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ORIGINAL RESEARCH ARTICLE

Effect of Empagliflozin on the Steady-State Pharmacokinetics of Ethinylestradiol and Levonorgestrel in Healthy Female Volunteers

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Abstract

Background Empagliflozin is a potent, selective inhibitor of sodium glucose cotransporter 2 in development for the treatment of patients with type 2 diabetes mellitus. Oral contraceptives may be co-administered with antidiabetic agents over long periods of time, therefore potential drug-drug interactions between oral contraceptives and antidiabetic drugs should be investigated.

Objective The effect of multiple oral doses of empagliflozin 25 mg once daily (qd) on the steady-state pharmacokinetics of the combined oral contraceptive ethinylestradiol (EE) 30 μg/levonorgestrel (LNG) 150 μg qd was investigated.

Study Design This was a phase I, open-label, two-period, fixed sequence study.

Setting The study was performed at the Human Pharmacology Centre/Department of Translational Medicine, Boehringer Ingelheim, Biberach, Germany.

Participants Eighteen healthy premenopausal women participated in the study.

Intervention There was a mandatory run-in period in which participants received EE 30 μg/LNG 150 μg qd for 21–48 days followed by a treatment-free interval of 7 days. Participants then received EE 30 μg/LNG 150 μg qd for 14 days (reference; period 1), followed by EE 30 μg/LNG 150 μg qd plus empagliflozin 25 mg qd for 7 days (test; period 2).

Main Outcome Measures The pharmacokinetics of EE and LNG at steady state based on the primary endpoints of area under the steady-state plasma concentration-time curve during a dosage interval τ ($AUC_{\tau,ss}$) and maximum steady-state plasma concentration during a dosage interval ($C_{max,ss}$) were the main outcome measures.

Results The pharmacokinetics of EE and LNG were not affected by co-administration with empagliflozin. Geometric mean ratios (90 % CI) of $AUC_{\tau,ss}$ and $C_{max,ss}$ for EE were 102.82 % (97.58, 108.35) and 99.22 % (93.40, 105.39), respectively. For LNG, these values were 101.94 % (98.54, 105.47) and 105.81 % (99.47, 112.55), respectively. The 90 % CIs were within the standard bioequivalence boundaries of 80–125 %. There were no relevant changes in the time to reach peak levels ($t_{max,ss}$) or terminal elimination half-life ($t_{½,ss}$) of EE and LNG between test and reference treatments. Ten women in each treatment had at least one adverse event (AE). Severe AEs were reported by three women in the reference period and one woman in the test period. There were no serious AEs or premature discontinuations.

Conclusion The combination of EE 30 μg/LNG 150 μg and empagliflozin 25 mg was well tolerated. Based on standard bioequivalence criteria, empagliflozin had no effect on the pharmacokinetics of EE and LNG, indicating that no dose adjustment of EE 30 μg/LNG 150 μg is required when empagliflozin is co-administered.

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1 Background

The prevalence of diabetes mellitus in women is increasing, and approximately 90–95 % of women with diabetes have type 2 diabetes (T2DM) [1, 2]. Global trends in diabetes prevalence from 1980 to 2008 indicate that the age-standardized prevalence of diabetes in women rose from 7.5 % in 1980 (equating to ~76 million women) to 9.2 % in 2008 (equating to ~173 million women) [1]. The progressive nature of T2DM means that currently available therapies, which work via insulin-dependent mechanisms, are often ineffective for long-term glycemic control [3]. In addition, the use of anti-diabetic agents may be limited by adverse effects such as gastrointestinal events, hypoglycemia and weight gain [3]. There is a need for novel antidiabetic agents with an acceptable tolerability profile that can be added to existing agents to improve glycemic control in patients with T2DM.

