


A Randomized, Open-Label, Two-Way Crossover, Single-Dose Bioequivalence Study of Temozolomide 200 mg/m² (Dralitem[®] vs. Temodal[®] Capsules) in Patients with Primary Tumors of the Central Nervous System Under Fasting Conditions

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Abstract

Background Temozolomide is an antineoplastic agent of proven efficacy against high-grade gliomas.

Purpose The objective of this crossover, single-dose, bioequivalence study was to compare the rate and extent of absorption of oral temozolomide after administration of the study product (Dralitem[®], Monte Verde Sociedad Anónima) and the reference product (Temodal[®], originator product manufactured by Schering Plough Laboratories) in patients with primary central nervous system (CNS) tumors under fasting conditions.

Methods Sixteen male and female subjects with primary CNS tumors (excluding CNS lymphoma) were recruited, and were administered temozolomide 200 mg/m² (Dralitem[®]) on days 1, 2 and 5 of a 5-day treatment. On days 3 and 4, subjects received the same dose of the test product (Dralitem[®]), or the reference product (Temodal[®]) on alternate days. The single dose of 200 mg/m² was reached with three different temozolomide capsule strengths: 20, 100 and 250 mg. On days 3 and 4, blood samples were obtained for pharmacokinetic (PK) evaluation after drug administration.

Results Bioequivalence assessment was made for the 90% confidence interval (CI) for the ratio of log-transformed means ($\mu T/\mu R$) of the area under the concentration–time curve (AUC from time zero to the final quantifiable sample

[AUC_t] and AUC from time zero to infinity [AUC_∞]) and maximum concentration (C_{max}) of both the test (Dralitem[®]) and reference (Temodal[®]) products. The point estimate and 90% CI of the ratios of C_{max} , AUC_t and AUC_∞ values were 94.37 (82.69–107.69), 100.99 (97.81–104.28) and 101.53 (98.60–104.54), respectively. The ratio met the predefined bioequivalence criteria (i.e. 90% CI between 80.00 and 125.00) for C_{max} and AUC. The most commonly reported adverse events (AE) on this study were vomiting, abdominal pain, asthenia and weakness. One subject experienced expressive aphasia, possibly unrelated to the study drug and with no significant sequelae upon recovery. No serious AEs or unexpected AEs were reported.

Conclusions Temozolomide Dralitem[®] capsules, 20, 100 and 250 mg, were bioequivalent to Temodal[®] capsules under fasting conditions in patients with CNS primary tumors, supporting that they are therapeutic equivalents. ClinicalTrials.gov Identifier: NCT02343081.

Key Points

In the present study, the test product (temozolomide capsules 20, 100 and 250 mg) was bioequivalent, under fasting conditions, to the reference product in a population of patients with primary central nervous system tumors.

All three dose strengths were administered to all patients in order to reach the single dose of 200 mg/m². Thus, it can be concluded that both formulations were bioequivalent at 20, 100 and 250 mg.

The safety and tolerability profile of both drug products were comparable.

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1 Introduction

Temozolomide is an oral DNA alkylating agent with a very important role in chemotherapy for central nervous system (CNS) tumors [1]. Pharmacokinetic (PK) analysis of temozolomide has consistently shown that temozolomide has linear PKs over the recommended daily dose range, with 100% bioavailability after oral administration [2]. Once administered, oral temozolomide is rapidly and completely absorbed from the gastrointestinal tube, with time to reach maximum concentration (T_{\max}) values of 1–2 h, a half-life of nearly 1.8 h, and a maximum concentration (C_{\max}) of 6 $\mu\text{g/mL}$ with a dose of 150 mg/m^2 [3].

