

Amtrel® 5mg/10mg Tablets

5 mg Amlodipine and 10 mg Benazepril Hydrochloride

【Description】

Amtrel® is a white round tablet with a cutting line through the middle. tsh and CVI are written on the surface.

【Indications】

Therapy of hypertension. The fixed combination drug is not indicated for the initial therapy.

In using Amtrel, consideration should be given to the fact that an ACEI has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that benazepril does not have a similar risk (please see Warnings, Neutropenia/Agranulocytosis).

【Dosage and Administration】 (Prescription drug)

Route of administration: Oral

The recommended dose is amlodipine 5 mg/benazepril hydrochloride 10 mg orally once daily.

The initial recommended dose is amlodipine 2.5mg/ benazepril hydrochloride 5mg or amlodipine 5mg/ benazepril hydrochloride 10mg once daily.

If the initial recommended dose is amlodipine 2.5mg/benazepril hydrochloride 5mg, it could be titrated to amlodipine 5mg/ benazepril hydrochloride 10mg once daily after 4 weeks treatment.

Amtrel tablets can be split into halves. Only split the tablet that you're about to take. Don't cut them all at once, as factors like heat, humidity, and moisture can affect split tablets that are stored.

The hazards of benazepril are generally independent of dose; those of amlodipine are a mixture of dose-dependent phenomena (primarily peripheral edema) and dose-independent phenomena, the former much common than the latter. When benazepril is added to a regimen of amlodipine, the incidence of edema is substantially reduced. Therapy with any combination of amlodipine and benazepril will thus be associated with both sets of dose-independent hazards, but the incidence of edema will generally be less than that seen with similar (or higher) doses of amlodipine monotherapy.

To minimize the hazards, the fixed combination drug is not indicated for the initial therapy of hypertension. And it is recommended to begin therapy with Amtrel only after a patient has either (1) failed to achieve the desired antihypertensive effect with one or the other monotherapy, or (2) demonstrated inability to achieve adequate antihypertensive effect with amlodipine therapy without developing edema.

Therapy Replacement: This product is adequate for patient failed to achieve the desired antihypertensive effect with one or the other monotherapy. For convenience, patients receiving amlodipine and benazepril from separate tablets may instead wish to receive Amtrel containing the same component doses.

Use in Patients With Metabolic Impairments:

Elderly (aged 65 or older)

In geriatric patients, exposure to amlodipine is increased, thus consider lower initial doses of Amtrel [see Clinical Pharmacology]. The recommended initial dose of amlodipine, as a monotherapy, is 2.5 mg.

Pediatric

The recommended dose in pediatric patients has not been established.

Hepatic Impairment

Exposure to amlodipine is increased in patients with hepatic insufficiency, thus consider using lower doses of Amtrel [see Clinical Pharmacology].

The recommended initial dose of amlodipine, as a monotherapy, is 2.5 mg.

Renal Impairment

Regimens of therapy with Amtrel need not take account of renal function as long as the patient's creatinine clearance is $>30\text{mL/min/1.73m}^2$ (serum creatinine roughly $\leq 3\text{mg/dL}$ or $265\text{ }\mu\text{mol/L}$). In patients with more severe renal impairment, the recommended initial dose of benazepril is 5 mg. Amtrel is not recommended in these patients.

【Clinical Pharmacology】

Mechanism of Action

The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine is a dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. However, the inhibition effect of calcium ion influx across cell membranes by Amlodipine selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Besides, serum calcium concentration is not affected by amlodipine.

Within the physiological pH range, amlodipine is an ionized compound ($pK_a=8.6$), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

Benazepril and benazeprilat inhibit angiotensin-converting enzyme (ACE) in human subjects and in animals. ACE is a peptidyl dipeptidase that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II also stimulates aldosterone secretion by adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase of serum potassium. Hypertensive patients treated with benazepril and amlodipine for up to 56 weeks had elevations of serum potassium up to 0.2 mEq/L. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma rennin activity. In animal studies, benazepril had no inhibitory effect on the vasopressor response to angiotensin II and did not interfere with the hemodynamic effects of the autonomic neurotransmitters acetylcholine, epinephrine, and norepinephrine.

While the mechanism through which benazepril lowers blood pressure is believed to be primarily suppression of the renin-angiotensin-aldosterone system, benazepril has an antihypertensive effect even in patients with low-renin hypertension.

