

Bioequivalence study between two formulations of 25 mg lenalidomide capsules in healthy male subjects

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Abstract

Background: Lenalidomide, derived from thalidomide, is vital for treating multiple myeloma and other blood cancers due to its immunomodulatory and anti-angiogenic effects. Ensuring bioequivalence between generic and branded forms is crucial, especially for public health affordability. **Objective:** To evaluate pharmaceutical bioequivalence between two formulations of 25 mg lenalidomide capsules in healthy male subjects under fasting conditions. **Method:** Conducted as an open label, monocentric, randomized, 2 x 2 crossover trial with 32 participants in fasting state, analyte concentrations were measured using UPLC-MS/MS, and then the pharmacokinetic parameters were determined. **Results:** Statistical analysis has determined the geometric mean ratio (90% CI) of the test drug/reference drug for lenalidomide were 90.03 to 114.13% for C_{max} and 88.21 to 101.02% for AUC_{0-t}. Power of the test was 92.8% for C_{max} and 100.0% for AUC_{0-t}. **Conclusion:** Both formulations are bioequivalent and, therefore, they are interchangeable, according to the Brazilian criteria, since confidence intervals for C_{max} and AUC_{0-t} ratios were within 80 and 125%.

Keywords: Lenalidomide. Bioequivalence. Capsules. Liquid chromatography-tandem mass spectrometry. Immune modulator. Antineoplastic.

Estudio de bioequivalencia entre dos formulaciones de lenalidomida de 25 mg en sujetos hombres sanos

Resumen

Antecedentes: La lenalidomida, derivada de la talidomida, es vital para tratar el mieloma múltiple y otros cánceres de la sangre debido a sus efectos inmunomoduladores y antiangiogénicos. Asegurar la bioequivalencia entre las formas genéricas y las de marca es crucial, sobre todo, para la accesibilidad de la sanidad pública. **Objetivo:** Evaluar la bioequivalencia farmacéutica entre dos formulaciones de cápsulas de lenalidomida de 25 mg en 32 hombres sanos en ayunas. **Método:** Ensayo abierto, monocéntrico, aleatorizado, cruzado, donde se midieron las concentraciones de analitos por UPLC-MS/MS determinando los parámetros farmacocinéticos. **Resultados:** El análisis estadístico ha determinado que la relación media geométrica (IC 90%) del fármaco de test/referencia fue de 90.03 a 114.13% para C_{max} y de 88.21 a 101.02% para AUC_{0-t}, con poder del test de 92.8 y 100.0% respectivamente. **Conclusión:** Ambas formulaciones cumplieron los criterios brasileños de bioequivalencia, con intervalos de confianza para las relaciones C_{max} y AUC_{0-t} dentro del intervalo 80-125%, lo que confirma su intercambiabilidad.

Palabras clave: Lenalidomida. Bioequivalencia. Cápsulas. LC-MS/MS. Inmunomodulador. Antineoplásico.

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Introduction

Lenalidomide (IUPAC 3-(7-amino-3-oxo-1H-isoindol-2-yl)piperidine-2,6-dione), a thalidomide analog, is an immunomodulatory (IMiD) and antineoplastic agent used in multiple myeloma therapy¹. Multiple myeloma is a malignant B-cell neoplasia characterized by the excess of monoclonic plasma cells in the bone marrow. Established for the 1st time as agents with antiangiogenic properties, thalidomide, and the other IMiDs inhibit the production of interleukin, which is a growth factor for the proliferation of myeloma cells. In addition, they activate apoptotic pathways through cellular death by means of caspases 8².

In 2005, the Food and Drug Administration (FDA) approved the marketing of 5 mg and 10 mg Revlimid® (Lenalidomide) capsules for the treatment of transfusion-depending anemia patients due to low-risk myelodysplastic syndrome (MDS) associated to 5q deletion abnormality with or without additional cytogenetic abnormalities and multiple myeloma in combination with dexamethasone^{3,4}. The European Medicines Agency issued the authorization to market lenalidomide in 2007⁵. In Brazil, ANVISA issued a public opinion for the approval of Revlimid in 2018 for the treatment of patients with relapsed/refractory multiple myeloma who had received at least one prior treatment; and for the treatment of patients with transfusion-depending anemia derived from low to intermediate-1 risk MDS associated to 5q deletion cytogenetic abnormality, with or without additional cytogenetic abnormalities⁶.

