately 4.00, 8.00- and 12.00-hours post-dose in each period. During housing, the meal menu was identical in terms of content and quantity for all periods. Drinking water was not allowed from one hour before until one hour after dosing in each period (except for approximately 240 ± 02 mL of water given during dosing).

Safety Assessment:
All subjects who had received at least one dose of the investigational product were included in the safety evaluation. Safety assessment was based on clinical laboratory evaluation, ECG recordings, clinical examination, along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) measurement and post-study clinical laboratory safety evaluation. Laboratory assessments (hematology, biochemistry, serology and urine analysis) and ECG recordings were done at the time of screening. Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure, respiratory rate) and questioning for well-being were undertaken at the time of screening, during check-in and before check-out of each period. Vital signs (axillary temperature, radial pulse rate and sitting blood pressure) and questioning for well-being were recorded within 2.00 hours prior to dosing in each period. Vital signs (sitting blood pressure and radial pulse rate) and questioning for well-being were measured and recorded at 1.00, 3.00 and 8.00 hours after dosing (within ± 45 minutes of the scheduled time). A urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, marijuana, cocaine and morphine) and a breath test for

alcohol consumption were done during check-in of each period. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs. Clinical examination, measurement of vital signs and questioning for well-being was performed prior to check-out only for the subjects who were dosed.
A safety sample was collected for post-study safety assessment (haematology and biochemistry) from all dosed subjects at the end of the study.

Pharmacokinetics:
PK analysis was performed to characterize the pharmacokinetic profile of the test product in comparison to the reference product. Plasma concentrations of Tedizolid were determined using a LC-MS/MS method developed at Bion Clinicals Pvt. Ltd., Pune, India.
Intra-subject variability of the pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ of Tedizolid was estimated using the root mean square error obtained after carrying out an analysis of variance for bioequivalence assessment. Also, the relative bioavailability was evaluated by calculating least squares mean ratios for Cmax, AUC0–s, and AUC0–∞ for tedizolid to tedizolid (reference). The 90% confidence intervals for the ratios of least squares means between drug formulations were calculated for the Ln-transformed data of both $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ of Tedizolid. Additionally, the power of the test to detect a 20% difference between the test product (T) and reference product (R) was computed and reported for Tedizolid.

OBSERVATIONS AND RESULTS

1. Demographic And Other Baseline Characteristics:

Table 1: Demographic and other baseline characteristics of study participants (N = 24)

Variable		**Profile**		**Percentage**
Race		Asian		100.00 %
		Others		0.00 %
Gender		Male		100.00 %
		Female		0.00 %
Diet		Non-Vegetarian		95.83 %
		Vegetarian		4.17 %
Smoking status		Non-smokers		100.00 %
		Smokers		0.00 %
Alcohol Consumption		Non alcoholics		100.00 %
		Alcoholics		0.00 %
	Mean	**SD**	**Min**	**Max**
Age (yr)	28.3	5.73	21	40
Height (cm)	167.5	5.44	157	176
Weight (Kg)	68.17	8.484	51.9	86.0
BMI (Kg/m^2)	24.28	2.675	18.8	29.4

The mean of age, height, weight and BMI of the subjects who received the dose in the study were 28.3 ±5.73years, 167.5±5.44 cms, 68.17±8.48 Kgs and 24.28±2.67 Kg/m2 respectively. All subjects were of Asian origin, non-smokers and non-alcohol. Out of the 24 subjects, 23 were non-vegetarians, while 1 was a vegetarian.