Pharmacodynamics

Single and multiple doses of 10 mg or more of benazepril cause inhibition of plasma ACE activity by at least 80%-90% for at least 24 hours after dosing. For up to 4 hours after a 10-mg dose, pressor responses to exogenous angiotensin I were inhibited by 60%-90%. Administration of benazepril to patients with mild-to-moderate hypertension results in a reduction of both supine and standing blood pressure to about the same extent, with no compensatory tachycardia. Symptomatic postural hypotension is infrequent, although it can occur in patients who are salt and/or volume depleted (see WARNINGS, Hypotension). The antihypertensive effects of benazepril were not appreciably different in patients receiving high- or low-sodium diets. In normal human volunteers, single doses of benazepril caused an increase in renal blood flow but had no effect on glomerular filtration rate. 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. Plasma concentrations correlate with effect in both young and elderly patients.

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 humans, even when coadministered with beta blockers to humans. Amlodipine does not change sinoatrial (SA) nodal function or atrioventricular (AV) conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. Over 950 patients received amlodipine and benazepril single pill combination once daily in six double-blind, placebo-controlled studies. It lowered blood pressure within 1 hour, with peak reductions achieved 2-8 hours after dosing. The antihypertensive effect of a single dose persisted for 24 hours. Once-daily doses of benazepril/amlodipine using benazepril doses of 10-20 mg and amlodipine doses of 2.5-10 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10-25/6-13 mmHg. Combination therapy was effective in blacks and nonblacks. Both components contributed to the antihypertensive efficacy in nonblacks, but virtually all of the antihypertensive effect in blacks could be attributed to the amlodipine component. Among nonblack patients in placebo-controlled trials comparing amlodipine and benazepril single pill combination to the individual components, the blood pressure lowering effects of the combination were shown to be additive and in some cases synergistic. During chronic therapy with amlodipine and benazepril single pill combination, the maximum reduction in blood pressure with any given dose is generally achieved after 1-2 weeks. The antihypertensive effects of amlodipine and benazepril single pill combination have continued during therapy for at least 1 year. Abrupt withdrawal of amlodipine and benazepril single pill combination has not been associated with a rapid increase in blood pressure.

Pharmacokinetics

Absorption

The rate and extent of absorption of benazepril and amlodipine from Amtrel are not significantly different, respectively, from the rate and extent of absorption of benazepril and amlodipine from individual tablet formulations. Absorption from the individual tablets is not influenced by the presence of food in the gastrointestinal tract; food effects on absorption from Amtrel have not been studied. Following oral administration of Amtrel, peak plasma concentrations of benazepril are reached in 0.5-2 hours. Cleavage of the ester group (primarily in the liver) converts benazepril to its active metabolite, benazeprilat, which reaches peak plasma concentrations in 1.5-4 hours. The extent of absorption of benazepril is at least 37%. Peak plasma concentrations of amlodipine are reached 6-12 hours after administration of Amtrel; the extent of absorption is 64%-90%.

Distribution

The apparent volumes of distribution of amlodipine and benazeprilat are about 21 L/kg and 0.7 L/kg, respectively. Approximately 93% of circulating amlodipine is bound to plasma proteins, and the bound fraction of benazeprilat is slightly higher. On the basis of in vitro studies, benazeprilat's degree of protein binding should be unaffected by age, by hepatic dysfunction, or—over the therapeutic concentration range—by concentration.

Metabolism

Benazeprilat has much greater ACE-inhibitory activity than benazepril, and the metabolism of benazepril to benazeprilat is almost complete. Only trace amounts of an administered dose of benazepril can be recovered unchanged in the urine; about 20% of the dose is excreted as benazeprilat, 8% as benazeprilat glucuronide, and 4% as benazepril glucuronide. Amlodipine is extensively metabolized in the liver, with 10% of the parent compound and 60% of the metabolites excreted in the urine. In patients with hepatic dysfunction, decreased clearance of amlodipine may increase the area-under-the-plasma-concentration curve by 40%-60%, and dosage reduction may be required (see DOSAGE AND ADMINISTRATION). In patients with renal impairment, the pharmacokinetics of amlodipine are essentially unaffected.