The kidney plays a pivotal role in glucose homeostasis. In healthy individuals, the kidney is responsible for filtering approximately 180 g of glucose per day [4]. Almost all of this filtered glucose is reabsorbed from the glomerular filtrate into the bloodstream by the sodium glucose co-transporters (SGLTs), which are found on the luminal surface of epithelial cells lining the S1, S2 (SGLT2) and S3 (SGLT1) segments of the proximal tubule of the nephron [4]. SGLT2 is responsible for approximately 90 % of renal glucose reabsorption, with the remaining 10 % being reabsorbed via SGLT1 [4]. In patients with T2DM, SGLT2 expression is upregulated [5], and the amount of glucose reabsorbed by the kidneys is increased [6]. This increased glucose reabsorption contributes to the development and maintenance of hyperglycemia [6]. Inhibition of SGLT2 results in reduced renal glucose reabsorption, leading to increased urinary glucose excretion and a reduction in hyperglycemia [6]. Thus, SGLT2 inhibition is an attractive target for the treatment of T2DM.

Empagliflozin is an orally available, potent, selective inhibitor of SGLT2 [7] in development for the treatment of T2DM. By inhibiting SGLT2, empagliflozin has been shown to promote urinary glucose excretion [8–10] and reduce fasting plasma glucose levels [8, 9, 11, 12]. In addition, empagliflozin is well tolerated in both healthy subjects [10] and in patients with T2DM [11, 12]. In vitro studies have shown that empagliflozin does not inhibit, inactivate or induce the major cytochrome P450 (CYP) isozymes (data on file); therefore, no CYP-mediated drug-drug interactions are expected.

Ethinylestradiol (EE) 30 μg/levonorgestrel (LNG) 150 μg is indicated for use as a combined oral contraceptive (COC) [13]. EE undergoes CYP 3A-mediated hydroxylation in the liver [14], and is excreted in urine (40 %) and bile (60 %) [13]. LNG is metabolized to glucuronide and sulfate conjugates, which are then excreted in the urine (~45 %) and the feces (~32 %) [15].

As oral contraceptives may be co-administered with antidiabetic agents over long periods of time, potential drug-drug interactions between oral contraceptives and antidiabetic drugs should be investigated. The objective of this study was to investigate the effects of multiple oral doses of empagliflozin 25 mg on the steady-state pharmacokinetics of EE 30 μg/LNG 150 μg in healthy premenopausal women.

2 Methods

2.1 Participants

Premenopausal healthy women aged 18–39 years with a body mass index (BMI) of 18.5–27 kg/m^2 were eligible to participate in the study. Major exclusion criteria included: repeated measurements of systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg; gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders; systemic or anticipated use of drugs known to act via the CYP enzyme system; use of an oral contraceptive-containing intrauterine device, depot injection or contraceptive implants; drug/alcohol abuse or regularly smoking more than three cigarettes/day; history of migraine, pancreatitis, thrombotic events; any medical or laboratory results considered clinically relevant. All participants gave written informed consent prior to any study-related procedure.

2.2 Study Design

The study protocol was approved by the local Independent Ethics Committee, the State Medical Council of Baden-Württemberg (Landesärztekammer Baden-Württemberg), Stuttgart, Germany, and the German Competent Authority—the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte), Bonn, Germany. The study was conducted at the Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany, in accordance with the Declaration of Helsinki (1996) and the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines.

This was an open-label, two-period, fixed sequence, phase I study. A fixed sequence study design was chosen to ensure that pharmacokinetic parameters were determined at the same time point in the menstrual cycle of all subjects. Screening examinations were performed at visit 1, between days −80 and −55. A run-in phase of 21–48 days, during which subjects received EE 30 μg/LNG 150 μg

(Microgynon®, Bayer Vital GmbH, Germany) once daily (qd) until day −8, was mandatory. EE 30 μg/LNG 150 μg was then withdrawn for 7 days (days −7 to −1) to induce bleeding, after which treatment was initiated (day 1). On days 1–14 (reference period), subjects were treated with one EE 30 μg/LNG 150 μg tablet qd. On days 15–21 (test period), subjects received one EE 30 μg/LNG 150 μg tablet qd in combination with one empagliflozin 25 mg tablet qd. On pharmacokinetic sampling days (days 14 and 21), subjects were admitted to the trial site and kept under close medical surveillance for at least 24 h.

