1. NAME OF THE MEDICINAL PRODUCT

AMLOZEST 10MG TABLETS

2. Generic Name

AMLODIPINE BESILATE

3. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet Contains:

Amlodipine Besilate BP.....10 mg

Excipients .....QS

4. PHARMACEUTICAL FORM

Solid Oral Dosage Form. Film coated Tablets

Clinical particulars

4.1 Therapeutic indications

Hypertension

Amlodipine is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Chronic Stable Angina

Amlodipine is indicated for the treatment of chronic stable angina. Amlodipine may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)

Amlodipine is indicated for the treatment of confirmed or suspected vasospastic angina. Amlodipine may be used as monotherapy or in combination with other antianginal drugs.

4.2 Posology and method of administration

Tablets should be swallowed whole with sufficient water. Amlodipine may be administered with or without food.

Posology

Adults: The usual initial antihypertensive oral dose of amlodipine is 5 mg once daily with a maximum dose

of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine to other antihypertensive therapy. Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.
The recommended dose for chronic stable or vasospastic angina is 5-10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect.

Children: The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients.

Co-administration with Other Antihypertensive and/or Antianginal Drugs: amlodipine has been safely administered with thiazides, ACE inhibitors, beta-blockers, long-acting nitrates, and/or sublingual nitroglycerin.

4.3 Contraindications

Amlodipine is contraindicated in patients with known sensitivity to amlodipine.

4.4 Special warnings and precautions for use

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS

General: Since the vasodilation induced by Amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering Amlodipine, particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. Amlodipine (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure).

Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal: Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure: Since Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering Amlodipine to patients with severe hepatic impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions: *In vitro* data indicate that Amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of other agents on Amlodipine.

CIMETIDINE: Co-administration of Amlodipine with cimetidine did not alter the pharmacokinetics of Amlodipine.

GRAPEFRUIT JUICE: Co-administration of 240 ml of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Antacid: Co-administration of the antacid with a single dose of Amlodipine had no significant effect on the pharmacokinetics of Amlodipine.

SILDENAFIL: A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of Amlodipine. When Amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of Amlodipine on other agents.

ATORVASTATIN: Co-administration of multiple 10 mg doses of Amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

DIGOXIN: Co-administration of Amlodipine with digoxin did not change serum digoxin levels or

digoxin renal clearance in normal volunteers.

ETHANOL (alcohol): Single and multiple 10 mg doses of Amlodipine had no significant effect on the pharmacokinetics of ethanol.

WARFARIN: Co-administration of Amlodipine with warfarin did not change the warfarin prothrombin response time.

In clinical trials, Amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

4.6 Pregnancy and Lactation

Pregnancy

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding

It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility.

4.7 Effects on ability to drive and use machines

Amlodipine may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines.

4.8 Undesirable effects

Common side effects include swelling of ankles or legs, sleepiness, stomach pain, nausea, dizziness, a hot or warm feeling in your face (flushing), irregular or fast heart rate, and problems with muscle movement.

Adverse Effect

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with Amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with Amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing Amlodipine (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of Amlodipine due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies

	AMLODIPINE (%) (N=1730)	PLACEBO (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as shown in the following table:

	AMLODIPINE		PLACEBO	
Adverse Event	Male=% (N=1218)	Female=% (N=512)	Male=% (N=914)	Female=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

Musculoskeletal System: arthralgia, arthrosis, muscle cramps, myalgia.

Psychiatric: sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.

Respiratory System: dyspnea, epistaxis.

Skin and Appendages: angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Special Senses: abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.

Urinary System: micturition frequency, micturition disorder, nocturia.

Autonomic Nervous System: dry mouth, sweating increased.

Metabolic and Nutritional: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred in <0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal

visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and he-patic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hos-pitalization have been reported in association with use of amlodipine.

4.9 Overdose

Single oral doses of amlodipine equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more time times the maximum recommended human dose on a mg/m ^{2} basis) caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of Amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As Amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Mechanism of action: Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.
The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but Amlodipine reduces total ischaemic burden by the following two actions:
1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2. The mechanism of action of Amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilation increases myocardial oxygen delivery in patients with coronary artery spasm (prinzmetals or variant angina).

Hemodynamics: Following administration of therapeutic doses to patients with hypertension, Amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with Amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90-104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/-2 mmHg).

In hypertensive patients with normal renal function, therapeutic doses of Amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with Amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, Amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving Amlodipine and concomitant beta blockers. In clinical studies in which Amlodipine was administered in com-bination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, Amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Clinical Studies

Effects in Hypertension

Adult Patients: The antihypertensive efficacy of Amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on Amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Pediatric Patients: Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to Amlodipine 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Effects in Chronic Stable Angina:

The effectiveness of 5-10 mg/day of Amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for Amlodipine 10 mg, and averaged 7.9% (38 sec) for Amlodipine 5 mg. Amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina

attack rate. The sustained efficacy of Amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

Effects in Vasospastic Angina:

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, Amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 Amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

Studies in Patients with Congestive Heart Failure:

Amlodipine has been compared to placebo in four 8-12 week studies of patients with NYHA class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of Amlodipine 5-10 mg in 1153 patients with NYHA classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, Amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on Amlodipine and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitor (99%), digitalis (99%) and diuretics (99%), to placebo (n=827) or Amlodipine (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between Amlodipine and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on Amlodipine). With Amlodipine there were more reports of pulmonary edema.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absorption of amlodipine is not influenced by concomitant food intake. Absolute

bioavailability of the unchanged active substance is estimated to be 64-80%. Peak plasma levels are reached 6-12 hours after administration.

Distribution

The volume of distribution is approximately 21 l/kg. The pKa of amlodipine is 8.6. In vitro studies have shown that amlodipine is bound to plasmatic proteins up to 97.5%.

Biotransformation

Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound.

Elimination

The plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. 60% of metabolites are excreted in the urine.

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

Elderly

The time to reach peak plasma concentrations is similar in elderly and younger patients. The clearance tends to be decreased with resulting increases in (AUC) and terminal elimination half-life in elderly patients. Increase in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.

Paediatric population

A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S. No.	Ingredients	Specification	Quantity per tablet	Active or Inactive
1.	Amlodipine Besilate	BP	14.000 mg	Active
2.	Dibasic Calcium Phosphate	BP	100.000 mg	Inactive
3.	Maize Starch	BP	110.000 mg	Inactive
4.	Micro Crystalline Cellulose	BP	100.000 mg	Inactive
5.	Copovidone (K – 30)	BP	15.000 mg	Inactive
6.	Isopropyl Alcohol	BP	90.000 mg	Inactive
7.	Purified Talc	BP	4.00 mg	Inactive
8.	Magnesium Stearate	BP	7.00 mg	Inactive
9.	Colloidal Anhydrous Silica	BP	3.00 mg	Inactive
10.	Croscarmellose Sodium	BP	10.000 mg	Inactive

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing.

Special precautions for storage.

Store in a cool & dry place below 30°C. Protect from Light.

Keep all medicines out of the reach of children.

6.4 Nature and contents of container

3 x 10 Alu Alu Strip are packed in a printed carton along with 1 package insert.

6.5 Special precautions for disposal and other handling

Any unused portion should be discarded as per local regulations

7. Applicant

Synermed Nigeria LTD

No 3 Abike jokogbola street, Solebo Estate ,Aga Ikorodu, Lagos

8. MANUFACTURER

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