Office of Clinical Pharmacology Review

NDA Number	212895
Link to EDR	\\cdsesub1\evsprod\nda212895
Submission Date	February 28, 2019
Submission Type	Standard review
Brand Name	Conjupri
Generic Name	Levamlodipine
Dosage Form and Strength	Tablet; 1.25 mg, 2.5 mg and 5 mg
Route of Administration	Oral
Proposed Indication	Treatment of hypertension
Applicant	CSPC Ouyi Pharmaceutical Co. Ltd.
Associated IND	IND124947
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1. EXECUTIVE SUMMARY

CSPC Ouyi Pharmaceutical Co. Ltd is seeking approval for Conjupri (levamlodipine), a calcium channel blocker for the treatment of hypertension via 505(b)(2) new drug application. This application relies on the agency's previous finding of safety and efficacy of the reference product, Norvasc® (amlodipine besylate; NDA019787) tablets.

Amlodipine is a racemic mixture of dextroamlodipine and levoamlodipine. Literature reports indicate that levoamlodipine is primarily responsible for calcium channel antagonism. Furthermore, levoamlodipine does not convert to dextroamlodipine and vice versa in humans. Therefore, to establish the pharmacokinetic (PK) bridge, the applicant has submitted a pivotal bioavailability (BA) study comparing PK of levoamlodipine between 5 mg Conjupri (levamlodipine tablet - test) and 10 mg Norvasc (racemic amlodipine besylate tablet - reference) under fasting condition. A food effect study was also conducted as part of the pivotal BA study.

This review primarily addresses (i) PK bridging for levoamlodipine between the proposed Conjupri tablet and Norvasc tablet in healthy subjects, (ii) effect of food on Conjupri tablet.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP I) finds the PK bridge between the proposed Conjupri tablet and the reference product, Norvasc acceptable. Therefore, the applicant can rely on safety and effectiveness of Norvasc for the treatment of hypertension. Based on these findings, the review team recommends the approval of Conjupri tablet for the treatment of hypertension.

1.2 Post-Marketing Requirements and Commitments

None

1.3 Key Clinical Pharmacology Findings

- Under fasting condition, the geometric mean ratio (GMR: Conjupri/Norvasc) and 90% confidence intervals (CIs) for levoamlodipine PK parameters including peak plasma concentration [Cmax: 1.02 (0.97-1.07)], area under the plasma concentration-time curve [$AUC_{0\text{-tlast}}$: 0.97 (0.94-1.00)] and $AUC_{0\text{-inf}}$ [0.96 (0.93-1.00)] are within the bioequivalence range of 0.8 to 1.25. This shows that 5 mg Conjupri tablet is bioequivalent to 10 mg Norvasc tablet. Therefore, the applicant can rely on the findings of safety and effectiveness of Norvasc for the treatment of hypertension.

- Food did not affect the PK of Conjupri tablet. This observation is similar to that reported for Norvasc.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacokinetics

Absorption

After oral administration, Conjupri reaches peak plasma concentrations between 6 and 12 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. Absolute bioavailability ranges from 64% to 90%. Food did not affect the bioavailability of Conjupri.

Distribution

Approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Metabolism

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic CYP3A metabolism with 10% of the parent compound and 60% of the metabolites excreted in to urine.

Excretion

Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The initial dose is 2.5 mg once daily. The dose can be titrated over 7 to 14 days based on blood pressure goals. However, if clinically warranted, titration can be done more rapidly, provided the patient is assessed frequently. The maximum dose is 5 mg.

Initiate at 1.25 mg when it is used along with other antihypertensive medications.

The effective antihypertensive oral dose in pediatric patients ages 6–17 years is 1.25 mg to 2.5 mg once daily.

2.2.2 Therapeutic individualization

Elderly patients and patients with severe hepatic insufficiency: Because levoamlodipine is extensively metabolized in the liver, elderly patients and patients with severe hepatic insufficiency showed a reduced clearance and increase in AUC of 40-60%. Therefore, a lower initial dose of 1.25 mg once daily is recommended. Adjust the dose based on blood pressure goals.

