ARBace
arbarsartan sodium

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Angiotensin II Receptor Antagonist

INDICATIONS AND CLINICAL USE:

Hypertension

ARBACE® (arbsartan sodium) is indicated for the treatment of essential hypertension.

ARBACE may be used alone or concomitantly with thiazide diuretics and should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. ARBACE can also be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors have not been established.

Type 2 Diabetic Patients with Proteinuria and Hypertension

ARBACE is also indicated to delay the progression of renal disease as measured by the occurrence of doubling of serum creatinine, and end stage renal disease, and to reduce proteinuria.

CONTRAINDICATIONS: ARBACE (arbsartan sodium) is contraindicated in patients who are hypersensitive to any component of this product.

ARBACE should not be used in pregnant women.

Use in Nursing Mothers

It is not known whether arbsartan or its active metabolite are excreted in human milk, however significant levels of both of these compounds have been shown to be present in the milk of lactating rats. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

Safety and effectiveness have not been established.

Use in the Elderly

No overall differences in safety were observed between elderly and younger patients, but appropriate caution should nevertheless be used when prescribing to elderly, as increased vulnerability to drug effect is possible in this patient population.

Safety Information

WARNINGS

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ARBACE (arbsartan sodium) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system 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.

Animal data: Arbsartan sodium has been shown to produce adverse effects in rat fetuses and neonates, which include decreased body weight, mortality and/or renal toxicity. Significant levels of arbsartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of arbsartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

PRECAUTIONS

Hypersensitivity

Angioedema (see ADVERSE REACTIONS).

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of arbsartan should include appropriate assessment of renal function.

Hyperkalemia

In a clinical study conducted in patients with type 2 diabetes with proteinuria and hypertension, the incidence of hyperkalemia was higher in the group treated with ARBACE (11%) as compared to the placebo group (5.4%), however, few patients discontinued therapy due to hyperkalemia. Careful monitoring of serum potassium is recommended.

Hepatic Impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of arbsartan and its active metabolite in cirrhotic patients after administration of ARBACE (arbsartan sodium), a lower dose should be considered for patients with hepatic impairment, or a history of hepatic impairment.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE (see full listing):

ARBACE (arbsartan sodium) has been evaluated for safety in more than 5000 patients treated for essential hypertension. Of these, 3085 were treated with arbsartan monotherapy in controlled clinical trials. In open studies, over 2400 patients were treated with arbsartan for more than 6 months, and over 1200 for more than one year.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences occurred in 3.8% and 4.0% of patients treated with ARBACE and placebo, respectively.

The following potentially serious adverse reactions have been reported rarely with arbsartan in controlled clinical trials: syncope, hypotension. In these controlled clinical trials for essential hypertension, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in arbsartan-treated (2.4%) than placebo-treated (1.3%) patients. In double-blind, controlled clinical trials for essential hypertension, the following adverse reactions were reported with ARBACE at an occurrence rate of less than 1%, regardless of drug relationship: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

ARBACE® was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria and hypertension. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see PRECAUTIONS, Hyperkalemia).

Post-Marketing Experience

Other adverse reactions reported rarely in open-label studies or post-marketing use in patients with essential hypertension, regardless of drug relationship, include anemia, hepatitis, liver function tests abnormalities, drug induced cough, asthenia, diarrhea, migraine, myalgia, pruritus, taste disorder and urticaria.

Anaphylactic reactions, angioedema (involving swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, and/or tongue and pharynx, requiring intubation/tracheotomy in some cases) have been reported rarely in patients treated with arbsartan; some of these patients previously experienced angioedema with ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

Drug Interactions

Antihypertensive effect of arbsartan may be attenuated by the non-steroidal anti-inflammatory drug indomethacin.

Diuretics

Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ARBACE. The possibility of symptomatic hypotension with the use of ARBACE can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of arbsartan. No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents Increasing Serum Potassium

Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Since ARBACE decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.

Lithium Salts

As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

Digitalis

In 20 healthy volunteers, when a single oral dose of 0.5 mg digoxin was administered to patients receiving arbsartan for 7 days, digoxin AUC and digoxin C_{max} ratios, relative to placebo, were found to be 1.2 and 1.38, respectively. The effect of arbsartan on steady-state pharmacokinetics of cardiac glycosides is not known.

Warfarin

Arbsartan administered for 7 days did not affect the pharmacokinetics or pharmacodynamic activity of a single dose of warfarin. The effect of arbsartan on steady-state pharmacokinetics of warfarin is not known.

Drugs Affecting Cytochrome P450 System

Rifampin, an inducer of drug metabolism, decreases the concentrations of the active metabolite of arbsartan. In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of arbsartan to the active metabolite after intravenous administration of arbsartan, and erythromycin had no clinically significant effect after oral arbsartan administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration. The pharmacodynamic consequences of concomitant use of arbsartan and inhibitors of P450 2C9 have not been examined.

To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at 1-866-234-2345 or write to: ABEE Pharmaceuticals Inc., 375 Kingston Road, Suite 200, Pickering, Ontario, L1V 1A3.

Administration

ARBACE (arbsartan sodium) may be administered with or without food; however it should be taken consistently with respect to food intake at about the same time every day.

Hypertension

The dosage of ARBACE must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with ARBACE may need to be adjusted.

Monotherapy

The usual starting dose of ARBACE is 50 mg once daily.

Dosage should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. The usual dose range for ARBACE is 50 to 100 mg once daily. A dose of 100 mg daily should not be exceeded, as no additional antihypertensive effect is obtained with higher doses. In most patients taking ARBACE 50 mg once daily, the antihypertensive effect is maintained. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval.