The primary endpoints of this study were the area under the steady-state plasma concentration-time curve during a dosage interval τ ($AUC_{\tau,ss}$) and maximum steady-state plasma concentration during a dosage interval τ ($C_{max,ss}$) of EE and LNG. Secondary endpoints included time to reach $C_{max,ss}$ ($t_{max,ss}$) and terminal elimination half-life at steady state ($t_{½,ss}$) of EE and LNG.

2.3 Safety Assessments

Adverse events (AEs) were monitored throughout the study and coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 14.0). The frequency of AEs, vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECGs), physical examinations, clinical laboratory tests (hematology, differentials, coagulation, electrolytes, enzymes, substrates, urine pH, C-reactive protein) and an overall tolerability assessment by the investigator ('good,' 'satisfactory,' 'not satisfactory' or 'bad') formed the basis of the safety evaluation. Vital signs and ECG were measured and a physical examination performed during the screening visit and at the end-of-study examination (3–10 days after the last study drug administration). Clinical laboratory tests were conducted at the screening visit, on the first and last day of dosing of EE 30 μg/LNG 150 μg alone and at the end-of-study examination.

2.4 Sample Collection and Analysis

A total of 300 mL of blood was collected for the pharmacokinetic and safety evaluations; approximately 230 mL of blood was collected for the measurement of empagliflozin, EE and LNG plasma concentrations. For quantification of empagliflozin plasma concentrations, 2.7 mL of blood was taken from a forearm vein in an ethylenediaminetetraacetic acid (EDTA) blood drawing tube; 7.5 mL of blood was drawn for the quantification of EE and LNG plasma concentrations. EE and LNG pharmacokinetic assessments were carried out on days 14 and 21 at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h post-dose. Pre-dose plasma concentrations of EE and LNG (reference period: days 12, 13 and 14; test period: days 19, 20 and 21) were measured to determine attainment of steady state and pre-dose plasma concentrations of empagliflozin during test treatment (days 19, 20, and 21) and were used to confirm empagliflozin drug exposure. All samples were centrifuged for 10 min at approximately 2,000–4,000 *g* and 4–8 °C within 60 min of collection. The EDTA plasma obtained was stored at −20 °C until it was shipped on dry ice for analysis.

Plasma concentrations of empagliflozin, EE and LNG were determined using a validated high-pressure liquid chromatography-tandem mass spectrometry assay. Using a sample volume of 0.15 mL, the lower limit of quantification for empagliflozin in plasma was 1.11 nmol/L with linearity to 1,110 nmol/L. The limits of quantification for EE and LNG were 5–500 pg/L and 0.1–10 ng/mL, respectively. Results were calculated using peak area ratios, and calibration curves were created using weighted ($1/x^2$) quadratic regression.

2.5 Pharmacokinetic Assessments

The linear trapezoidal rule was used for ascending concentrations and the log-trapezoid rule for descending concentrations to calculate $AUC_{\tau,ss}$. The plasma concentration-time profiles of each subject were used to determine $C_{max,ss}$ and $t_{max,ss}$ directly. The equation $t_{½} = \ln 2/\lambda_z$ was used to calculate $t_{½,ss}$, where λ_z is the terminal rate constant in plasma. Non-compartmental pharmacokinetic analyses of the plasma concentration-time data were carried out using WinNonlin® software (Version 5.2; Pharsight Corp., Mountain View, CA, USA).

2.6 Statistical Analysis

The primary analysis was based on the pharmacokinetic analysis set (all subjects who provided at least one observation for at least one primary pharmacokinetic endpoint, with no relevant protocol violations). Safety analyses were performed on the treated set (all subjects who received at least one dose of study medication). An analysis of variance (ANOVA), which included 'subject' as a random effect and 'treatment' as a fixed effect, was performed on log-transformed (natural logarithm) $AUC_{\tau,ss}$ and $C_{max,ss}$. The difference between the expected means for log(test) versus log(reference) was estimated by the difference in the corresponding least square means (point estimate), and 2-sided 90 % confidence intervals (CIs) based on the t-distribution were calculated. These quantities were then back-transformed to the original scale to give the geometric mean ratio with 90 % CIs for the response under test versus reference.