Temozolomide undergoes spontaneous pH-dependent hydrolysis to the active cytotoxic metabolite 5-(3-methyl-1H-imidazol-4-yl)imidazole-4-carboxamide (MTIC) at physiologic pH. MTIC is responsible for temozolomide cytotoxicity, which appears to be mediated mainly through methylation of DNA of tumor cells at the O⁶ and N⁷ positions of guanine. In turn, MTIC is transformed into 5-aminoimidazole-4-carboxamide (AIC) due to another non-enzymatic reaction [3, 4]. Studies of oral ¹⁴C-temozolomide in patients with advanced cancer indicate that the primary pathway for its clearance from plasma is temozolomide conversion to MTIC, with further degradation to AIC. On the basis of these radiolabeled studies, profiling of total radioactive metabolite excretion in urine revealed that temozolomide was eliminated renally as an unchanged drug in a minor fraction of cases (5.5%), and as AIC in a higher percentage of cases (12%). This evidence indicates that the main temozolomide clearance mechanism was the pH-dependent formation of MTIC, with renal excretion playing a secondary role in the compound's elimination [5].

Unlike the first-generation alkylating agent dacarbazine, which requires hepatic conversion to MTIC catalyzed by cytochrome P450 oxidases, and whose therapeutic efficiency in the CNS has raised concerns due to its poor blood–brain barrier permeability, temozolomide is a highly lipophilic molecule. Furthermore, temozolomide is stable under acid conditions [6], but the rate of metabolic conversion to AIC (the final degradation product) increases greatly when moving from neutral to basic pH [7]. As CNS tumors are known to have a higher pH compared with surrounding brain tissue, the pH-dependent activation of temozolomide provides an important basis of targeted therapy toward CNS gliomas [8].

The antitumor activity of temozolomide against highly resistant solid malignancies, its predictable bioavailability, and its relatively low toxicity profile make temozolomide an appropriate option for malignant gliomas.

Temozolomide is currently indicated for the treatment of adult patients with glioblastoma multiforme (newly diagnosed or showing recurrence or progression after standard therapy) or with anaplastic astrocytoma (as a first-line therapy or for refractory tumors).

The test drug product (Dralitem[®]) was an oral formulation of temozolomide, with mannitol as excipient, while the reference drug product (Temodal[®]) has lactose as the capsule filler. This lactose-free formulation was intended to provide a clear advantage for those patients who suffer from lactose malabsorption, a condition that could preclude susceptible CNS tumor patients from taking medications containing lactose.

The purpose of this randomized, crossover, single-dose, bioequivalence study was to compare the rate and extent of absorption of oral temozolomide 20, 100 and 250 mg capsules after the administration of the study product (Dralitem[®], Monte Verde Sociedad Anónima [S.A.], a mannitol-based formulation) and the reference product (Temodal[®], originator brand manufactured by Schering Plough, a lactose-based formulation) in patients with primary CNS tumors under fasting conditions.

2 Methods

2.1 Eligibility

Eligible subjects were male and female patients with a primary CNS tumor (excluding CNS lymphoma), who were at least 21 years of age, with a time gap of at least 2 weeks between the last surgery and/or radiotherapy procedure and the day of randomization (or 4 weeks if the procedure had been intra-abdominal). All subjects were required to have a neutrophil count $>1.5 \times 10^9/\text{L}$, a platelet count $>100 \times 10^9$, and adequate hepatic and renal function.

Exclusion criteria included any condition that might interfere with the absorption or oral administration of the study drug, hypersensitivity to temozolomide or any of its excipients, and reception of chemotherapy or biologic anticancer therapy 4 weeks prior to study entry.

Subjects who had a clinical status that might reduce study drug safety or could interfere with PK evaluation were excluded at the discretion of the investigator. Pregnant women or women planning to become pregnant during the study were also not considered for recruitment. The study was compliant with Good Clinical Practice (GCP) [9] and the World Medical Association Declaration of Helsinki regarding written informed consent and the protection of rights of human subjects [10]. Furthermore, the study was previously approved by the Institutional Review Board and

by the Institutional Ethics Committee of the clinical site where the study was performed.¹

2.2 Study Design and Procedures

This randomized, two-period, two-treatment, two-way crossover, bioequivalence study compared two temozolomide oral formulations (Dralitem[®] vs. Temodal[®]), in patients with primary CNS tumors under fasting conditions.