2. PHARMACOKINETIC AND STATISTICAL EVALUATION:

Table 2: Descriptive Statistics of Pharmacokinetic Parameters of Test Product (T) for Tedizolid (N = 24)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	Std Error	%CV	Geometric Mean
AUCEP	T	24	4.078	1.642	2.066	3.939	8.556	0.335	40.262	3.782
$AUC_{0-\infty}$	T	24	3149.959	686.956	1401.182	2993.404	4209.316	140.224	21.808	3067.438
AUC_t	T	24	3013.804	624.629	1371.335	2888.511	3925.707	127.502	20.726	2941.939
C_{max}	T	24	248.025	41.693	182.612	244.534	370.518	8.511	16.810	244.852
K_{el}	T	24	0.069	0.013	0.052	0.067	0.105	0.003	18.083	0.069
T_{half}	T	24	10.244	1.598	6.624	10.273	13.398	0.326	15.601	10.115
T_{max}	T	24	2.535	1.072	1.000	2.665	4.000	0.219	42.299	2.277

Table 3: Descriptive Statistics of Pharmacokinetic Parameters of Reference Product (R) for Tedizolid (N = 24)

Parameter	Treatment	N	Mean	Std Dev	Minimum	Median	Maximum	Std Error	%CV	Geometric Mean
AUCEP	R	24	4.082	1.642	0.919	4.156	7.546	0.335	40.220	3.720
$AUC_{0-\infty}$	R	24	3266.683	736.414	1656.279	3152.201	4685.254	150.320	22.543	3183.396
AUC_t	R	24	3124.042	660.814	1614.265	3026.010	4375.283	134.888	21.153	3053.013
C_{max}	R	24	266.496	42.345	208.599	263.942	380.884	8.644	15.890	263.502
K_{el}	R	24	0.068	0.011	0.052	0.065	0.093	0.002	15.645	0.067
T_{half}	R	24	10.424	1.527	7.416	10.587	13.317	0.312	14.645	10.313
T_{max}	R	24	2.245	1.193	0.330	2.330	4.000	0.244	53.132	1.856

Table 4: Geometric Least Squares Means, Ratios, 90% Confidence Intervals, ISCV and Power for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Tedizolid (N= 24)

Parameter	GLSMT	GLSMR	(T/R) Ratio	90% CI Lower	90% CI Upper	Power	ISCV	BE
C_{max}	244.9	263.5	92.92%	88.49%	97.57%	100.0%	9.9%	YES
AUC_t	2941.9	3053.0	96.36%	93.96%	98.82%	100.0%	5.1%	YES
$AUC_{0-\infty}$	3067.5	3183.4	96.36%	94.06%	98.71%	100.0%	4.9%	YES

Geometric Least Squares Means of C_{max} for test drug was 244.9 and that of reference drug was 263.5 which showed T/R ratio of 92.9% (90%CI 88.5%-97.6%) and ISCV of 9.9% suggesting that the test drug was bioequivalent.

Geometric Least Squares Means of AUC_t for test drug was 2941.9 and that of reference drug was 3053.0 which showed T/R ratio of 96.36% (90%CI 93.96%-98.82%) and ISCV of 5.1% suggesting that the test drug was bioequivalent.

Geometric Least Squares Means of $AUC_{0-\infty}$ for test drug was 3067.5 and that of reference drug was 3183.4 which showed T/R ratio of 96.36% (90%CI 94.06%-98.71%) and ISCV of 4.9% suggesting that the test drug was bioequivalent.

3. PHARMACOKINETIC DATA :

Table 5: Ratio Analysis of Tedizolid for Pharmacokinetic Parameter

Subject	Sequence	C_{max}	AUC_t	AUC_{inf}
01	RT	86.34%	95.11%	95.55%
02	TR	103.23%	105.76%	106.28%
03	RT	89.38%	100.77%	101.87%
04	TR	90.89%	98.27%	97.42%
05	TR	96.16%	93.04%	93.01%
06	RT	92.38%	98.23%	98.34%
07	RT	94.97%	84.95%	84.60%