In 2017, ANVISA issued resolution RDC 191 (regarding the control of lenalidomide and any drugs containing it, among other provisions), later revoked in 2022 by a resolution with the same name (RDC 735/2022). Due to the risks associated to the teratogenic effects of lenalidomide-based drugs, the resolution stated, among other provisions, the design of a Risk Management Plan, including a pregnancy prevention program, which requires training of the physicians prescribing the drug by the register holder⁷.

In 2020, ANVISA issued RDC 393/2020, which included lenalidomide therapeutic indications for the treatment of multiple myeloma, in combination with bortezomib and dexamethasone, for patients with no prior treatment; for the treatment of follicular lymphoma or previously treated patients with marginal zone lymphoma, in combination with rituximab (anti-CD20 antibody), and relapsed/refractory mantle cell lymphoma⁸.

As to the security profile, the authors report that lenalidomide is well tolerated and that most usual adverse

events include hematologic toxicity with controllable neutropenia and thrombocytopenia^{9,10}. According to the panel released by ANVISA through VigiMed, in the period between January 01, 2018, and September 09, 2022, 652 lenalidomide suspected adverse events were informed, out of which 16.10% corresponded to neutropenia and 4.45% to thrombocytopenia¹¹.

The objective of this trial was to verify whether the rate and extent of absorption of the 25 mg lenalidomide immediate release capsule formulation manufactured by Eurofarma Laboratórios S.A. are equivalent to those of the reference product, REVLIMID® when administered in one single dose and under fasting conditions in adult healthy male subjects.

Methods

Study protocol and reporting

Bioequivalence studies are a type of study that follows specific rules dictated by the regulatory agencies in each country. Thus, study protocol drafting requirements follow the SPIRIT Statement¹²⁻¹⁴, where applicable. Data reporting is also carried out in the form of standardized reports by the agencies, but they contain all the information recommended for reporting according to the CONSORT Statement^{14,15}. In Brazil, the following standards must be followed: (1) RE 894/23¹⁶, which defines the standardization for the preparation of bioequivalence study protocols, and (2) RE 895/23¹⁷, which defines the form of study reporting.

Study formulations

The test drug –25 mg lenalidomide immediate release capsule–, was manufactured by Eurofarma Laboratórios S/A. The reference product used in the study was Revlimid® (25 mg lenalidomide immediate release capsule), manufactured by Celgene Europe B.V. and registered in Brazil by Bristol-Myers Squibb Farmacêutica LTDA.

Study volunteers

Adult male healthy volunteers willing to participate in the study were selected based on the protocol eligibility criteria 90 days before the first study period. A sufficient number of eligible volunteers appeared in the research center facilities, and the 32 volunteers who fulfilled the protocol requirements were given

information regarding the study, after having their inquiries clarified and having decided to willingly take part in the study, each subject signed the informed consent form, previously approved by the Avant Santé Research Center Research Committee (COFEPRIS 18 CI 19 019 021) along with the study protocol. Initially, 32 study subjects were selected and randomized, out of which only 28 completed all the study procedures due to exclusion and/or dropout reasons.

Study design

Single dose, randomized, open-label, two-treatment, two-sequence, two-period crossover bioequivalence study of 25 mg lenalidomide capsules manufactured by Eurofarma Laboratórios S.A. *versus* REVLIMID® (25 mg lenalidomide immediate release capsule) manufactured by Celgene Europe B.V. and registered in Brazil by Bristol-Myers Squibb Farmacêutica LTDA in adult male healthy volunteers under fasting conditions.

Drug administration

Study subjects were kept in fasting conditions for 10 h before the dose administration and at least 4 h afterward, on each period. The study was conducted under fasting conditions as required by ANVISA - Agência Nacional de Vigilância Sanitária¹⁸.

On each period of the study, a single dose (25 mg) of the test or the reference product was administered orally to the volunteers, in a seated position, with 200 mL of water at room temperature, under fasting conditions. The washout period was 7 days.

Blood sampling

A total number of 19 blood samples were collected from each volunteer in each period in tubes with K₂EDTA. Blood samples (4 mL each) were collected at time points 0.00 h (before dose) and after administration at time points 0.25, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 h.

Biological samples processing

After collection, blood samples were processed in a refrigerated centrifuge at 3000 rpm for 10 min at 4 ± 2°C. The plasma obtained from the blood samples was transferred to two different cryogenic tubes (aliquot 1 and aliquot 2) previously identified and stored at a temperature below -50°C.