The study was open-label to patients and investigators, and blinded to the bioanalytical and clinical laboratories. The study was structured in three stages: recruitment period (day -21 to day 0), treatment cycle (days 1–5), and the safety surveillance period (days 6–21). All patients were pre-medicated with ondansetron 8 mg 30 min prior to the start of drug administration in order to prevent nausea and vomiting associated with temozolomide chemotherapy. Patients were administered temozolomide (Dralitem[®]) 200 mg/m² on the first 2 days of the treatment cycle, and were then admitted to the clinical site on the evening of day 2. On the morning of day 3, the patients were randomized into two groups of equal size. Subjects were randomly assigned to any of the formulation sequences (test–reference [T–R], or reference–test [R–T]) in accordance with the randomization scheme previously generated using computerized software. According to his or her randomly assigned number, each subject received a single oral dose of temozolomide 200 mg/m² (either the Monte Verde S.A. product [Dralitem[®]] or the Schering-Plough product [Temodal[®]]).

The single dose of 200 mg/m² was reached with three different temozolomide capsule strengths: 20, 100 and 250 mg. All three dose strengths were administered to patients in order to conclude that both tested formulations were bioequivalent at the proposed strengths. Table 2 depicts the capsule combinations given to each patient based on the daily dose according to their body surface area. Drug products were administered with 200–240 mL of water in a semi-seated upright position. On the following day (day 4), subjects received an oral dose of temozolomide 200 mg/m² of whichever product they had not received the day before. On days 3 and 4 after drug administration, blood samples were obtained for PK evaluation. Patients were discharged from the clinical site on day 4 after completion of sampling for PK analysis. On day 5, all patients received temozolomide 200 mg/m² (Dralitem[®]).

On days 3 and 4, samples of venous blood were collected from the forearm vein of each volunteer prior to the study drug administration (0 or predose) and then 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 and 10.0 h postdose on each period. Patients were required to fast for at least 2 h before and after each dose of temozolomide. The washout period between the treatment arms was 10 h, on days 3 and 4.

The primary outcomes were the rate and extent of temozolomide absorption based on the ratio of the log-transformed means for area under the concentration–time curve (AUC) and C_{\max} for both drug products. According to US FDA bioequivalence recommendations, only the parent drug was measured as analyte in plasma [11] since its concentration–time profile is more sensitive to changes in formulation performance than those of metabolites. Moreover, biotransformation of temozolomide to its active metabolite is a constant rate stoichiometric degradation, therefore the appearance and disappearance of MTIC paralleled that of the parent compound in plasma [3].

2.3 Determination of Temozolomide Plasma Concentrations

Plasma temozolomide samples were collected and processed in accordance with a previously validated bioanalytical procedure. This procedure was developed and validated by the laboratory that performed the bioanalysis of the study samples. The bioanalytical method was validated for selectivity, sensitivity, precision, and accuracy. The temozolomide plasma assay was linear over the range of 0.1–25 µg/mL weighted least squares. The accuracy ranged from 102.3–110.7% and the precision was 4.05–7.09%. The lower limit of quantification (LLOQ) for temozolomide was 0.1 µg/mL, and the internal standard was temozolomide-d3 [12]. Both the validated range and the sensitivity of the bioanalytical method allowed the analysis of a sufficient number of plasma samples to properly characterize the PK profiles of the products under study.

Blood samples (6 mL each) were collected in prechilled tubes with ethylenediaminetetraacetic acid (EDTA) and centrifuged at 4 °C. Immediately after centrifugation, plasma was acidified by adding 50 µL of a 10% formic acid solution to each milliliter of plasma (since temozolomide is unstable at physiological pH in human plasma but remains stable in acidified human plasma [pH <4] and for at least 30 days at -20 °C). Samples were then separated into two aliquots and were stored at -20 °C until assayed. To extract the analyte (parent drug) from its plasma matrix, a protein-precipitation technique was used. Plasma concentrations of temozolomide were determined by liquid chromatography followed by tandem mass spectrometry (LC–MS/MS).