2.3 Outstanding Issues

None.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product

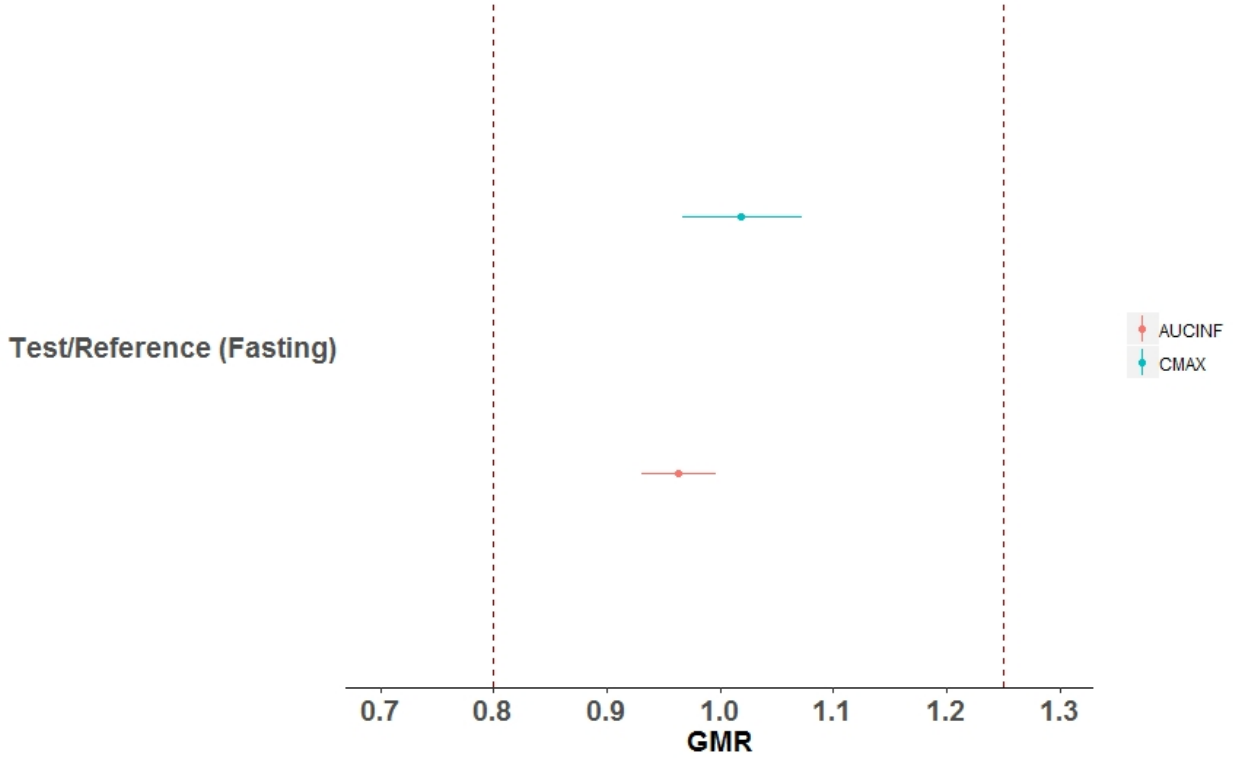
Norvasc, a racemic amlodipine besylate was approved for the treatment of hypertension. Given that levoamlodipine is primarily responsible for calcium channel antagonism, CSPC Ouyi Pharmaceutical Co. Ltd has developed Conjupri for the treatment of hypertension. Conjupri can be used either alone or in combination with other antihypertensive medications.

3.2 Clinical Pharmacology Review Questions

3.3.1 Is there an appropriate PK bridge for levoamlodipine between Conjupri 5 mg tablet (test) and Norvasc 10 mg tablet (reference)?