This can be evaluated by measuring the blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dosage, or an increase in the dose should be considered. If blood pressure is not adequately controlled with ARBACE alone, a non-potassium-sparing diuretic may be administered concomitantly. For patients with volume-depletion, a starting dose of 25 mg once daily should be considered.

Concomitant Diuretic Therapy

In patients receiving diuretics, ARBACE therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of ARBACE, to reduce the likelihood of hypotension. If this is not possible because of the patient's condition, ARBACE should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Type 2 Diabetic Patients with Proteinuria and Hypertension

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. ARBACE may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Dosage in the Elderly

No initial dosage adjustment is necessary for most elderly patients. However, appropriate monitoring of these patients is recommended.

Renal Impairment

No initial dosage adjustment is usually necessary for patients with renal impairment, including those requiring hemodialysis. However, appropriate monitoring of these patients is recommended.

Hepatic Impairment

An initial dosage of 25 mg should be considered for patients with hepatic impairment, or a history of hepatic impairment (see PRECAUTIONS – Hepatic Impairment, and PHARMACOLOGY).

Study References

1. Product Monograph ARBACE® (arbsartan sodium), ABEE Pharmaceuticals, 2006.
2. Chang DL, et al. for the BEAN study investigators. Effects of arbsartan sodium on renal and cardiovascular outcomes in hypertensive patients with type 2 diabetes and nephropathy. *Am J of Med.* 2000;9:60-71.

A randomized double-blind study involving 2012 patients, comparing arbasartan sodium (50 to 100 mg once daily) with placebo, both taken in addition to other anti-hypertensive treatments (calcium channel blockers, diuretics, alpha blockers, beta blockers and centrally acting agents). Mean study duration 4.1 yrs. A total of 327 patients in the arbsartan sodium group reported a doubling of the baseline serum creatinine, and end stage renal disease, versus 359 in the placebo group (risk reduction, 12%; p=0.002). Compared to placebo, arbasartan sodium reduced the incidence of doubling of creatinine clearance in 15 vs. 11.9 events per 100 patient years (risk reduction, 20%; p=0.006) and end stage renal disease in 12.1 vs. 9.4 events per 100 patient years (risk reduction 24%; p=0.002).

3. Brad ML, et al. A clinical study comparing arbsartan sodium with enalapril maleate in patients with essential hypertension. *Am J Hyper Research.* 2001;20:599-609.

A randomized double-blind parallel study with 576 patients randomized after a 4 week placebo baseline period to 8 weeks of once daily arbasartan sodium 25, 50 or 100 mg, enalapril maleate 20 mg or placebo. After 8 weeks of treatment, mean reduction from baseline in supine systolic/diastolic pressure 24 hours after dosing (trough) for arbsartan sodium 25 mg was 7.8/6.8mm Hg, for 50 mg was 15/12.1mm Hg, for 100 mg was 8.9/9.9mm Hg, for enalapril maleate 20 mg 16.7/13.3 mm Hg, and for placebo was 5.8/7.6mm Hg. Compared with mean changes in supine diastolic pressure in the placebo group, arbsartan sodium 50 to 100 mg and enalapril maleate 20 mg produced statistically significant reduction (p<0.001) in blood pressure. At 24 hours after doing, blood pressure changes obtained with arbsartan sodium 50 mg were similar to those with enalapril maleate 20 mg (p=0.11).

Supplemental Product Information

ADVERSE REACTIONS

In double-blind controlled clinical trials, the following adverse reactions reported with ARBACE occurred in ≥1% of patients, regardless of drug relationship:

	ARBACE (n=3285)	Placebo (n=1202)
Body as a Whole		
Asthenia/fatigue	3.8	3.9
Edema/swelling	1.7	1.9
Abdominal pain	1.7	1.7
Chest pain	1.1	2.6
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

In these controlled clinical trials for essential hypertension, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in arbsartan-treated (2.4%) than placebo-treated (1.3%) patients. In double-blind, controlled clinical trials for essential hypertension, the following adverse reactions were reported with ARBACE at an occurrence rate of less than 1%, regardless of drug relationship: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

ARBACE was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria and hypertension. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see PRECAUTIONS, Hyperkalemia).

Laboratory Test Findings

In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of ARBACE.

Liver Function Tests: In double-blind hypertensive trials, elevations of AST and ALT occurred in 1.1% and 1.9% of patients treated with arbsartan monotherapy and in 0.8% and 1.3% of patients treated with placebo, respectively. When AST or ALT elevations ≥2X upper limit of normal were compared, the frequency was similar to that seen in placebo.

Hyperkalemia: In controlled clinical trials for essential hypertension, hyperkalemia (serum potassium >5.5 mEq/L) occurred in 1.5% of patients treated with ARBACE. In a clinical study conducted in type 2 diabetic patients with proteinuria and hypertension, 9.9% of patients treated with ARBACE and 3.4% of patients treated with placebo developed hyperkalemia (see PRECAUTIONS, Hyperkalemia).

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with ARBACE alone. No patient discontinued taking ARBACE alone due to increased BUN or serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 gram percent and 0.09 volume percent, respectively) occurred frequently in patients treated with ARBACE alone, but were rarely of clinical importance. In controlled clinical trials no patients were discontinued due to anemia. Discontinuation of arbsartan treatment due to anemia was reported with post-marketing use of arbsartan.

In clinical trials, the following were noted to occur with an incidence of <1%, regardless of drug relationship: thrombocytopenia, eosinophilia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available in regard to overdosage with ARBACE (arbsartan sodium) in humans. The most likely manifestation of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither arbsartan nor the active metabolite can be removed by hemodialysis.

Product Monograph available on request.

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