08	TR	88.66%	87.02%	86.98%
09	TR	76.65%	100.97%	100.74%
10	RT	112.01%	99.64%	100.31%
11	TR	107.20%	98.65%	96.58%
12	RT	101.85%	99.01%	98.72%
13	TR	95.94%	102.01%	101.91%
14	RT	104.30%	97.48%	97.29%
15	RT	97.28%	94.78%	95.94%
16	TR	91.72%	94.86%	94.77%
17	RT	82.98%	93.83%	93.66%
18	TR	106.63%	103.71%	103.20%
19	RT	87.93%	102.64%	103.28%
20	TR	77.16%	89.80%	89.14%
21	RT	62.69%	77.22%	79.87%
22	TR	84.91%	105.89%	103.64%
23	RT	102.57%	95.31%	95.14%
24	TR	115.62%	99.42%	99.40%

Table 6: Post-Study Laboratory Assessments (Clinically Non-Significant Abnormal Laboratory Parameters)

Subject No.	Abnormal Lab Parameter	Baseline Value (Mean values)	Post study Safety Assessment Value (Mean values)	Reference Range
01	SGPT	37	55	0-50 U/L
03	Lymphocytes	35	42	20 – 40 %
	Eosinophils	07	08	1 – 6 %
	Creatinine	0.69	0.64	0.66 - 1.25 mg/dL
04	Lymphocytes	32	44	20 – 40 %
05	Lymphocytes	29	42	20 – 40 %
	Creatinine	0.54	0.64	0.66 - 1.25 mg/dL
06	Haemoglobin	11.9	11.9	13 – 17 g/dl
	RBC	5.72	5.71	4.5 - 5.5 mil/ µL
	Eosinophils	03	07	1 – 6 %
	Creatinine	0.63	0.63	0.66 - 1.25 mg/dL
07	Haemoglobin	12.9	12.0	13 – 17 g/dl
	RBC	4.35	4.05	4.5 - 5.5 mil/ µL
	Haematocrit	40.3	38.8	40 – 50 %
	SGPT	44	55	0-50 U/L
	Creatinine	0.66	0.62	0.66 - 1.25 mg/dL

09	Urea	13	14.1	15 – 45 mg/dL
	Blood Urea Nitrogen	6.07	6.59	7 – 20 mg/dL
	Creatinine	0.64	0.65	0.66 - 1.25 mg/dL
10	RBC	5.82	5.53	4.5 - 5.5 mil/ µL
11	Haemoglobin	11.9	12.4	13 – 17 g/dl
	RBC	5.25	5.52	4.5 - 5.5 mil/ µL
	Lymphocytes	26	44	20 – 40 %
	Creatinine	0.65	0.63	0.66 - 1.25 mg/dL
12	RBC	6.01	5.62	4.5 - 5.5 mil/ µL
	SGPT	55	55	0-50 U/L
	Urea	17	14.2	15 – 45 mg/dL
	Blood Urea Nitrogen	7.94	6.64	7 – 20 mg/dL
13	SGPT	44	56	0-50 U/L
	SGOT	48	62	17 – 59 U/L
14	RBC	5.46	5.58	4.5 - 5.5 mil/ µL
	Urea	23	14.1	15 – 45 mg/dL
	Blood Urea Nitrogen	10.75	6.59	7 – 20 mg/dL
15	Urea	16	14.2	15 – 45 mg/dL
	Blood Urea Nitrogen	7.48	6.64	7 – 20 mg/dL
16	WBC	9700	10400	4000-10000 /cmm
	Urea	22	14.1	15 – 45 mg/dL
	Blood Urea Nitrogen	10.28	6.59	7 – 20 mg/dL
17	Haemoglobin	17.6	17.4	13 – 17 g/dl
	RBC	5.62	5.58	4.5 - 5.5 mil/ µL
	Haematocrit	50.4	51.9	40 – 50 %
18	Haemoglobin	17.6	17.5	13 – 17 g/dl
	RBC	6.00	6.00	4.5 - 5.5 mil/ µL
	Haematocrit	51.3	53.1	40 – 50 %
19	Haemoglobin	11.9	11.9	13 – 17 g/dl
	Haematocrit	35.0	37	40 – 50 %

