Oral Bioavailability and Pharmacokinetic Study of Clarithromycin in Different Dosage Forms in Iranian Healthy Volunteers

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Abstract

The objective of the present study was to study the bioavailability and pharmacokinetic parameters of three formulations of clarithromycin after oral administration in 12 normal adult male volunteers. Each subject received 500 mg of clarithromycin as two 250 mg tablets, one 500 mg tablet or suspension in a randomized crossover sequence. Blood samples were collected at selected time intervals up to 24 hours and plasma concentrations of CLR were determined using a validated HPLC method.

The pharmacokinetics parameters including $t_{\text{max}}$, $t_{\frac{1}{2}}$, $C_{\text{max}}$, AUC, AUMC were determined from inspection of the individual subject concentration time curves and by model independent methods.

The results showed that these parameters were not influenced by dosage form. Although higher maximum concentrations were achieved with the suspension, this was not statistically different from the other formulations. The tablets were not found to be statistically different from the suspension in any pharmacokinetic parameter.

Bioequivalence of the test versus reference formulations was accepted for both AUC$_{0-\infty}$ and $C_{\text{max}}$ because the 90% CIs lie within the acceptable range of 80-125%.

In the light of the results of the studies reported here, it can be concluded that CLR test formulations, i.e. tablets and suspension are bioequivalent to the respective reference formulations.

Keywords: Clarithromycin; Oral formulations; pharmacokinetic parameters; Bioequivalence

Introduction

Clarithromycin (6-O-methyl erythromycin) is a relatively new antibiotic belonging to the macrolide family. Structurally, it differs from erythromycin only in the substitution of an O-methyl group for the hydroxyl group at position 6 of the lactone ring.

This semisynthetic macrolide antibiotic inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit of susceptible organisms and inhibiting protein synthesis through translocation of aminoacyl transfer RNA [1-3].

CLR exhibits broad spectrum activity against gram-positive, gram-negative bacteria, and it is indicated for the treatment of a wide variety of respiratory and dermatologic infections and treatment of Mycobacterium avium complex infection and peptic ulcers due to Helicobacter pylori [4-7]. The FDA approved dosage regimen for CLR ranges from 250 to 500 mg twice daily (respiratory tract and skin infections) [8-10].

Once absorbed, CLR undergoes first pass metabolism, with ~25% of the parent compound converted to the active metabolite, 14-hydroxy clarithromycin [11]. CLR is stable in gastric acid and rapidly absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability of 250 mg CLR tablets was approximately 50%. For a single 500 mg dose of CLR, food slightly delays the onset of its absorption, increasing the peak time from approximately 2 to 2.5 hours and peak plasma concentration by about 24%, without change to the extent of drug bioavailability.

CLR has serum protein binding ranging from 42 to 50% over a concentration range from 0.25 to 5 µg/L, predominantly to the albumin fraction and high affinity for α1-acid glycoprotein.

Although several generic oral formulations of CLR are available, information concerning the bioavailability of each formulation in the Iranian population was unavailable. Thus, the purpose of the present study was to compare the bioavailability of oral formulations used in clarithromycin, clarithromycin (Tehran Chimi, test) and Klaricid (Abbott, reference) formulations.

The primary aim of this study was to evaluate the pharmacokinetic parameters of CLR after single oral administration of tablets and suspension forms and pharmacokinetic comparison of them in the present population. In the next section, in vivo bioavailability and pharmacokinetic profiles of new generic formulations of this drug

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were compared with those of a reference product. A sensitive and reproducible HPLC analysis method for the determination of drug in human plasma was developed and used in the pharmacokinetic study.

**Subjects and Methods**

**In vitro dissolution test**

A dissolution test was performed according to the procedure described in USP 27 Dissolution Test. The paddle rotation speed was maintained at 50 rpm at 37°C. Release test was carried out in 900 ml of acetate buffer (0.01 M) using a dissolution tester. Samples of 1 ml were withdrawn at predetermined time intervals and replaced with the same volume of fresh buffer. Each sample solution was analyzed by high-performance liquid chromatography (HPLC) to determine the dissolution rate of CLR. An AUV absorption spectrometer was used as the HPLC detector at a detection wavelength of 210 nm. The analytical column was a Shimpack CLC-ODS (Shimadzu, Kyoto, Japan), 150 mm×4.6 mm i.d., 5 µm particle size which was protected by a Shim-pack G-ODS guard column (1 cm×4.0 mm i.d., 5 µm particle size). The mobile phase was 0.05 M phosphate buffer (pH 4.0) and methanol (65:35, v/v).