3 Results

3.1 Study Population

Eighteen women entered the study and all completed the study according to the protocol. All participants were healthy, white premenopausal women with a median (range) age of 26 (20–37) years and a median (range) BMI of 22.8 (19.4–26.0) kg/m^2. Thirteen subjects (72 %) were non-smokers. All women were included in both analysis sets.

3.2 Pharmacokinetic Results

EE and LNG plasma concentrations were at steady state at day 14 of treatment with EE 30 μg/LNG 150 μg alone and at day 21 with combined treatment. Following oral administration of EE 30 μg/LNG 150 μg alone, EE and LNG were rapidly absorbed, with a median (range) $t_{max,ss}$ of 1.3 (1.0–3.1) and 1.0 (0.5–1.5) h, respectively. Mean [% coefficient of variation (CV)] $t_{½,ss}$ was 15.9 (32.4) h for EE and 38.6 (34.0) h for LNG (Table 1). Plasma concentration-time profiles of EE and LNG were similar whether EE 30 μg/LNG 150 μg was administered alone or in combination with empagliflozin (Figs. 1a, b). EE $AUC_{\tau,ss}$ values were similar when administered alone or in combination with empagliflozin, and there were no changes in $C_{max,ss}$ on co-administration with empagliflozin. LNG $AUC_{\tau,ss}$ and $C_{max,ss}$ were also similar on co-administration with empagliflozin versus administration of EE 30 μg/LNG 150 μg alone (Table 1). The geometric mean ratios (GMRs) of $AUC_{\tau,ss}$ and $C_{max,ss}$ for EE and LNG were comparable when EE 30 μg/LNG 150 μg was administered alone or in combination with empagliflozin (Table 2). The 90 % CIs of the GMRs were all within the accepted bioequivalence limits of 80–125 %.

Mean trough concentrations of empagliflozin were similar on days 19–21 and ranged from 51.0 to 52.7 nmol/L, indicating that empagliflozin plasma concentrations were at steady state.

3.3 Safety and Tolerability

Co-administration of EE 30 μg/LNG 150 μg and empagliflozin 25 mg was well tolerated. The overall frequency of volunteers with any AE was the same in volunteers treated with EE 30 μg/LNG 150 μg alone (55.6 %; 10/18) or in combination with empagliflozin 25 mg (55.6 %; 10/18), and there were no serious AEs or AEs leading to study discontinuation. The frequency of volunteers with severe AEs was 16.7 % (3/18) for those treated with EE 30 μg/LNG 150 μg alone and 5.6 % (1/18) for volunteers treated with EE 30 μg/LNG 150 μg in combination with empagliflozin. Investigator-defined drug-related AEs were reported in 11.1 % (2/18) of volunteers treated with EE 30 μg/LNG 150 μg alone and 16.7 % (3/18) of those receiving combination treatment. The most commonly reported AE was headache, in four volunteers [three during treatment with EE 30 μg/LNG 150 μg alone (16.7 %) and one during combined treatment (5.6 %)]. All incidences of headache were classified as severe AEs but were not considered to be related to study medication by the investigator. Other common AEs reported during treatment with EE 30 μg/LNG 150 μg alone and in combination with empagliflozin, respectively, were dizziness (11.1 and 5.6 % of volunteers), oropharyngeal pain (0 and 11.1 %), myalgia (11.1 and 0 %), oral herpes (0 and 11.1 %) and nausea (5.6 and 5.6 %).

There were no clinically relevant changes in laboratory parameters, vital signs or ECG recordings. At the end of the treatment period, the overall tolerability assessment by the investigator was considered as 'good' in 17 subjects and 'satisfactory' in one subject in both treatments.