Lenalidomide quantification in plasma

METHOD VALIDATION

The validation of the bioanalytical method for quantification of lenalidomide in human plasma using Lenalidomide-d5 as internal standard and K₂EDTA as anticoagulant through extraction in solid phase (Strata-X® 33 µm cartridge) and ultra-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) was performed in compliance with the acceptance criteria for selectivity, calibration curve, precision, accuracy, residual effect, matrix effect, and stability test in solution and the biological matrix (Table 1).

Chromatographic conditions adopted for the validation and quantification of the study subject samples included the use of a Luna omega 1.6 µm PS C18 50 × 2.1 mm chromatographic column, at 35 ± 2°C. Samples were kept at 5 ± 4°C. Mobile phase A used was Formic Acid 0.1% and mobile phase B was LC-MS grade Acetonitrile in an 87:13 v/v proportion. The injection volume was 3.0 µL and retention times were 1.07 ± 0.3 min for the analyte and 1.05 ± 0.3 for the internal standard, the running time being 2.10 min.

The method proved linear between concentrations of 2.044 ng/mL to 1015.506 ng/mL according to equation $y = a + bx [1/x]$, where “y” is the response, “x” is the analyte concentration and “1/x” is the selected weight.

The lower limit of quantification (LLQ) established for the method was 2.044 ng/mL and validated quality control samples were 5.148 ng/mL, 411.867 ng/mL, and 792.052 ng/mL.

STABILITY

Stability analysis was carried out in plasma in concentrations of 5.148 ng/mL and 792.052 ng/mL and they complied with the acceptance criteria when the samples were subjected to 6 h and 18 min at room temperature (approximately 25°C) (short-term stability), for 2 days 8 h and 38 min in auto-injector (5 ± 4°C) after sample extraction completion (post-processing stability) 4 freeze-and-thaw cycles and 106 long-term days.

STANDARD SOLUTIONS

Reference standards: lenalidomide (TRC/Canada) was used as an analyte and Lenalidomide-d5 (TRC/Canada) was used as an internal standard for the preparation of the primary standard solutions in methanol HPLC grade. Working solutions were prepared using milli-Q water: methanol (20:80; v/v) as eluent. All solutions were stored at a temperature between 2 and 8°C.

Table 1. Summary of the bioanalytical method

Analyte	Lenalidomide
Internal standard	Lenalidomide-d5
Biological matrix	Human Plasma
Anticoagulant	EDTA
Linearity	2.044 ng/mL-1015.506 ng/mL
Curve equation	$y = a + bx [1/x]$
Lower quantification limit	2.044 ng/mL
Low quality control	5.148 ng/mL
Medium quality control	411.867 ng/mL
High quality control	792.052 ng/mL
Post-processing stability time	2 days 8 h 38 min
Freeze/thaw cycles	4 cycles
Short-term stability time	6 h 18 min
Long-term stability time	106 days

EDTA: ethylenediaminetetraacetic acid.

Compounds quantification in biological samples

Compounds were extracted from human plasma samples and quantified through LC-MS/MS using the Xevo TQ-S/Acquity UPLC I-Class (Waters) spectrometer, equipped with positive electrospray (ESP+) ionization source, and the analyte and internal standard were detected using multiple reaction monitoring with m/z transitions $260.21 > 149.11$ and $265.23 > 151.13$, respectively.

Software used

Software Masslynx version 4.1 was used for calculating sample concentrations in the analytic phase.

Software *Phoenix WinNonlin*™ version 8.3 and *Statistical Analysis System* (SAS®) version 9.4 were used to perform the statistical analysis.

Results

Study population

The study began with 32 volunteers and ended with 28 healthy male volunteers between 18 and 42 years of age, who complied with the inclusion and exclusion criteria set forth in the protocol.

Pharmacokinetics and statistical analysis

Pharmacokinetic parameters C_{max} and AUC_{0-t} were established using software *Phoenix WinNonlin*™ version 8.3 and *Sistema de Análise Estatística* (SAS®) version 9.4.

Pharmacokinetic parameters are shown in table 2.

The maximum concentration of C_{max} obtained for the reference product Revlimid® was 439.761 ng/mL in 1.5 h. For the test product, lenalidomide, a C_{max} of 477.742 ng/mL occurred at 1.1 h. Figure 1 shows intermediate concentrations of lenalidomide for the 28 study subjects along collection times.

Tolerability/safety analysis

Eight adverse events were reported during the study: 3 headaches, 1 erythema, 1 rash, 1 hypertriglyceridemia, 1 rectal hemorrhage, and 1 normochromic normocytic anemia. No serious adverse events were reported; 6 events were classified as mild and 2 as moderate.