**Study design and subject selection**

Twelve healthy male volunteers with a mean age of 29 ± 2.3 years, mean weight of 75.3 ± 9.5 kg and mean height of 172.8 ± 7.6 cm, participated in the study after giving written informed consent about the nature and implications of the trial. All volunteers had normal examination and clinical laboratory test results, and none were on any medications for at least two weeks prior to and during the period of the study.

**Drug administration and blood sampling**

This was a randomized-sequence, open-label, 2-period, 2 way crossover study to compare the relative bioavailability and other pharmacokinetics of CLR administered to healthy subjects as two 250 mg tablet (Tehran Chimi, Iran) and Klaricid (Abbott company, UK), 500 mg tablet (Tehran Chimi, Iran) and Klaricid (Abbott company, UK) and suspension (125 mg/5ml, Tehran Chimi, Iran) and Klaricid (Abbott company, UK) as the test and reference products, respectively.

The washout period in this study was 2 weeks. CLR has a t½ of 3 to 4 hours; therefore, a washout period of ≥7 days was necessary to ensure that 5 times the t½ was exceeded, in accordance with the requirements set by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [11,12].

Blood samples (5 ml) were collected from an indwelling catheter in the antecubital vein of the forearm just before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 after the drug administration and collected in heparinized tubes. Blood samples were centrifuged at 3000 rpm for 5 min and serum stored at -70°C until analyzed.

**CLR quantitation in human plasma**

The HPLC system used consisted of dual pump of Shimadzu LC-10A solvent delivery system, a system controller (SCL 10AD), a spectrofluorometric detector (RF-551) operated at an excitation and emission wavelengths of 265 and 315 nm, respectively, a column oven (CTO-10A), a degasser (DGU-3A) and a data processor (C-R4A) all from Shimadzu, Kyoto, Japan. The analytical column was a Shimpack CLC-ODS (Shimadzu, Kyoto, Japan), 150 mm×4.6 mm i.d., 5 µm particle size which was protected by a Shim-pack G-ODS guard column (1 cm×4.0 mm i.d., 5 µm particle size). A mixture of 0.05 M sodium phosphate buffer containing triethylamine (2 ml L⁻¹; pH 3.8) and methanol (17:83, v/v) was used as the mobile phase. The column oven temperature was set at 58°C and the mobile phase was filtered, degassed and pumped at a flow rate of 2.0 ml min⁻¹ [13].

**Sample preparation**

Serum samples were stored at −40°C until assay. Frozen serum samples were thawed in water at 37°C. Aliquots of blank, calibration standard or unknown human serum samples (1 ml) were pipetted into 100 mm×16 mm disposable glass tubes, containing 100 µl of working internal standard (Amantadine) solution. The samples were mixed with 200 µl of a phosphate buffer (0.05 M; pH 3) and extracted with 5 ml of dichloromethane as extracting solvent. After vortex mixing for 30 s and centrifugation (5 min at 6000g) the organic phase was removed and evaporated to dryness under a stream of nitrogen at 50°C. The residue was reconstituted in 100 µl of the FMOCl-Cl solution. Following the addition of 25 µl phosphate buffer (0.05 M; pH 8.5) and brief mixing, the samples were kept at 60°C for 15 min and then a volume of 20 µl of the reaction mixture was injected into the HPLC system [13].