¹ Ethics Committee on Biomedical Research. Institute of Neurological Research “Raúl Correa”. Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI). Buenos Aires, Argentina. Date of approval: 26 February 2008 (Reference: Protocol RFF 0208).

Data from subjects/samples were excluded from the primary PK analysis (per-protocol population) in case of protocol violations, insufficient dosing, or possible sample procedure errors (e.g. patients who vomited within 4 h of oral dosing on days 3 and 4, or who were not within 10% of the recommended dose). Additionally, safety analysis included any subject who received at least one dose of the study drug products (intention-to-treat population).

2.4 Pharmacokinetic (PK) and Statistical Analysis

Non-compartmental analyses were conducted on individual concentration–time data, and the AUC and C_{\max} values were obtained for each subject. The log-transformed values of these parameters were used for statistical comparisons (mixed effects analysis of variance [ANOVA]), including potential effects due to treatment, sequence, subject within sequence, and period. All the fixed factors were assessed at the 5% two-sided level, and the limits of the 90% confidence interval (CI) for the ratio of the log-transformed means were calculated. According to universally accepted regulatory guidelines [13, 14], bioequivalence is declared when each calculated 90% CI for the ratio of these log-transformed means is within the range of 80–125%. The alpha error was set at 0.05 to define statistical significance. Additionally, Schuirmann's two one-sided test (TOST) procedure for bioequivalence was performed. After decomposing the interval hypothesis of bioequivalence (H_0) into two sets of one-sided null hypothesis (H_{01} and H_{02}), and after applying two separate t tests, the conclusion on average bioequivalence was taken when both H_{01} and H_{02} were rejected at the predetermined alpha level of significance.

Assuming an intrasubject coefficient of variation (ISCV) of 15% [1, 3], a target enrollment of 16 subjects was selected to provide a minimum of 80% power for the 90% CI of the ratio of log-transformed means. Secondary endpoints included other PK parameters (half-life [$t_{1/2}$], elimination rate constant [K_{el}]) and safety and tolerability analysis.

3 Results

3.1 Subject Disposition

A total of 16 patients were enrolled at the FLENI Research Center (see Table 1 for subject demographics). Patients were randomized and received 5 days of treatment with temozolomide (once-daily oral dosing of Dralitem[®] for the first 2 days, and the same dose of either the test product Dralitem[®] or the reference product Temodal[®] for 1 day, either on day 3 or day 4). With the exception of one subject who was administered temozolomide at a dose of 150 mg/m² by medical prescription (see Table 2), all subjects were administered a dose of 200 mg/m², according to the approved protocol. No other important protocol deviation or violation was reported. All 16 subjects were included in the PK analysis.

3.2 PK Assessments

The mean values for C_{\max} , AUC from time zero to the final quantifiable sample (AUC_t) and AUC from time zero to infinity (AUC_{∞}) of both orally administered temozolomide formulations were similar (Table 3) and showed low variability (ISCV = 4.7–21.4%) (Table 4).

The ratios of the least-squares geometric means (point estimates) for the parameters of C_{\max} , AUC_t and AUC_{∞} for both temozolomide drug products (Dralitem[®]/Temodal[®]) were 94.37, 100.99 and 101.53, respectively (Table 4). The mean plasma concentration–time profiles for both temozolomide products following oral administration were nearly superimposed (Fig. 1). The 90% CI for the ratio of the log-transformed means for C_{\max} , AUC_t and AUC_{∞} for both Dralitem[®] and Temodal[®] were within the 80–125% range of bioequivalence (Table 4). ANOVA of log-transformed PK parameters (C_{\max} and AUC) did not demonstrate any effects due to treatment, sequence, subject within sequence, and period (Table 5).