Pharmacokinetics of levoamlodipine was compared between Conjupri 5 mg tablet and Norvasc 10 mg tablet under fasting condition in healthy subjects. The GMR (Conjupri/Norvasc) and 90% CI for the PK parameters, C_{max} and $AUC_{0\text{-}inf}$ of levoamlodipine are within the bioequivalence range of 0.8-1.25 (See Appendix, Table 2). This suggests that 5 mg Conjupri tablet is bioequivalent to 10 mg Norvasc tablet (Figure 1). Between subject variability in C_{max} and $AUC_{0\text{-}inf}$ of levoamlodipine are also similar between Conjupri and Norvasc (See Appendix, Table 2). These results establish a pharmacokinetic bridge for the proposed Conjupri tablet to the reference product, Norvasc.

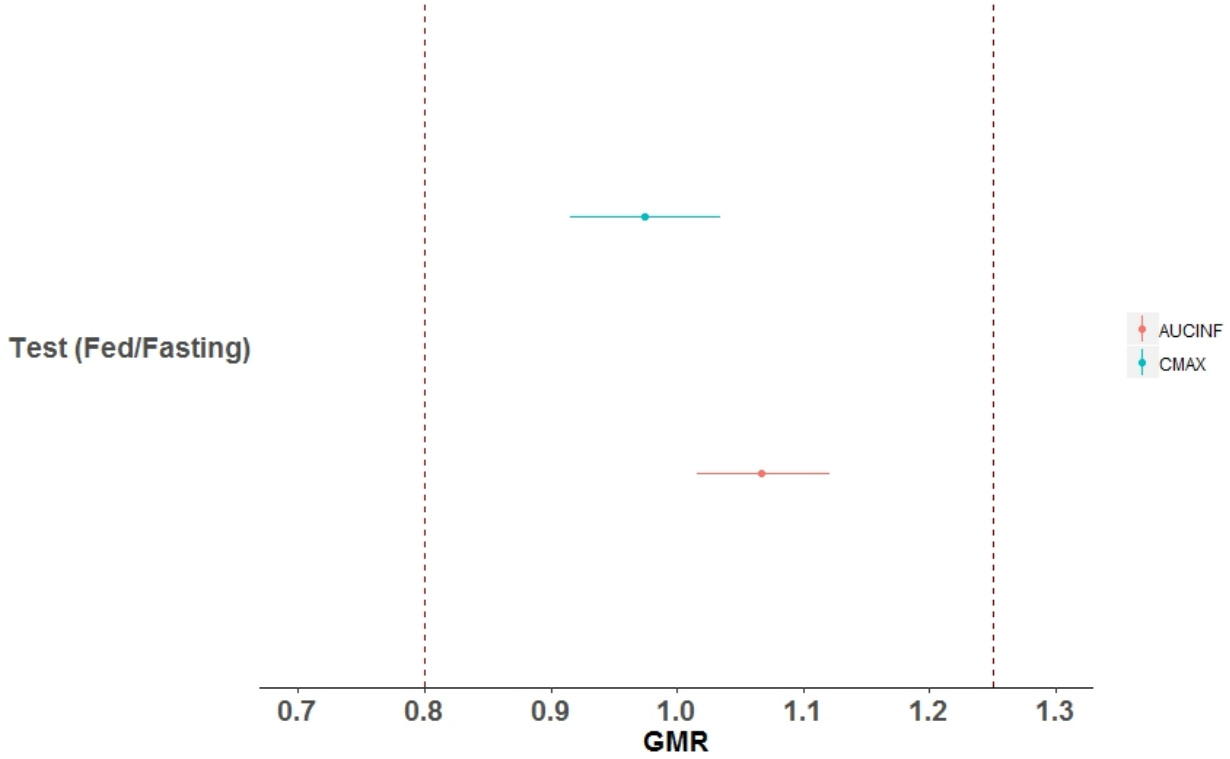
Figure 1 shows the geometric mean ratio (GMR) and 90% CI for levoamlodipine between Conjupri 5 mg tablet (test) and Norvasc 10 mg tablet (reference) under fasting condition.



3.3.2 What is the effect of food on the exposures of Conjupri? Does this product require specific dosing instruction with regard to food in the product insert?