**Pharmacokinetic analysis**

CLR pharmacokinetic parameters were determined by noncompartmental methods. The elimination rate constant (K) was estimated by the least-square regression of plasma concentration time data points lying in the terminal log-linear region of the curves. The elimination half life was calculated as 0.693 divided by K. The area under the plasma concentration-time curve from time zero to the last measurable concentration at time t (AUC₀-t) was calculated using the trapezoidal rule. The area was extrapolated to infinity (AUC₀-∞) by addition of C t/K to AUC₀-t where C is the last measured drug concentration. Peak plasma concentration (Cₚmax) and time to peak concentration (Tₚmax) were determined by inspection of the individual subject concentration time curves. The relative bioavailability of the test formulation was estimated as the AUC₀-∞ ratio of the test to the reference product. The Wagner-Nelson method was used to estimate fractional absorption. Fractional absorbed data for each subject and treatment was used for estimation of the apparent absorption rate constant (Ka). Absorption half-life (T½(abso)) was calculated by 0.693/Ka. The apparent oral clearance (Cl/F) and apparent volume of distribution (Vd/F) were calculated by Eq. 1 and 2, respectively:

\[
\text{Cl/F} = \frac{\text{Dose}}{\text{AUC}_{0-\infty}}
\]

\[
\text{Vd/F} = \frac{\text{Cl}}{K}
\]

Meantime residence (MRT), the average time for all the drug molecules to reside in the body was estimated according to the following equation:

\[
\text{MRT} = \frac{\text{AUMC}_{0-\infty}}{\text{AUC}_{0-\infty}}
\]

Where AUMC is the area under the first moment of plasma drug concentration [14,15].

**Statistical analysis**

The in vitro dissolution data was compared with two-tailed student’s t-test. Logarithmic transformation of AUC₀-∞, AUC₀-∞ and Cₚmax were compared by the analysis of variance (ANOVA) for a crossover design followed by 90% confidence interval test for the arithmetic mean pharmacokinetic parameters of CLR formulations. The non-parametric ‘Wilcoxon test’ was also performed for analyzing...
Results

Dissolution curves of tablets and suspension are shown in Figure 1. Two-way ANOVA showed no significant difference in dissolution curves between the two formulations of each dosage form (p>0.05).

Clarithromycin was well tolerated in all subjects after oral administration of each dosage form. No subject’s reported any adverse effects, and physical examinations and laboratory studies done at the completion of the protocol were within normal limits.

Average plasma concentration of drug versus the time course after oral administration of the reference (Klaricid) and test (Tehran Chimi) products in 12 healthy volunteers are shown in Figure 2.

Clarithromycin was rapidly absorbed after oral administration of all three dosage forms in the first 2.5 h after dosing.

Multivariate analysis was conducted for the following parameters: maximum concentration of drug in serum, time to maximum concentration of drug in serum, AUC, elimination half-life, elimination rate constant, apparent distribution volume and total clearance.

The results of these analyses are shown in Table 1. When significant variation due to dosage form was observed, a posteriori testing (using Tukey’s test) was performed to identify differences between the formulations.

Development of the analytical method for CLR quantitation in plasma

The proposed method was considered suitable for CLR quantification in plasma samples. The method showed good linearity in the range of 0.025–10 µg/ml of drug concentrations [r² = 0.9982].

The recovery, limit of quantification and detection limit, were 93 ± 4%, 0.025 µg/ml and 0.01 µg/ml, respectively. The coefficient variation values of both within day and between days were all less than 16.6% whereas accuracy never deviated from 100% by more than 7.3%. Plasma samples were stable at -40°C for 60 days. Drug in plasma samples was also stable following freeze-thaw cycles [15].

Bioequivalence evaluation

The pharmacokinetics parameters calculated from individual plasma level-time data are shown in Table 2. In order to confirm the bioequivalence of the products; the 90% confidence intervals for the arithmetic mean of test/reference, individual ratios of Cmax, AUC0-24, AUC0-∞, and Cmax/AUC0-∞ were calculated. All values were found to be within the conventional bioequivalence ranges of 0.8–1.25 (Table 2). Wilcoxon Signed Rank non-parametric analysis did not reveal significant differences between Tmax values (P = 0.137).

As shown in Table 2, the parametric point estimate of the difference (T-R) for Tmax is 0.33 h and thus within the stipulated bioequivalence range (±20% of the mean of the reference product). No significant differences were observed between the Cmax, Tmax, AUC0-24, AUC0-∞, T1/2, K, Cl/F, Vd/F and MRT of the two products (P>0.05).

Figure 1: Dissolution profiles of clarithromycin in three formulations, A: Tablet 500 mg, B: Tablets 250 mg, C: Suspension (125 mg/5 ml). Error bars indicate standard errors.
Comparisons were made between the test and reference formulations and between each of the test formulations.