Table 1 Subject demographics ($n = 16$)

Variable	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)	Body surface ^a (m ²)	Dose ^b TMZ/day (mg)
Mean ± SD	48.44 ± 14.50	170.00 ± 0.08	79.40 ± 12.00	27.26 ± 2.82	1.92 ± 0.19	371.25 ± 46.08
Median	52.00	171.00	81.70	27.73	1.96	385.00
Range	24.00–67.00	154.00–182.00	55.00–98.00	22.31–31.18	1.54–2.19	250.00–420.00
Q1	38.00	165.25	74.00	24.87	1.85	350.00
Q3	61.00	179.00	88.75	29.73	2.06	407.50

BMI body mass index, SD standard deviation, Q1 quartile 1, Q3 quartile 3

^a According to the DuBois and DuBois formula

^b Single dose of 200 mg/m² of body surface area

Table 2 Capsule combinations based on daily dose per subject

Subject	Dose (mg/day)	Dose units
1	320	3 Capsules of 100 mg + 1 capsule of 20 mg
2	400	4 Capsules of 100 mg
3	400	4 Capsules of 100 mg
4	410	1 Capsule of 250 mg + 1 capsule of 100 mg + 3 capsules of 20 mg
5	390	1 Capsule of 250 mg + 1 capsule of 100 mg + 2 capsules of 20 mg
6	410	1 Capsule of 250 mg + 1 capsule of 100 mg + 3 capsules of 20 mg
7	300	3 Capsules of 100 mg
8	370	1 Capsule of 250 mg + 1 capsule of 100 mg + 1 capsule of 20 mg
9	350	1 Capsule of 250 mg + 1 capsule of 100 mg
10	420	4 Capsules of 100 mg + 1 capsule of 20 mg
11	370	1 Capsule of 250 mg + 1 capsule of 100 + 1 capsule of 20 mg
12	400	4 Capsules of 100 mg
13	250 ^a	1 Capsule of 250 mg
14	380	3 Capsules of 100 mg + 4 capsules of 20 mg
15	420	4 Capsules of 100 mg + 1 capsule of 20 mg
16	350	1 Capsule of 250 mg + 1 capsule of 100 mg

^a Patient with daily dose based on 150 mg/m² instead of 200 mg/m² (reported significant thrombocytopenia and neutropenia during the induction phase of treatment)

Table 3 Pharmacokinetic parameters of temozolomide following oral administration

Parameter	C_{max} , µg/mL (SD)	AUC_t , µg h/mL (SD)	AUC_{∞} , µg h/mL (SD)	AUC/AUC_{∞} , % (SD)	T_{max} , h (range)	K_e , 1/h (SD)	$T_{1/2}$, h (SD)
Dralitem [®]	10.58 (2.81)	31.10 (4.02)	32.29 (4.17)	96.3 (1.4)	1.13 (0.50–4.00)	0.37 (0.03)	1.89 (0.13)
Temodal [®]	11.11 (2.49)	30.80 (3.89)	31.82 (4.16)	96.9 (1.2)	0.63 (0.25–3.00)	0.37 (0.05)	1.87 (0.20)

Data are expressed as arithmetic means (SDs), except T_{max} , which is expressed as median (range)

SD standard deviation, $T_{1/2}$ half-life, T_{max} time to reach C_{max} , C_{max} maximum concentration of drug after dosing, K_e elimination rate constant, AUC_t area under the concentration–time curve from time zero to the final quantifiable sample, AUC_{∞} area under the concentration–time curve from time zero to infinity

Table 4 Bioequivalence statistics (with log-transformed data)

Parameter	C_{max} (µg/mL)	AUC_t (µg h/mL)	AUC_{∞} (µg h/mL)
ISCV (%)	21.4	5.2	4.7
Geometric least-squares means			
Temodal [®]	10.83	30.56	31.55
Dralitem [®]	10.22	30.86	32.03
Test/reference ratios (point estimates)			
Ratio (%)	94.37	100.99	101.53
90% confidence intervals			
Estimated limits (%) [lower–upper]	82.69–107.69	97.81–104.28	98.60–104.54
Schuirmann’s two one-sided test			
Probability <80.00%	0.0224	<10 ⁻⁸	<10 ⁻⁸
Probability >125.00%	0.0011	<10 ⁻⁸	<10 ⁻⁸