The effect of food on the PK of Conjupri 5 mg tablet was evaluated in healthy subjects. The GMR (Fed/Fasting) and 90% CI for the PK parameters, C_{max} and $AUC_{0\text{-}inf}$ of Conjupri are within the bioequivalence range of 0.8-1.25 (See Appendix, Table 3). This suggests that food did not influence the C_{max} and $AUC_{0\text{-}inf}$ of Conjupri (Figure 2). The food effect results observed in this study for Conjupri are similar to those reported for Norvasc (Ref: Norvasc United States Package Insert). Therefore, Conjupri can be administered without regards to food.

Figure 2 represents the GMR and 90% CI for levoamlodipine following administration of Conjupri 5 mg tablet under fed and fasting condition.



4. APPENDICES

This section includes information on bioanalytical method validation and performance, and brief description of study design and detailed pharmacokinetic results from the pivotal bioavailability study submitted in this application.

4.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of levoamlodipine were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. It was found that:

- The precision and accuracy values (Table 1) of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were within ±15% (±20% at the LLOQ).
- Levoamlodipine was found to be stable in plasma after at least three freeze-thaw cycles at -80˚ C, at room temperature in human plasma over at least 24 h (short-term), in whole blood at room temperature over 2 h, and at auto-sampler storage at 4˚ C for at least 98 h.
- The QC sample accounting for dilution showed an acceptable precision (<2%) and bias (≤2%). The carry over effects were negligible for levoamlodipine.
- More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable.

Note: Bioanalysis of levoamlodipine was performed at (b) (4). Because approval of the Conjupri tablet relies on bridging PK to the reference product, Norvasc, a relative BA study LAM-US-101, was considered important. Therefore, OCP requested a routine inspection of the clinical and bioanalytical site of this study via Office of Study Integrity and Surveillance (OSIS). Both clinical and bioanalytical sites were inspected, and the results of the inspection revealed no issues (NDA212895, Bioequivalence Establishment Inspection Report Reviews, DARRTS, 05/14/2019 and 09/06/2019).

Table 1. Summary of bioanalytical methods and validation in each clinical study

Bioanalytical study no	Facility	Analytical method	Analyte	Sample volume	Analytical range (ng/ml)	Precision (CV %)	Accuracy (%)
1802037	(b) (4)	LC-MS/MS	Levoamlodipine	100 µl	0.05-5	≤8.0%	98.6 - 101.0

4.2 Clinical PK Assessments

Study LAM-US-101:

Part 1: Relative bioavailability of levoamlodipine between Conjupri 5 mg tablet (test) and Norvasc 10 mg tablet (reference) in healthy subjects under fasting condition.

This relative bioavailability study was conducted to evaluate whether the PK of levoamlodipine is similar between 5 mg Conjupri tablet and 10 mg Norvasc tablet in healthy adults under fasting condition. Also, to understand the effect of high-fat/high calorie meal on the PK of Conjupri in healthy subjects.

Sample size was determined based on an approximate between subject variability of 20%, a within subject variability was calculated to be 14% for C_{max} and 11% for AUC_{inf}, respectively. Considering a drop-out rate of 20%, a sample size of approximately 27 completed subjects were required for the proposed bioequivalence study.

A single center, randomized, single dose, open-label, two treatment, two period crossover study in healthy adults under fasting condition. A total of 36 subjects were randomized to treatment period sequence 1/2 or 2/1 (18 subjects per sequence). All 36 subjects completed period 1. However, two subjects (one from Conjupri and one from Norvasc treatment) withdrew from participating the study prior to the completion of period 2. Overall, 35 subject per treatment completed the study and were included for the PK analysis.

Treatment A (test): a single oral dose of 5 mg Conjupri tablet under fasting condition

Treatment B (reference): a single oral dose of 10 mg Norvasc tablet under fasting condition

At least 14 days wash-out period after the last dose was given between treatment period 1 and period 2. Similarly, atleast 14 days after the last dose, subjects who completed part I were rolled over to part 2.

Part 2: Effect of food on the PK of Conjupri in healthy subjects.

