

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 or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE 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 ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) 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.

Neutropenia/Agranulocytosis

As with other ACE inhibitors, rarely, a mild – in isolated cases severe – reduction in the red blood cell count and hemoglobin content, white blood cell or platelet count may develop. In isolated cases, agranulocytosis, pancytopenia, and bone marrow depression may occur. Hematological reactions to ACE inhibitors are more likely to occur in patients with collagen vascular disease (e.g. systemic lupus erythematosus, scleroderma) and renal impairment. 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

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, ACE inhibitors should be discontinued as soon as possible.

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.

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), 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 intraamniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress 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 dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE which crosses the placenta can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a body surface area basis, the doses used were up to approximately 400 times (in rats and monkeys) and 2 times (in rabbits) the recommended human dose.

PRECAUTIONS

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, 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 angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function. (See **DOSAGE AND ADMINISTRATION**.)

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE (ramipril). In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. 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, which should be used cautiously, if at all, with ALTACE. (See **Drug Interactions**.)

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.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function. However, since the renin-angiotensin system may be activated in patients with severe liver cirrhosis and/or ascites, particular caution should be exercised in treating these patients.

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

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions

With nonsteroidal anti-inflammatory agents: Rarely, concomitant treatment with ACE inhibitors and non-steroidal anti-inflammatory agents have been associated with worsening of renal failure and an increase in serum potassium.

With 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 ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced. (See **DOSAGE AND ADMINISTRATION**.)

With potassium supplements and potassium-sparing diuretics: ALTACE 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. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

With Oral Hypoglycemic Agents or Insulin: Rarely, hypoglycemia has been reported during concomitant therapy. Upon initiation of ALTACE or with an increase in dose, such patients should be closely monitored for symptoms of hypoglycemic reactions with dosage adjustment of concomitant oral hypoglycemic agents or insulin therapy as necessary.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, antacid, furosemide, cimetidine, indomethacin, and simvastatin. The combination of ALTACE and propranolol showed no adverse effects on dynamic parameters (blood pressure and heart rate). The co-administration of ALTACE and warfarin did not adversely affect the anticoagulant effects of the latter drug. Additionally, co-administration of ALTACE with phenprocoumon did not affect minimum phenprocoumon levels or interfere with the subjects' state of anti-coagulation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats for up to 24 months at doses of up to 500 mg/kg/day or to mice for up to 18 months at doses of up to 1000 mg/kg/day. (For either species, these doses are about 200 times the maximum recommended human dose when compared on the basis of body surface area.) No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters). See **WARNINGS: Fetal/Neonatal Morbidity and Mortality**.

Nursing Mothers

Ingestion of single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, women receiving ALTACE should not breast feed.

Geriatric Use

Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported 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.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypertension

ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), “dizziness” (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), “dizziness” (0.5%), and impotence (0.4%).

Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE, only asthenia (fatigue) was more common on Altace than placebo (2% vs. 1%).

PATIENTS IN US PLACEBO CONTROLLED STUDIES

	ALTACE (n=651)		Placebo (n=286)	
	n	%	n	%
Asthenia (Fatigue)	13	2	2	1

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group, not attributed at that time to ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of patients requiring discontinuation of treatment.

Heart Failure Post Myocardial Infarction

Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients and more frequently on ramipril are shown below. The incidences represent the experiences from the AIRE study. The follow-up time was between 6 and 46 months for this study.

Percentage of Patients with Adverse Events Possibly/ Probably Related to Study Drug

Adverse Event	Placebo-Controlled (AIRE) Mortality Study	
	Ramipril (n=1004)	Placebo (n=982)
Hypotension	11	5
Cough Increased	8	4
Dizziness	4	3
Angina Pectoris	3	2
Nausea	2	1
Postural Hypotension	2	1
Syncope	2	1
Vomiting	2	0.5
Vertigo	2	0.7
Abnormal Kidney Function	1	0.5
Diarrhea	1	0.4

HOPE Study:

Safety data in the HOPE trial were collected as reasons for discontinuation or temporary interruption of treatment. The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials (see **WARNINGS**).

	RAMIPRIL (N=4645)	PLACEBO (N=4652)
	%	%
Discontinuation at any time	34	32
Permanent discontinuation	29	28
Reasons for stopping Cough	7	2
Hypotension or Dizziness	1.9	1.5
Angioedema	0.3	0.1

Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain):

Body As a Whole: Anaphylactoid reactions. (See **WARNINGS**.)

Cardiovascular: Angina/chest pain, arrhythmias including bradycardia or tachycardia, cardiac arrest, congestive heart failure, symptomatic hypotension (reported in 0.5% of patients in US trials) (See **WARNINGS** and **PRECAUTIONS**), syncope, palpitations, transient ischemia attack, and myocardial infarction or cerebrovascular accident possibly due to excessive hypotension.

Hematologic: Pancytopenia, hemolytic anemia and thrombocytopenia.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See **WARNINGS**.) Acute renal failure.

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See **WARNINGS**.)