The pharmacokinetic exposures for CLR obtained from the different formulations compared to their references, appeared to have similar profiles. The plasma concentration of all formulations then declined mono-exponentially (Figure 2).

**Discussion**

The bioequivalence and pharmacokinetics of three CLR products were studied in 12 volunteers following a single dose of 2×250 mg, 500 mg tablets and 500 mg suspension (125 mg/5mL) products. The plasma concentration of CLR was determined using a simple, sensitive and reproducible HPLC method, developed in this laboratory. Increased sensitivity, evident from lower limit of detection (LOD) and limit of quantitation (LOQ), and the high recovery of extraction of the HPLC assay are comparable to the published methods [17,18].

The mean plasma concentration-time profiles of CLR following oral administration of the products are shown in Figure 2. The blood sampling schedule was designed according to FDA regulations. Sampling was accomplished up to at least 3 terminal elimination half lives of the drug in the present study, and the time intervals between sampling did not exceed one terminal half life of CLR.

The time to maximum concentration of drug in serum, elimination rate constant and total clearance were not influenced by dosage form (Table 1). Although higher maximum concentrations were achieved with the suspension, this was not statistically different from the other formulations. The 500 mg tablets were not found to be statistically different from the suspension in any pharmacokinetic parameter (p>0.05).

The AUC_{0-24} was greater than 80% of the AUC_{0-\infty} in all subjects, indicating adequate sampling time and intervals to estimate the extent of absorption. The power of ANOVA was estimated to be >0.8 at 90% CI, indicating that 12 subjects would suffice for the purposes of the study. Two-way ANOVA for crossover design was performed on log-transformed data to assess the effect of formulations, periods, sequences and subjects nested in sequence on the parameters. The effect of periods, sequence or treatment did not differ from any of pharmacokinetic parameters.

No significant differences were observed between the formulations in terms of pharmacokinetic parameters. All three test and the reference formulations were readily absorbed after oral administration; the CLR level was measured at the first sampling time (0.5 hour) for all formulations. No subjects had measurable levels of CLR (20 ng/mL) at predose time points in any treatment period. Thus, no pharmacokinetic carryover was observed in this study; these results suggest that the washout period of 7 days was adequate for total elimination of the drug between treatment periods. The concentration–time curve variability, as measured by %CV, was lower when the concentration was high, which was generally between 4 and 24 hours, but increased after 24 hours when the mean concentrations were generally lower.

The results of this study showed that CLR pharmacokinetic followed one compartment kinetics with a rapid absorption rate (1.48- 1.94 h) and long elimination phase (6.08- 7.92 h). The average plasma decay

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**Figure 2:** Mean serum concentrations vs. time profile of clarithromycin in three formulations in 12 human volunteers after administration of a single 500 mg oral dose. A: two tablets 250 mg, B: one tablet 500 mg, C: Suspension (125 mg/5 ml).
1. Maximum plasma concentrations of CLR were about 2825.00-(649.70) ng/ml. 

2. The pharmacokinetic parameters were in agreement with those of the reported mean values of total body clearance and renal clearance in adults have ranged from 29.2 to 58.1 L/h and 6.7 to 12.8 L/h, respectively [18].

3. In non-fasting healthy human subjects (males and females), peak plasma concentrations were attained within 2 to 3 hours after oral dosing. The elimination half-life of clarithromycin was about 3 to 4 hours with 250 mg administered every 12 hours but increased to 5 to 7 hours with 500 mg administered every 8 to 12 hours. The nonlinearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered every 8 to 12 hours [19].

4. These data are also in accordance with those estimated in our report. No major adverse effects were observed during the study period. Therefore, the results are indicative of a good safety profile of the regimen. However, this study is limited in that only a small number of safety parameters were evaluated in this group. This effect must be taken into account in future pharmacodynamic studies in this age group.

5. Conclusion

In this study, the in vitro dissolution and in vivo pharmacokinetics of three formulations of CLR, following administration of a single oral dose of 500 mg tablets and suspension was investigated. Plasma concentration profiles were characterized in 12 healthy volunteers and the pharmacokinetic parameters of CLR following a single oral dose administration were estimated. The 90% confidence intervals for the ratio of CLR formulations were within the 80-125% interval proposed by FDA. It was concluded that the CLR products were bio-equivalent in their rate and extent of absorption.