	Eosinophils	06	08	1 – 6 %
	Urea	12	14.3	15 – 45 mg/dL
	Blood Urea Nitrogen	5.61	6.68	7 – 20 mg/dL
20	Haemoglobin	11.9	12.2	13 – 17 g/dl
	RBC	5.34	5.66	4.5 - 5.5 mil/ µL
	Eosinophils	06	07	1 – 6 %
21	RBC	5.56	5.63	4.5 - 5.5 mil/ µL
	SGPT	40	56	0-50 U/L
22	SGPT	51	51	0-50 U/L
	Alkaline Phosphatase	130	131	38 – 126 U/L
23	RBC	6.05	5.82	4.5 - 5.5 mil/ µL
	WBC	6300	3800	4000-10000 /cmm
	Urea	21	14	15 – 45 mg/dL
	Blood Urea Nitrogen	9.81	6.54	7 – 20 mg/dL
24	Urea	32	14.1	15 – 45 mg/dL
	Blood Urea Nitrogen	14.95	6.59	7 – 20 mg/dL

Haemoglobin was reduced in five subjects and was found higher than normal range in two subjects. Haematocrit was slightly increased in two cases and decreased in two cases. There was slight increase upto 10% in SGPT and SGOT parameters in three cases.

Figure 1: Linear Plot of Mean Plasma Concentrations of Tedizolid vs. Actual Time for Test Product (T) and Reference Product (R) (N = 24)

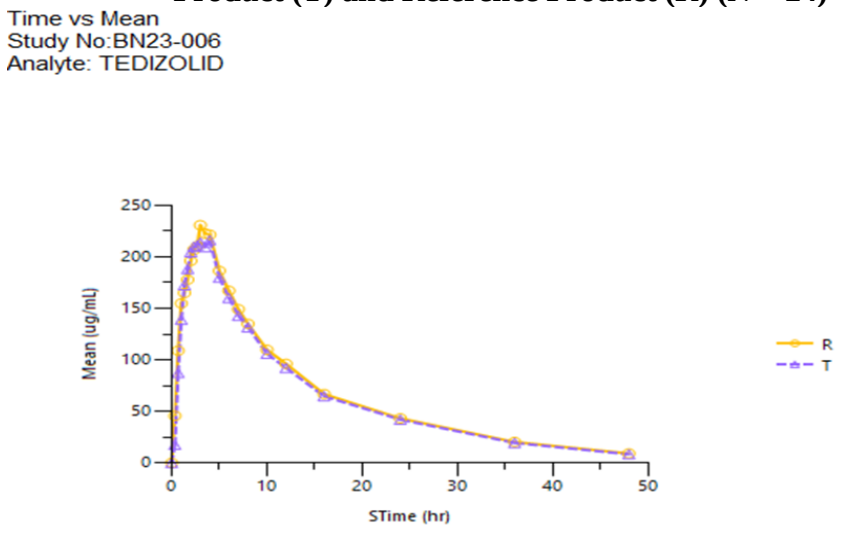
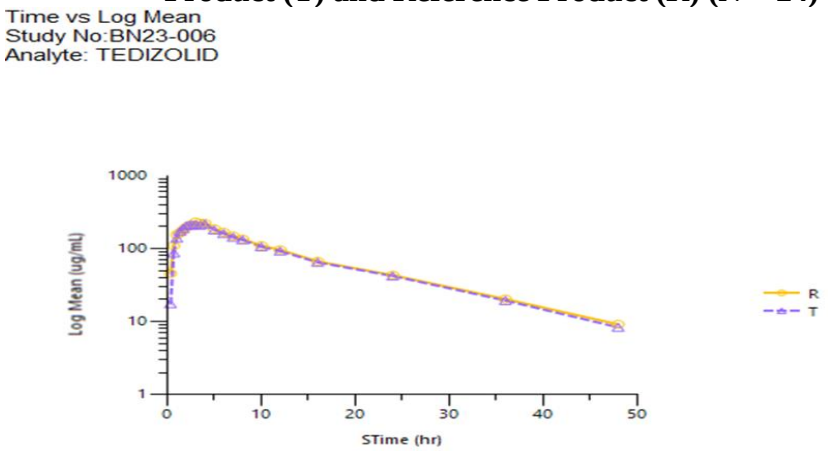