Gastrointestinal: Pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, hepatitis, increased salivation and taste disturbance.

Dermatologic: Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura, oncholyxis, pemphigus, pemphigoid, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Miscellaneous: As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported.

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

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, hypoglycemia (see **PRECAUTIONS, Drug Interactions**), impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings:

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values 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 **WARNINGS** and **PRECAUTIONS**.) Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See **WARNINGS** and **PRECAUTIONS**.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE

Single oral doses in rats and mice of 10–11 g/kg resulted in significant lethality. In dogs, oral doses as high as 1 g/kg induced only mild gastrointestinal distress. Limited data on human overdosage are available. The most likely clinical manifestations would be symptoms attributable to hypotension.

Laboratory determinations of serum levels of ramipril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of ramipril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of ramipril and its metabolites. Similarly, it is not known which, if any, of these substances can be usefully removed from the body by hemodialysis.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of ramipril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION

Blood pressure decreases associated with any dose of ALTACE depend, in part, on the presence or absence of volume depletion (e.g., past and current diuretic use) or the presence or absence of renal artery stenosis. If such circumstances are suspected to be present, the initial starting dose should be 1.25 mg once daily.

Reduction in Risk of Myocardial Infarction, Stroke, and Death from Cardiovascular Causes

ALTACE should be given at an initial dose of 2.5 mg, once a day for 1 week, 5 mg, once a day for the next 3 weeks, and then increased as tolerated, to a maintenance dose of 10 mg, once a day. If the patient is hypertensive or recently post myocardial infarction, it can also be given as a divided dose.

Hypertension

The recommended initial dose for patients not receiving a diuretic is 2.5 mg once a day. Dosage should be adjusted according to the blood pressure response. The usual maintenance dosage range is 2.5 to 20 mg per day administered as a single dose or in two equally divided doses. In some patients treated once daily, the anti-hypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice daily administration should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic can be added.

Heart Failure Post Myocardial Infarction

For the treatment of post-infarction patients who have shown signs of congestive failure, the recommended starting dose of ALTACE is 2.5 mg twice daily (5 mg per day). A patient who becomes hypotensive at this dose may be switched to 1.25 mg twice daily, and after one week at the starting dose, patients should then be titrated (if tolerated) toward a target dose of 5 mg twice daily, with dosage increases being about 3 weeks apart.

After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See **WARNINGS** and **PRECAUTIONS, Drug Interactions**.) If possible, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of ALTACE does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension.

The ALTACE Capsule is usually swallowed whole. The ALTACE Capsule can also be opened and the contents sprinkled on a small amount (about 4 oz.) of apple sauce or mixed in 4 oz. (120 ml) of water or apple juice. To be sure that ramipril is not lost when such a mixture is used, the mixture should be consumed in its entirety. The described mixtures can be pre-prepared and stored for up to 24 hours at room temperature or up to 48 hours under refrigeration.

Concomitant administration of ALTACE with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium. (See **PRECAUTIONS**.)

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of ALTACE. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with ALTACE. (See **WARNINGS**.) Then, if blood pressure is not controlled with ALTACE alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used to avoid excess hypotension.

Dosage Adjustment in Renal Impairment

In patients with creatinine clearance <40 ml/min/1.73m² (serum creatinine approximately >2.5 mg/dl) doses only 25% of those normally used should be expected to induce full therapeutic levels of ramiprilat. (See **CLINICAL PHARMACOLOGY**.)

Hypertension: For patients with hypertension and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg.

Heart Failure Post Myocardial Infarction: For patients with heart failure and renal impairment, the recommended initial dose is 1.25 mg ALTACE once daily. The dose may be increased to 1.25 mg b.i.d. and up to a maximum dose of 2.5 mg b.i.d. depending upon clinical response and tolerability.

HOW SUPPLIED

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in hard gelatin capsules.

ALTACE 1.25 mg capsules are supplied as yellow, hard gelatin capsules in bottles of 100 (NDC 61570-110-01), and Unit Dose packs of 100 (NDC 61570-110-56).

ALTACE 2.5 mg capsules are supplied as orange, hard gelatin capsules in bottles of 100 (NDC 61570-111-01), 500 (NDC 61570-111-05), 1000 (NDC 61570-111-10) and Unit Dose packs of 100 (NDC 61570-111-56), and Bulk pack of 5000's (NDC 61570-111-50).

ALTACE 5 mg capsules are supplied as red, hard gelatin capsules in bottles of 100 (NDC 61570-112-01), 500 (NDC 61570-112-05), 1000 (NDC 61570-112-10) and Unit Dose packs of 100 (NDC 61570-112-56), and Bulk pack of 5000's (NDC 61570-112-50).

ALTACE 10 mg capsules are supplied as Process Blue, hard gelatin capsules in bottles of 100 (NDC 61570-120-01), 500 (NDC 61570-120-05), 1000 (NDC 61570-120-10).

Dispense in well-closed container with safety closure.

Store at controlled room temperature (59° to 86°F).

Rx only.



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