Table 1 Pharmacokinetic parameters of EE and LNG after oral administration of EE 30 μg/LNG 150 μg qd alone and in combination with empagliflozin 25 mg qd

Parameter	EE 30 μg/LNG 150 μg alone (n = 18)	EE 30 μg/LNG 150 μg + empagliflozin 25 mg (n = 18)
EE		
$AUC_{\tau,ss}$ (pg·h/mL)	932 (24.4)	956 (24.2)
$C_{max,ss}$ (pg/mL)	99.0 (17.0)	99.0 (22.1)
$t_{max,ss}$ (h)	1.3 (1.0–3.1)	1.5 (1.0–4.0)
$t_{½,ss}$ (h)	15.9 (32.4)	16.7 (21.7)
LNG		
$AUC_{\tau,ss}$ (ng·h/mL)	99.6 (38.6)	102 (41.2)
$C_{max,ss}$ (ng/mL)	8.2 (27.0)	8.7 (26.5)
$t_{max,ss}$ (h)	1.0 (0.5–1.5)	1.0 (0.5–1.5)
$t_{½,ss}$ (h)	38.6 (34.0)	40.8 (47.4)

Data are presented as arithmetic mean (% CV) except $t_{max,ss}$, which is presented as median (range)

EE ethinylestradiol, *LNG* levonorgestrel, $AUC_{\tau,ss}$ area under the plasma concentration-time curve over a uniform dosing interval τ at steady state, $C_{max,ss}$ maximum steady-state plasma concentration, *CV* coefficient of variation, *qd* once daily, $t_{max,ss}$ time to $C_{max,ss}$, $t_{½,ss}$ terminal elimination half-life at steady state

4 Discussion

This study evaluated the effects of multiple oral doses of empagliflozin 25 mg on the steady-state pharmacokinetics of the COC, EE 30 μg/LNG 150 μg. Based on standard criteria, empagliflozin had no effect on the pharmacokinetics of EE or LNG in healthy premenopausal women. The 90 % CIs of the GMRs for $AUC_{\tau,ss}$ and $C_{max,ss}$ were