Figure 2: Ln Linear Plot of Mean Plasma Concentrations of Tedizolid vs. Time for Test Product (T) and Reference Product (R) (N = 24)



4. SAFETY :

The test and reference products were comparable in their safety and tolerability in healthy, adult, human male subjects under fasting conditions.

5. ADVERSE EVENTS :

No mild, moderate, severe, serious or life-threatening adverse events were reported during the course of the study.

DISCUSSION

Bioequivalence studies are performed to determine the in vivo biological equivalence between two different proprietary pharmaceutical preparations in the pharmaceutical industry. Their rationale is to provide a resemblance between a generic medicine and its corresponding innovator medicine in terms of safety, quality, efficacy, dosage form, strength, and route of administration.[12,13] This study was performed in 24 healthy volunteers with single dose of 200 mg Tedizolid tablets in a crossover manner.

According to the CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence [14], two medicinal products are bioequivalent if their bioavailabilities (rate and extent) after administration of the same molar dose are similar to such degree that their effects with respect to both efficacy and safety will be essentially the same. This requirement is fulfilled, if the 90% confidence intervals of the AUC ratio and Cmax ratio are within a predefined acceptance range (80%–125%) [14].

This study compared the bioequivalence of single dose Tedizolid of 200 mg , a test and reference product. This study found that 90% CI for AUCt and AUCinf were within the bioequivalence acceptable range of 80% to 125%. Moreover, the Cmax profile of Tedizolid 200 mg was almost identical for test and reference products. The study found that Geometric Least Squares Means of C_{max} for test drug was 244.9 and that of reference drug was 263.5 which showed T/R ratio of 92.9% (90%CI 88.5%-97.6%) and ISCV of 9.9% suggesting that the test drug was bioequivalent.

The Geometric Least Squares Means of AUCt and AUC0-∞ for the test drug were 2941.9 and 3067.5, respectively, while for the reference drug, they were 3053.0 and 3183.4. Both ratios, 96.36% for AUC0-t and 96.36% for AUC0-∞, along with narrow confidence intervals (90%CI), indicated bioequivalence with low variability Intra Subject Coefficient of Variation(ISCV) for the test drug.

Early studies with TPD including TR701-101, TR701-103, a microdialysis study [15] and a phase II study [16] suggested the 200-mg dose had the most favorable pharmacokinetic, safety, and efficacy profile for therapeutic dosing.

The test product was well tolerated by all the volunteers under fasting conditions. No adverse events either mild or moderate were reported and all 24 subjects completed the study .

Tedizolid was very well tolerated in the present study with clinically non-significant changes in AST and ALT parameters noted in only 4 subjects . Study by Flagnan reported that Tedizolid pharmacokinetics was only minimally altered in subjects with moderate or severe hepatic impairment; the AUC was increased approximately 22% and 34%, respectively, compared with that of subjects in the control group. Tedizolid phosphate was generally well tolerated in all participants even in higher doses. [7]

Conclusion

For all three parameters AUC0-∞ ,AUC0-t and Cmax, the bioequivalence criteria were completely fulfilled in the present study. All other pharmacokinetic parameters were well comparable between the test and reference preparations, i. e. no relevant differences were found for Tmax and t1/2. Therefore, it can be concluded that the test and reference preparations are bioequivalent in the rate and extent of absorption and thus can be used interchangeably in medical practice. The results of this study with healthy Indian volunteers might serve as a reference for future controlled studies of Tedizolid in the Indian population

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