As to the relation with the study drug, 1 adverse event was classified as possibly related, 2 as probably related, and 5 as unlikely to be related to the study medication.

Discussion

The study was properly planned and conducted, obtaining pharmacokinetic parameters C_{max} and AUC_{0-t} which confidence interval values (90%) are within the acceptable limit for the ratio between the geometric means of the test and reference products (80–125%), according to the national legislation, ANVISA resolution RE nº 1170/2006¹⁹.

The planned number of 32 healthy male subjects is consistent with studies published by other authors^{20,21}. The population selected for the study was male gender only, as recommended by the FDA guidelines²² and consistent with resolution ANVISA RDC 735/2022⁷.

Both formulations were well tolerated during the study and no serious adverse events were reported. Headache was the most frequent adverse event, contrary to the reports of other authors and the ANVISA panel, who stated neutropenia and thrombocytopenia as the most frequent adverse events^{9,11,23}.

The 7-day washout period seemed adequate, as all base collection samples of the volunteers of the second period had a concentration below the LLQ.

As in other published works, the analytical technique selected for the study of lenalidomide quantification of in human plasma samples was LC-MS/MS²⁴⁻²⁶.

Table 2. Pharmacokinetic parameters (n = 28)

Ratio (test/reference)	Geometric mean (%)	CI (90%)	Test power (%)	p (sequence)
C _{max} (ng/mL)	101.4	90.03-114.13	92.8	0.5299
AUC _{0-t} (ng.h.mL ⁻¹)	94.4	88.21-101.02	100.0	0.1203

CI: confidence interval.

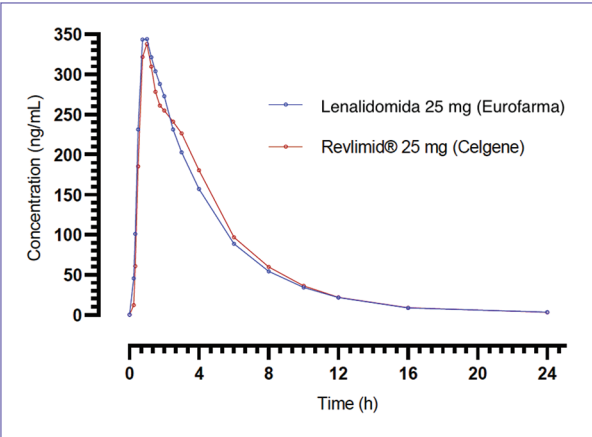


Figure 1. Lenalidomide intermediate concentrations along time for each formulation.

Lenalidomide was quantified in its unaltered form, as required by the national legislation²⁷.

Both reference and test drugs showed a maximum plasma concentration C_{max} of 439.761 ng/mL and 477.742 ng/mL, respectively, consistent with those found in the literature^{20,21}.

Conclusion

The results show test and reference formulations are considered bioequivalent regarding the absorption rate and extent, as the criteria required by the Brazilian regulatory authority have been complied with (CI 90% between 80 and 125%). Consequently, the test formulation, i.e. lenalidomide manufactured by Eurofarma Laboratórios S/A and the reference product Revlimid®, both in 25 mg capsules, are bioequivalent and therefore, interchangeable.

Authors contributions

C. Sverdlhoff participated in the study design and supervision. V. Marcondes Rezende performed the data curation and wrote the manuscript and reviews. L. de Cassia Val and L. Nerath Bonanato participated

in the Project Administration and supervision. M.E. Cedano Limón conducted the clinical investigation. S. Kakarla performed bioanalytical method validation and supervision of sample analysis. M.H. Badii performed the statistical analysis. M. Pendela performed general site supervision. N.C. Lemus Castro wrote the clinical protocol, supervised clinical investigation, and was the principal investigator. All authors contributed with data and revision and approved the final manuscript.

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Conflicts of interest

The authors declare that, except for LCV and LNB who are associates of Eurofarma Laboratórios S/A, there are no conflicts of interest in this study or publishing work.

Ethical disclosures

Protection of human subjects. The authors declare that the experiments were performed on humans for this research, and all ethical requirements were followed such as sign of the Inform Consent Form by the subjects before any procedure in the study, meet of Good Clinical Practices, Insurance for all subjects, and follow-up of all adverse events, until resolution.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the subjects referred to in the article. This document is in the possession of the Clinical Center.

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