A single-arm, open-label, single dose study to evaluate the effect of food on the PK of 5 mg Conjupri tablet in healthy subjects under high-fat/high-calorie meal. A total of 30 subjects enrolled and 28 subjects completed the study. One subject withdrew from the study during the course of PK sample collection over a period of 3 h, and the other subject for unknown reason, all concentrations of levoamlodipine were below the limit of quantitation except that from one time point (at 9 hours). Both subjects were removed based on an incomplete PK profile, and 28 subjects were included for the PK analysis of levoamlodipine in the fed state.

The high-fat/high-calorie meal contains approximately 150, 250 and 500-600 calories from protein, carbohydrate and fat, respectively.

Plasma concentrations of levoamlodipine was quantified using a validated LC-MS/MS assay.

Figure 3 shows the mean plasma concentration-time profile of levoamlodipine following single oral administration of 5 mg Conjupri tablet and 10 mg Norvasc tablet in healthy subjects under fasting condition. Data represents mean ± SD.

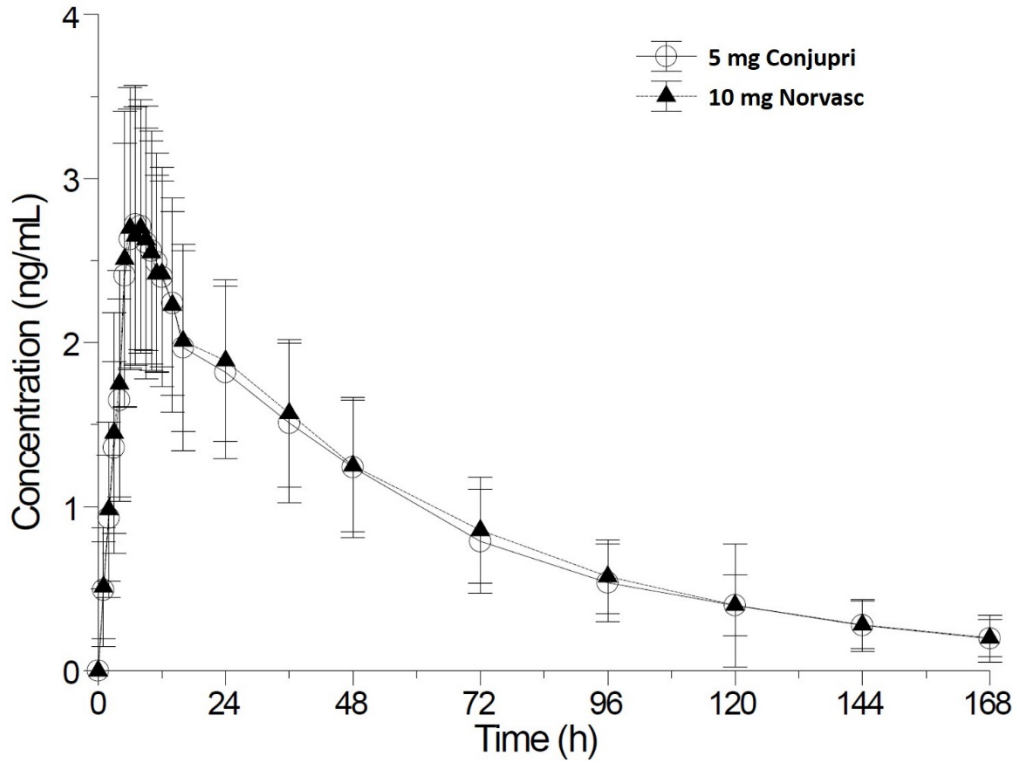


Table 2 shows the pharmacokinetic parameters and GMR (90% CI) of levoamlodipine following single oral administration of 5 mg Conjupri tablet and 10 mg Norvasc tablet in healthy subjects under fasting condition.