### Table 1: Pharmacokinetic parameters of 3 oral formulations of Clarithromycin after a 500 mg single dose (tablets 250,500 mg and 125 mg/5 ml of suspension). Values are mean ± (SD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CLR formulations</th>
<th>Klaricid (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1×500 mg Tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;, ng/ml</td>
<td>2886.67 (550.21)</td>
<td>3206.25 (489.39)</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>3.08 (1.00)</td>
<td>2.75 (1.27)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;, h</td>
<td>6.08 (1.51)</td>
<td>6.57 (1.74)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;, h</td>
<td>1.48 (0.91)</td>
<td>1.11 (0.71)</td>
</tr>
<tr>
<td>K&lt;sub&gt;h&lt;/sub&gt;</td>
<td>0.13 (0.07)</td>
<td>0.11 (0.03)</td>
</tr>
<tr>
<td>K&lt;sub&gt;h&lt;/sub&gt;</td>
<td>0.61 (0.30)</td>
<td>0.85 (0.49)</td>
</tr>
<tr>
<td>V&lt;sub&gt;L&lt;/sub&gt;, L</td>
<td>0.53 (0.21)</td>
<td>0.63 (0.31)</td>
</tr>
<tr>
<td>Cl, L/h</td>
<td>9.68 (1.57)</td>
<td>10.31 (2.01)</td>
</tr>
<tr>
<td>MRT, h</td>
<td>2825.00 (649.70)</td>
<td>2491.25 (495.04)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;, ng/ml/h</td>
<td>3152.92 (523.90)</td>
<td>3138.42 (691.61)</td>
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<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;, ng/ml/h</td>
<td>23479.73 (7253.05)</td>
<td>29494.56 (7765.30)</td>
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<tr>
<td>Tmax, h</td>
<td>9.17 (1.28)</td>
<td>7.61 (1.29)</td>
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<tr>
<td>Tmax, h</td>
<td>1.94 (1.16)</td>
<td>2.26 (1.10)</td>
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<tr>
<td>Tmax, h</td>
<td>0.10 (0.02)</td>
<td>0.09 (0.01)</td>
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<tr>
<td>Tmax, h</td>
<td>0.52 (0.32)</td>
<td>0.42 (0.28)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>0.53 (0.11)</td>
<td>0.57 (0.14)</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>0.05 (0.01)</td>
<td>0.05 (0.01)</td>
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<tr>
<td>Tmax, h</td>
<td>10.96 (1.40)</td>
<td>11.80 (1.65)</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;, ng/ml/h</td>
<td>23479.73 (5185.31)</td>
<td>23072.22 (5062.69)</td>
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<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;, ng/ml/h</td>
<td>26144.41 (5294.93)</td>
<td>26301.34 (5670.49)</td>
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<td>AUC&lt;sub&gt;MRT&lt;/sub&gt;, ng/ml</td>
<td>282799.95 (53362.66)</td>
<td>311297.68 (85460.60)</td>
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</table>

### Table 2: Parametric 90% confidence intervals for the mean pharmacokinetic parameters of CLR formulations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>90% CI</th>
<th>Test/Reference</th>
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<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.92</td>
<td>81.68-102.30</td>
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<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>0.94</td>
<td>80.76-107.32</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>0.93</td>
<td>82.13-119.79</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; difference</td>
<td>0.33</td>
<td>---</td>
</tr>
<tr>
<td>2×250 mg Tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.14</td>
<td>105.64-122.19</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>1.03</td>
<td>93.68-112.37</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>1</td>
<td>93.16-107.76</td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; difference</td>
<td>0.13</td>
<td>---</td>
</tr>
<tr>
<td>500 mg Suspension (125 mg/5 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1.03</td>
<td>94.01-111.40</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt;</td>
<td>1.05</td>
<td>95.05-115.16</td>
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<td>AUC&lt;sub&gt;0-t&lt;/sub&gt;</td>
<td>1.05</td>
<td>91.39-117.89</td>
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<td>T&lt;sub&gt;max&lt;/sub&gt; difference</td>
<td>0.38</td>
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References


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