C_{max} maximum concentration of drug after dosing, AUC_t area under the concentration–time curve from time zero to the final quantifiable sample, AUC_{∞} area under the concentration–time curve from time zero to infinity, $ISCV$ intrasubject coefficient of variation

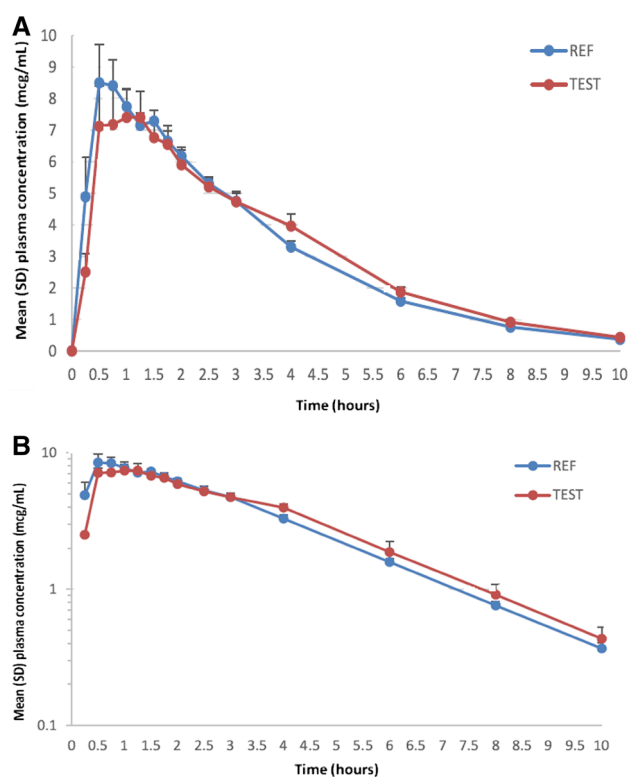


Fig. 1 Mean plasma temozolomide concentrations obtained for the test (Dralitem®) and reference (Temodal®) formulations following a single dose of 200 mg/m². **a** Linear scale; **b** log scale

3.3 Safety Evaluation

The type and frequency of adverse events (AEs) experienced on days 3 and 4 were similar to those already described in specific literature for temozolomide administration [15, 16]. All were of mild or moderate severity, in accordance with the Common Terminology Criteria for Adverse Events (CTCAE, grade 1 or 2) [17]. The most

commonly reported AEs in this study were vomiting, abdominal pain, asthenia, and weakness (Table 6). One subject experienced a severe expressive aphasia, possibly not related to the study drug, which was not considered a serious adverse event (SAE) because it produced no significant sequelae for the patient. No SAEs were reported. Most of the AEs were probably adjudged to temozolomide. Nevertheless, with the exception of one case of abdominal pain in which drug administration was discontinued, in all patients temozolomide intake was continued or only temporarily interrupted until the AE resolved. Aside from the patient who had to stop taking the medication, no other subjects were unable to complete the study treatment due to an AE.

4 Discussion

This study was designed to evaluate the comparative bioavailability and safety of two oral temozolomide formulations in patients with primary CNS tumors under fasting conditions. The goal was to establish comparable systemic exposure (based on the ratio of geometric mean values of C_{max} and AUC) to both temozolomide formulations following oral administration of a single dose of 200 mg/m². Bioequivalence of test and reference products was broadly demonstrated to be grounded based on the results of this study.