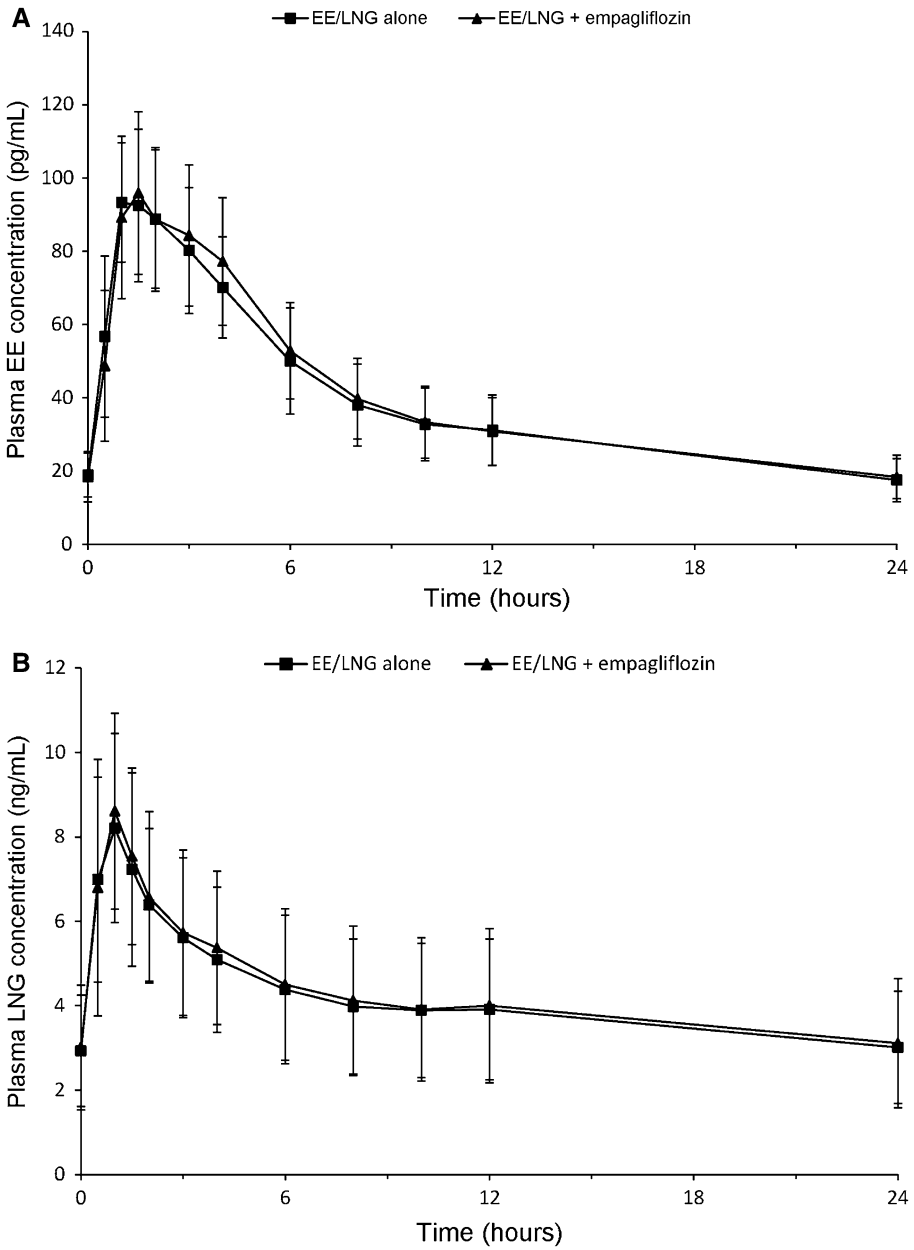

Fig. 1 Arithmetic mean (± SD) plasma concentrations of **a** EE and **b** LNG, after oral administration of EE 30 µg/LNG 150 µg qd alone and in combination with empagliflozin 25 mg qd. *EE* ethinylestradiol, *LNG* levonorgestrel, *qd* once daily, *SD* standard deviation

contained within the standard acceptance limits for bioequivalence of 80–125 %. The steady-state pharmacokinetic results for EE and LNG observed in this study are comparable to previously published results [16, 17]. Consistent with previous studies in healthy volunteers and patients with T2DM, empagliflozin steady state was reached by day 5 [18, 19]. In addition, the geometric mean plasma concentrations of empagliflozin at trough on days 19–21 of combined treatment were broadly comparable with plasma concentrations measured in previous studies [18, 19].

EE is a substrate and a moderate inhibitor of CYP3A4 [20, 21], and also an inhibitor of CYP1A2 [21], CYP2C19 [22] and CYP2B6 [21]. As both EE and LNG undergo hepatic metabolism, interactions with hepatic enzyme inducers can lead to decreased contraceptive efficacy [23, 24]. Data from in vitro studies (data on file), a recent drug-drug interaction study of empagliflozin with the CYP3A substrate, simvastatin [25], and the present study suggest that empagliflozin does not inhibit the CYP3A enzyme system.

The co-administration of empagliflozin 25 mg and EE 30 µg/LNG 150 µg was well tolerated. The most common AE observed in this study was headache, although these events were not considered related to treatment by the investigator.

Table 2 Comparison of primary pharmacokinetic parameters of EE and LNG after oral administration of EE 30 μg/LNG 150 μg qd alone (reference) and in combination with empagliflozin 25 mg qd (test)

Parameter	GMR test/ reference (%)	90 % CI for GMR		% gCV
		Lower limit (%)	Upper limit (%)	
EE				
$AUC_{\tau,ss}$	102.8	97.6	108.4	9.0
$C_{max,ss}$	99.2	93.4	105.4	10.4
LNG				
$AUC_{\tau,ss}$	101.9	98.5	105.5	5.9
$C_{max,ss}$	105.8	99.5	112.6	10.7

EE ethinylestradiol, *LNG* levonorgestrel, $AUC_{\tau,ss}$ area under the plasma concentration-time curve over a uniform dosing interval τ at steady state, *CI* confidence interval, $C_{max,ss}$ maximum steady-state plasma concentration, *gCV* geometric coefficient of variation, *GMR* geometric mean ratio, *qd* once daily

5 Conclusion

The combination of empagliflozin 25 mg and EE 30 μg/LNG 150 μg was well tolerated. Based on standard bioequivalence boundaries, the steady-state pharmacokinetics of EE and LNG were not affected by co-administration with empagliflozin in healthy premenopausal women, indicating that no dose adjustment of EE 30 μg/LNG 150 μg is required when co-administered with empagliflozin.

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