Elimination

Benazeprilat's effective elimination half-life is 10-11 hours, while that of amlodipine is about 2 days, so steady-state levels of the two components are achieved after about a week of once-daily dosing. The clearance of benazeprilat from the plasma is primarily renal, but biliary excretion accounts

for 11%-12% of benazepril elimination in normal subjects. In patients with severe renal insufficiency (creatinine clearance less than 30 mL/min), peak benazeprilat levels and the time to steady state may be increased (see DOSAGE AND ADMINISTRATION).

Specific populations

In patients with hepatic impairment, on the other hand, the pharmacokinetics of benazeprilat are essentially unaffected. Although the pharmacokinetics of benazepril and benazeprilat are unaffected by age, clearance of amlodipine is decreased in the elderly, with resulting increases of 35%-70% in peak plasma levels, elimination half-life, and area-under-the-plasma-concentration curve. Dose adjustment may be required.

【Contraindications】

Amtrel is contraindicated in patients who are hypersensitive to benazepril, to any other ACE inhibitor, or to amlodipine.

Amtrel is contraindicated coadministered with any drugs contain aliskiren in diabetes and renal impairment (GFR < 60 ml/min/1.73m²) patients.

Amtrel is contraindicated in combination with a neprilysin inhibitor (e.g., sacubitril). Do not administer Amtrel within 36 hours of switching to or from a neprilysin inhibitor, e.g., sacubitril/valsartan.

【Warnings】

Renin-angiotensin-aldosterone system, RAAS clinical evidence proved that coadministered with ACEI, ARB and/or drugs contain aliskiren will increase the risk of hypotension, hyperkalemia and renal function decrease (including acute renal failure). It is not recommended using ACEI, ARB or drugs contain aliskiren as combination therapy for dual RAAS blockade. Careful consideration of individual risks and benefits is needed. For those who need dual RAAS blockade treatment should closely monitor their renal function, electrolytes and blood pressure. ACEI and ARB should not use as combination therapy for diabetic renal impairment patients.

Anaphylactoid and Possibly Related Reaction

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors may be subject to a variety of adverse reactions, some of them serious. These reactions usually occur after one of the first few doses of the ACE inhibitor, but they sometimes do not appear until after months of therapy.

Head and Neck Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received benazepril. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Amtrel should be discontinued and appropriate therapy instituted immediately. When involvement of the tongue, glottis, or larynx appears likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3-0.5 mL), should be promptly administered (see ADVERSE REACTIONS).

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions.

Anaphylactoid Reaction During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

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.

Hypotension

Amtrel can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume and/or salt depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with Amtrel. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. Nonetheless, caution should be exercised when administering Amtrel as with any other peripheral vasodilator, particularly in patients with severe aortic stenosis. In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria, azotemia, and (rarely) with acute renal failure and death. In such patients, Amtrel therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of the benazepril component is increased or a diuretic is added or its dose increased. If hypotension occurs, the patient should be placed in a supine position, and if necessary, treated with intravenous infusion of physiologic saline. Amtrel treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients (< 1 / 10,000) but more frequently (> 1 / 1000) in patients with renal impairment, especially those who also have collagen-vascular diseases such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature.

When pregnancy is detected, Amtrel should be discontinued as soon as possible and monitoring of the fetal development should be performed on a regular basis. The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure.

In addition, use of ACE inhibitors during the first trimester of pregnancy has not been associated with a potentially increased risk of birth defects. In women planning to become pregnant, benazepril should not be used. Women of child-bearing age should be made aware of the potential risk and ACE inhibitors (including Amtrel) should only be given after careful counseling and consideration of individual risks and benefits. Rarely (less than 1 per 1000 pregnant women), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, benazepril should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. Benazepril, which crosses the placenta, can theoretically be removed from the neonatal circulation by these means; there are occasional reports of benefit from these maneuvers, but experience is limited. At the present, there are no clinical trials involving this formula in pregnant women. When rats received benazepril: amlodipine at doses ranging from 5:2.5 to 50:25 mg/kg/day, dystocia was observed with increasing dose-related incidence at all doses tested. On a mg/m² basis, the 2.5 mg/kg/day dose of amlodipine is 3.6 times the amlodipine dose delivered when the maximum recommended dose of Amtrel is given to a 50-kg woman. Similarly, the 5 mg/kg/day dose of benazepril is approximately 2 times the benazepril dose delivered when the maximum recommended dose of Amtrel is given to a 50-kg woman. No teratogenic effects were seen when benazepril and amlodipine were administered in combination to pregnant rats or rabbits. Rats received dose ratios up to 50:25 mg/kg/day (benazepril: amlodipine) (24 times the maximum recommended human dose on a mg/m² basis, assuming a 50-kg woman). Rabbits received doses of up to 1.5:0.75 (benazepril: amlodipine) mg/kg/day; on a mg/m² basis, this is 0.97 times the size of a maximum recommended dose of Amtrel given to a 50-kg woman. Similar results were seen in animal studies involving benazepril alone and amlodipine alone.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes even death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Precautions