	Levoamlodipine		
Parameter	**Conjupri [Test (T)] N = 35**	**Norvasc [Reference (R)] N = 35**	**Geometric mean ratio [T/R%] (90% CI)**
C_{max} (ng/mL)	2.9 (28)	2.9 (26)	102 (97-107)
$AUC_{0\text{-}tlast}$ (ng*h/mL)	142 (35)	148 (30)	97 (94-100)
$AUC_{0\text{-}inf}$ (ng*h/mL)	153 (40)	160 (32)	96 (93-100)
t_{max}@ (h)	8.0 (5-14)	7.0 (5-12)	-
$t_{1/2}$ (h)	43 (19)	44 (21)	-

Values represent geometric mean (% CV); @ indicates median (range)

Figure 4 shows the mean plasma concentration-time profile of levoamlodipine following single oral administration of 5 mg Conjupri tablet in healthy subjects under fed and fasting condition. Data represents mean ± SD.

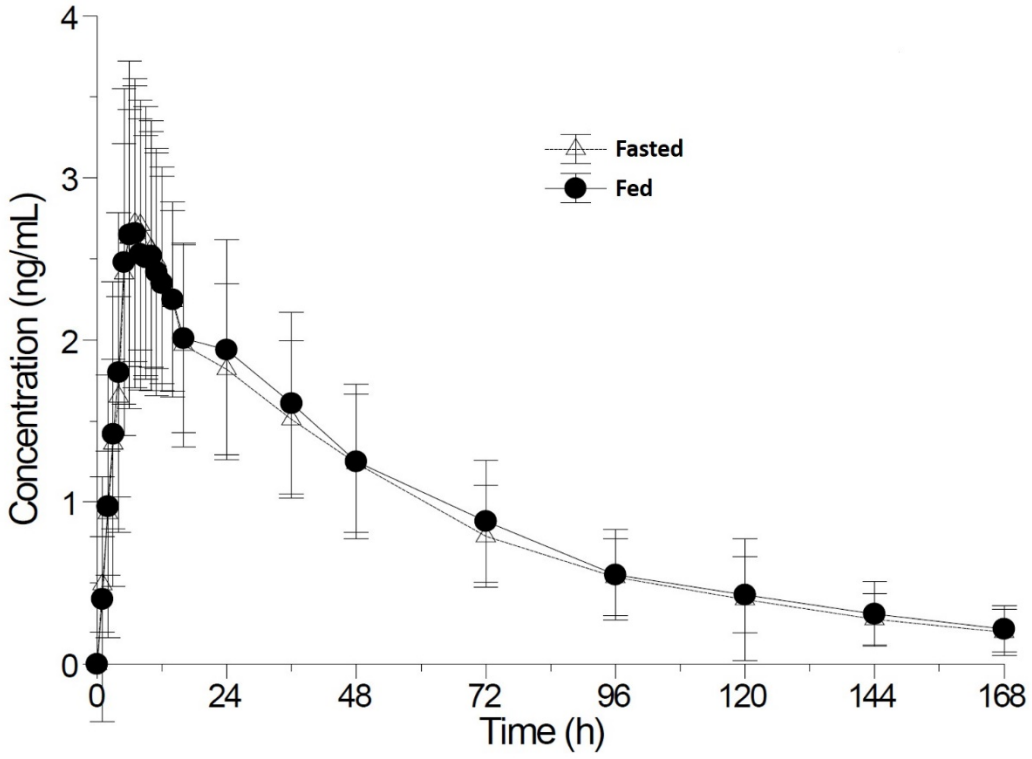


Table 3 shows the pharmacokinetic parameters and GMR (90% CI) of levoamlodipine following single oral administration of 5 mg Conjupri tablet in healthy subjects under fed and fasting condition.

	Levoamlodipine		
Parameter	**Fed [Test (T)] N = 28**	**Fasting [Reference (R)] N = 35**	**Geometric mean ratio [T/R] (90% CI)**
C_{max} (ng/mL)	2.8 (34)	2.9 (28)	97 (92-104)
$AUC_{0\text{-}tlast}$ (ng*h/mL)	147 (37)	142 (35)	106 (101-111)
$AUC_{0\text{-}inf}$ (ng*h/mL)	160 (40)	153 (40)	107 (102-112)
t_{max}@ (h)	8 (5-24)	8 (5-14)	-
$t_{1/2}$ (h)	44 (21)	43 (19)	-

Values represent geometric mean (% CV); @ indicates median (range)

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