The oral dose chosen for this study was reached with three different temozolomide capsule strengths (20, 100 and 250 mg), and was administered in a once-daily dose on days 3 and 4 during a 5-day treatment course. A 10-h washout period was considered appropriate since the temozolomide $t_{1/2}$ is nearly 1.8 h [3, 18]. A crossover design was used to decrease variability and the number of subjects required to be enrolled. In fact, the intrasubject variability in AUC_t , AUC_{inf} , and C_{max} for both temozolomide

Table 5 ANOVA of pharmacokinetic parameters (with log-transformed data)

Parameter	Source of variation	Degrees of freedom	Sum of squares	Mean squares	<i>F</i>	<i>p</i> value
C_{max}	Sequence treatment period	1	0.0029	0.0029	0.0319	0.8608
		1	0.0269	0.0269	0.5981	0.4522
		1	0.4522	0.0455	1.0122	0.3315
AUC_t	Sequence treatment period	1	0.0278	0.0278	0.8726	0.3661
		1	0.0008	0.0008	0.2940	0.5962
		1	0.0017	0.0017	0.6260	0.4420
AUC_{∞}	Sequence treatment period	1	0.0246	0.0246	0.7211	0.4101
		1	0.0018	0.0018	0.8337	0.3767
		1	0.0309	0.0009	0.3948	0.3767

ANOVA analysis of variance, C_{max} maximum concentration of drug after dosing, AUC_t area under the concentration–time curve from time zero to the final quantifiable sample, AUC_{∞} area under the concentration–time curve from time zero to infinity

Table 6 Treatment-related adverse events

Adverse events	<i>N</i>	%	Intensity ^a
Vomiting	5	22.72	Mild
Pruritus/skin rash	2	9.09	Moderate
Abdominal pain	3	13.63	Mild
Asthenia/adynamia	2	9.09	Mild
Hyporexia	2	9.09	Mild
Ageusia	1	4.54	Mild
Pyrosis	1	4.54	Mild
Diarrhea	1	4.54	Mild
Constipation	1	4.54	Mild
Proctorrhagia	1	4.54	Mild
Lower limb edema	1	4.54	Mild
Aphasia	1	4.54	Moderate
Febrile syndrome	1	4.54	Mild
Total	22	100	

^a According to the Common Terminology Criteria for Adverse Events (version 4.0)

formulations was low (CV = 4.7–21.4%) (Table 3). This is consistent with previous literature reports on this subject: oral temozolomide is rapidly absorbed with linear PKs over the therapeutic dose range and with nearly 100% bioavailability [1–3, 5], based mainly on its lipophilic characteristics and its spontaneous conversion into the active metabolite MTIC at physiological pH [1, 19–21].

In addition, T_{max} was 0.92–1.5 h and elimination $t_{1/2}$ was approximately 1.8 h, both parameters in accordance with literature-based data.

The calculated CIs for mean C_{max} , AUC_t , and AUC_{∞} for the Dralitem[®]/Temodal[®] ratios were within the 80–125% range for accepted bioequivalence under fasting conditions. Likewise, the Schuirmann tests showed significant results (Table 4). Intrasubject variability was between 5 and 21%, and the observed study power was over 80% in all cases.

Treatment-emergent AEs were consistent with those reported previously in patients with primary CNS tumors treated with oral temozolomide [22]. No new safety concerns arose in the present trial.

5 Conclusion

Based on this study, oral administration of Dralitem[®] (Monte Verde S.A.) resulted in equivalent systemic exposure compared with oral administration of Temodal[®] (Schering-Plough Laboratories) at the proposed dose range, and, as such, both products would be considered bioequivalent. With predictable bioavailability and minimal toxicity, both drug products could be considered interchangeable for patients with primary CNS tumors.

Compliance with Ethical Standards

Funding This study was funded by Monte Verde S.A.

Conflict of interest Miguel Vago, Fernando Costa, Mónica Rosenberg, Sebastián Pérez, Marcelo Rubio, Cristian Magariños and Cecilia González are employed by Laboratorios Raffo S.A. Alejandro Muggeri and Santiago Pérez Lloret have received research honoraria from FLENI-mrc/Centralab CR, the CRO (Contract Research Organization) hired by the sponsor to conduct this study.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the Institutional Review and Ethics Committee, GCP, and the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in this study.

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