General

Impaired Renal Function: Amtrel should be used with caution in patients with severe renal disease. When the renin-angiotensin-aldosterone system is inhibited by benazepril, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors (including benazepril) may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with unilateral or bilateral renal artery stenosis, treatment with benazepril was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of benazepril therapy, concomitant diuretic therapy, or both. When such patients are treated with Amtrel, renal function should be monitored during the first few weeks of therapy. Some benazepril-treated hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when benazepril has been given concomitantly with a diuretic. Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia: In U.S. placebo-controlled trials, hyperkalemia not present at baseline occurred in approximately 1.5% of hypertensive patients receiving similar formula. Increases in serum potassium were generally reversible. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium containing salt substitutes.

Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in patients with NYHA Class II-III heart failure have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Patients with Hepatic Failure: In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. However, 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 Amtrel to patients with severe hepatic impairment (see also WARNINGS).

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Drug Interactions

Clinical evidence shows combination therapy of using ACEI, ARB and/or drugs contain aliskiren for dual RAAS blockade, the adverse events rate such as hypotension, hyperkalemia and renal function decrease (including acute renal failure) is higher.

Diuretics: Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Amtrel. The possibility of hypotensive effects with Amtrel can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Amtrel.

Simvastatin: Coadministration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

CYP3A4 Inhibitors: Coadministration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is coadministered with CYP3A4 inhibitors to determine the need for dose adjustment.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Blood pressure should be monitored when amlodipine is coadministered with CYP3A4 inducers (e.g. rifampicin, St. John's Wort).

Potassium supplements and potassium-preserving diuretics: Benazepril can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. If concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. Amtrel and lithium should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, including benazepril, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving benazepril and NSAID therapy. The antihypertensive effect of ACE inhibitors, including benazepril, may be attenuated by NSAIDs.

Antidiabetic Agents: In rare cases, diabetic patients receiving an ACE inhibitor (including benazepril) concomitantly with insulin or oral antidiabetics may develop hypoglycemia. Such patients should therefore be advised about the possibility of hypoglycemic reactions and should be monitored accordingly.

Mammalian Target of Rapamycin (mTOR) Inhibitors: The risk of angioedema may be increased in patients receiving coadministration of ACE inhibitors and mTOR inhibitors (e.g., temsirolimus, sirolimus, everolimus).

Neprilysin Inhibitor: Patients taking concomitant neprilysin inhibitors may be at increased risk for angioedema.

Others: Benazepril has been used concomitantly with oral anticoagulants, beta-adrenergic-blocking agents, calcium-blocking agents, cimetidine, diuretics, digoxin, hydralazine, and naproxen without evidence of clinically important adverse interactions. In clinical trials, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs. In vitro data in human plasma indicate that amlodipine has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the coadministration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that coadministration with cimetidine did not alter the pharmacokinetics of amlodipine; and that coadministration with warfarin did not change the warfarin induced prothrombin response time.

Pregnancy

Risk Summary

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

Amtrel can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the RAS during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the RAS from other antihypertensive agents.

When pregnancy is detected, discontinue Amtrel as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of in utero exposure to Amtrel for hypotension, oliguria, and hyperkalemia. In neonates with a history of in utero exposure to Amtrel, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Data

Animal Data

Benazepril and Amlodipine:

When rats received benazepril:amlodipine at doses ranging from 5:2.5 to 50:25 mg/kg/day, dystocia was observed at an increasing dose-related incidence at all doses tested. On a body surface area basis, the 2.5 mg/kg/day dose of amlodipine is twice the amlodipine dose delivered when the maximum recommended dose of Amtrel is given to a 60 kg patient. Similarly, the 5 mg/kg/day dose of benazepril is approximately equivalent with the benazepril dose delivered when the maximum recommended dose of Amtrel is given to a 60 kg patient. No teratogenic effects were seen when benazepril and amlodipine were administered in combination to pregnant rats or rabbits. Rats received doses of up to 50:25 mg (benazepril:amlodipine)/kg/day (12 times the MRHD on a body surface area basis, assuming a 60 kg patient). Rabbits received doses of up to 1.5:0.75 mg/kg/day (equivalent to the maximum recommended dose of Amtrel given to a 60 kg patient).

INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY.

Nursing mothers

Only minimum amounts of benazepril and benazeprilat are secreted in the breast milk of breastfeeding women. Therefore, if the newborn consumes breast milk, less than 0.1% of the dosage received by the mother will be absorbed by the newborn.

It is currently unclear whether amlodipine may be found in the breast milk. Thus, it is recommended that when taking this product for treatment, breastfeeding should stop.

Geriatric Use

In clinical studies published in the United States, over 19% were 65 or older while about 2% were 75 or older. Overall differences in effectiveness or safety were not observed between these patients and younger patients. Clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

【Adverse Reactions】

The same formula has been evaluated for safety in over 1,600 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 400 were treated for more than 1 year. The reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects was required in approximately 4% of patients treated with the same formula and in 3% of patients treated with placebo. The most common reasons for discontinuation of therapy with the same formulation in these studies were cough and edema.*

Percent incidence in U.S placebo-controlled trials (%)

	Benazepril /Amlodipine N=760	Benazepril N=554	Amlodipine N=475	Placebo N=408
cough	3.3	1.8	0.4	0.2
headache	2.2	3.8	2.9	5.6
dizziness	1.3	1.6	2.3	1.5
edema*	2.1	0.9	5.1	2.2

* Edema refers to all edema, such as dependent edema, angioedema, facial edema.

The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination. Edema and certain other side effects are associated with amlodipine monotherapy in a dose-dependent manner, and appear to affect women more than men. The addition of benazepril resulted in lower incidences as shown in the following table; the protective effect of benazepril was independent of race and (within the range of doses tested) of dose.

Percent incidence by sex of certain adverse events

	Benazepril /Amlodipine		Benazepril		Amlodipine		Placebo	
	Male N=329	Female N=431	Male N=269	Female N=285	Male N=277	Female N=198	Male N=217	Female N=191
Edema	0.6	3.2	0.0	1.8	2.2	9.1	1.4	3.1
hot flushes	0.3	0.0	0.0	0.7	0.4	2.0	0.5	0.0
palpitation	0.3	0.5	0.4	1.4	0.4	2.0	0.5	0.5
lethargy	0.3	0.0	0.4	0.4	0.4	0.5	0.0	0.0

Other side effects considered possibly or probably related to study the formula that occurred in U.S. placebo-controlled trials of patients treated with the formula or in postmarketing experience were the following:

Angioedema: Includes edema of the lips or face without other manifestations of angioedema (see WARNINGS, Angioedema).

Systemic: Asthenia and fatigue.

CNS: Insomnia, nervousness, anxiety, tremor, and decreased libido.

Dermatologic: Flushing, hot flushes, rashes, skin nodule, and dermatitis.

Digestive: Dry mouth, nausea, abdominal pain, constipation, diarrhea, dyspepsia, and esophagitis.

Hematologic: Neutropenia

Metabolic and Nutritional: Hypokalemia.

Musculoskeletal: Back pain, musculoskeletal pain, cramps, and muscle cramps.

Respiratory: Pharyngitis.

Urogenital: Sexual problems such as impotence, and polyuria.

Other infrequently reported events were seen in clinical trials (causal relationship unlikely) or in postmarketing experience. These included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, alopecia and upper respiratory tract infection.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Monotherapies of benazepril and amlodipine have been evaluated for safety in clinical trials in over 6,000 and 11,000 patients, respectively. The observed adverse reactions to the monotherapies in these trials were similar to those seen in trials of Amtrel. In postmarketing experience with benazepril, there have been rare reports of Stevens-Johnson syndrome, pancreatitis, hemolytic anemia, pemphigus, and thrombocytopenia. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) severe enough to require hospitalization have been reported in association with use of amlodipine. Other potentially important adverse experiences attributed to other ACE inhibitors and calcium channel blockers include: eosinophilic pneumonitis (ACE inhibitors) and gynecomastia (CCB's).

Clinical Electrolytes Test Findings

Serum electrolytes: See PRECAUTIONS

Creatinine: Minor reversible increases in serum creatinine were observed in patients with essential hypertension treated with this combined formula. Increases in creatinine are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Others (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with Amtrel administration. Elevations of serum bilirubin and uric acid have been reported as have scattered incidents of elevations of liver enzymes.

【Drug Overdose】

Only a few cases of human overdose with amlodipine have been reported. One patient was asymptomatic after a 250-mg ingestion; another, who combined 70 mg of amlodipine with an unknown large quantity of a benzodiazepine, developed refractory shock and died. Human overdoses with any combination of amlodipine and benazepril have not been reported. In scattered reports of human overdoses with benazepril and other ACE

inhibitors, there are no reports of death. When mice were given single oral doses of benazepril/amlodipine, mortality was 20% at 50:25 mg/kg, 10% at 100:50 mg/kg, and 100% at 500:250 mg/kg. In rats, mortality was 25% at 500:250 mg/kg and 100% at 900:450 mg/kg.

Treatment: The most likely effect of overdose is vasodilation, with consequent hypotension and tachycardia. Simple repletion of central fluid volume may be sufficient therapy, but pressor agents (norepinephrine or high-dose dopamine) may be required. Overdoses of other dihydropyridine calcium channel blockers are reported to have been treated with calcium chloride and glucagon, but evidence of a dose-response relation has not been seen, and these interventions must be regarded as unproven. With abrupt return of peripheral vascular tone, overdoses of other dihydropyridine calcium channel blockers have sometimes progressed to pulmonary edema, and patients must be monitored for this complication. No data are available to suggest physiologic maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of amlodipine, benazepril, or their metabolites. Benazepril is only slightly dialyzable; attempted clearance of amlodipine by hemodialysis or hemoperfusion has not been reported, but amlodipine's high protein binding makes it unlikely that these interventions will be of value. Angiotensin II could presumably serve as a specific antagonist-antidote to benazepril, but angiotensin II is essentially unavailable outside of scattered research laboratories.

【Effects on ability to drive and use machines】

No studies on the effects of Amlodipine and Benazepril on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

【Preclinical Safety Data】

Carcinogenesis , Mutagenesis , Impairment of Fertility

No evidence of carcinogenicity was found when benazepril was given, via dietary administration, to rats and mice for 104 weeks at doses up to 150 mg/kg/day. On a body-weight basis, this dose is over 100 times the maximum recommended human dose; on a body-surface-area basis, this dose is 9-18 times the maximum recommended human dose. No mutagenic activity was detected in the Ames test in bacteria, in an in vitro test for forward mutations in cultured mammalian cells, or in nucleus anomaly test. At doses of 50-500 mg/kg/day (38-375 times the maximum recommended human dose on a body-weight basis; 6-61 times the maximum recommended dose on a body-surface-area basis), benazepril had no adverse effect on the reproductive performance of male and female rats. Rats and mice treated with amlodipine in the diet for 2 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. For mice, but not for rats, the highest dose was close to the maximum tolerated dose. On a mg/m² basis, this dose given to mice was approximately equal to the maximum recommended clinical dose. On the same basis, the same dose given to rats was approximately twice the maximum recommended clinical dose. Mutagenicity studies with amlodipine revealed no drug-related effects at either the gene or chromosome levels. There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg/kg/day (8 times the maximum recommended human dose of 10 mg on a mg/m² basis, assuming a 50-kg person). No adverse effects on fertility occurred when the benazepril: amlodipine combination was given orally to rats of either sex at dose ratios up to 15:7.5 mg/kg/day (benazepril: amlodipine), prior to mating and throughout gestation.

【Excipient】

Lactose Anhydrous, Croscarmellose Sodium, Microcrystalline Cellulose (pH101), Calcium Phosphate Dibasic Dihydrate, Sodium Lauryl Sulfate, Magnesium Stearate.

【Storage】

This product should not be used once the labeled expiry date has passed.

Do not store above (30°C).

Keep out of reach of children.

【Pack size】

28 tablets per box

【ATC code】

C09BB13

【MANUFACTURER】

TTY Biopharm Company Limited Lioudu Factory

【PLANT ADDRESS】

No. 5, Gongjian W. Rd., Qidu District, Keelung City, Taiwan, R.O.C.

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