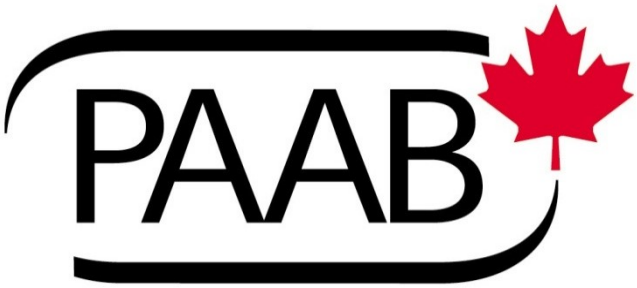
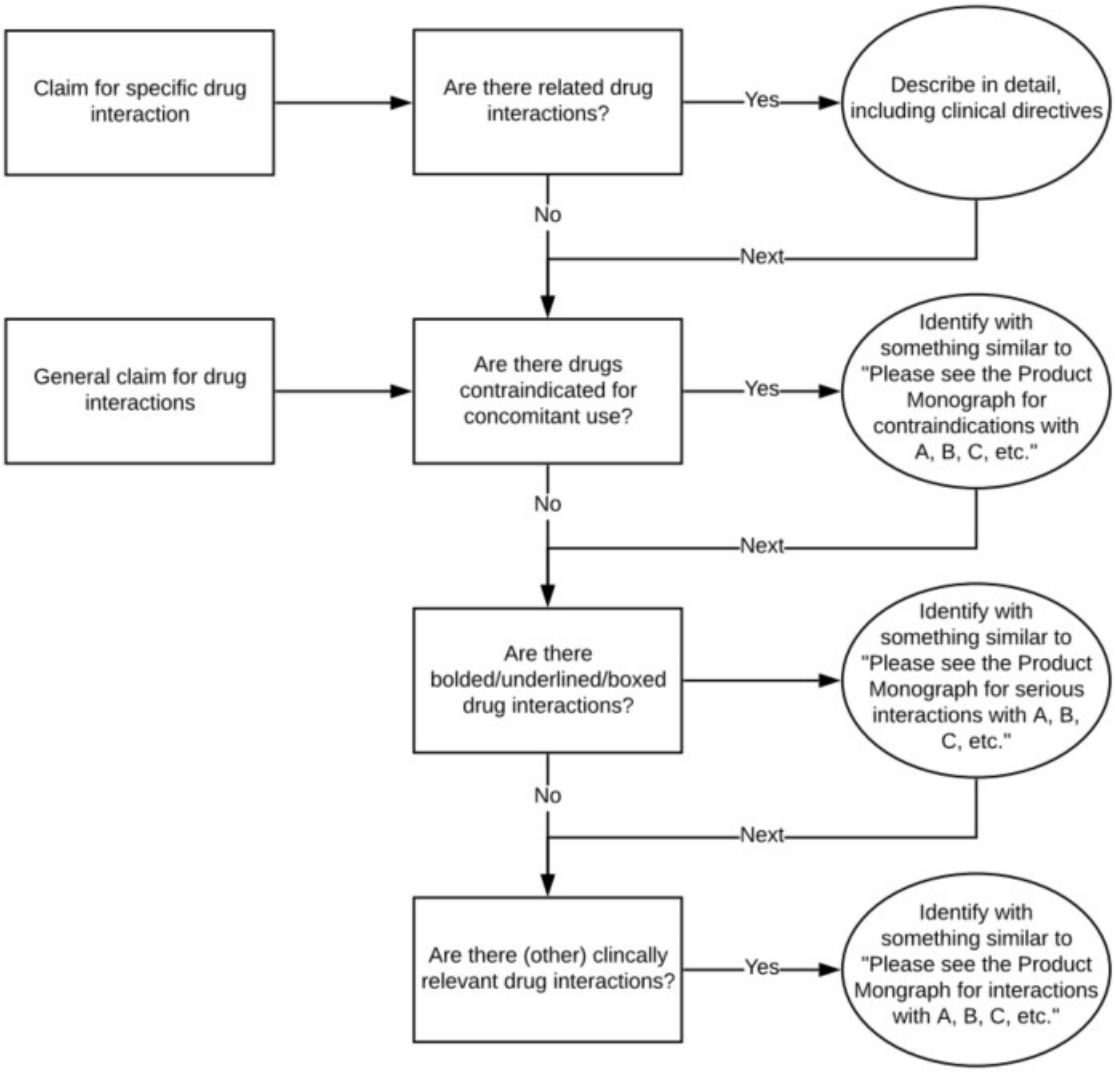


Guidance Document for Claims Relating to Drug Interactions

December 2019

Non-comparative claims for drug interactions require balance. We offer the following guidance:



Balancing information should be part of the body copy.

With respect to comparative drug interactions presentations, detailed and complete drug interaction information for all compared products is required for a fair and complete presentation.

Examples of acceptable presentations based on the attached mock Product Monograph for ARBACE

Specific claim relating to sertraline:

ARBACE does not interact with sertraline.

Concentrations of other selective serotonin reuptake inhibitors (SSRIs) may be increased when coadministered with ARBACE. Dose titration may be required for most drugs of the SSRI class and dose reduction should be considered when trazodone is coadministered with ARBACE.

Please see the Product Monograph for contraindications with ergot derivatives (dihydroergotamine, ergonovine, ergotamine), serious interactions with carbamazepine, phenobarbital and phenytoin, and interactions with colchicine, lovastatin, simvastatin, perphenazine and pimozide.

General claim:

Good drug-drug interaction profile.

Please see the Product Monograph for contraindications with ergot derivatives (dihydroergotamine, ergonovine, ergotamine), serious interactions with carbamazepine, phenobarbital and phenytoin, and interactions with SSRIs, trazodone, colchicine, lovastatin, simvastatin, perphenazine and pimozide.

Mock Product Monograph for ARBACE

PRODUCT MONOGRAPH

PrARBACE

(arbsartan sodium)
Tablets 25, 50 & 100 mg

Angiotensin II Receptor Antagonist

ABEE Pharmaceuticals Inc.
Toronto, Ontario

Control #: JA1234

PRODUCT MONOGRAPH

ARBACE

(arbsartan sodium)
Tablets 25, 50 & 100 mg

PHARMACOLOGICAL CLASSIFICATION

Angiotensin II Receptor Antagonist

ACTION AND CLINICAL PHARMACOLOGY

ARBACE (arbsartan sodium) antagonizes angiotensin II by blocking the angiotensin type one (AT_1) receptor. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin system. Its effects include vasoconstriction and the stimulation of aldosterone secretion by the adrenal cortex. Arbsartan, and its active metabolite, block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to AT_1 receptors found in many tissues, including vascular smooth muscle. A second type of angiotensin II receptor has been identified as the AT_2 receptor, but it plays no known role in cardiovascular homeostasis to date. Both arbsartan and its active metabolite do not exhibit any agonist activity at the AT_1 receptor, and have much greater affinity, in the order of 1000-fold, for the AT_1 receptor than for the AT_2 receptor. In vitro binding studies indicate that arbsartan itself is a reversible, competitive antagonist at the AT_1 receptor, while the active metabolite is 5 to 10 times more potent than arbsartan, and is a reversible, non-competitive antagonist of the AT_1 receptor.

Pharmacokinetics
Arbsartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite, Z-456, that is responsible for most of the angiotensin II receptor antagonism that follows oral arbsartan administration.
The terminal half-life of arbsartan itself is about 2 hours, and that of the active metabolite, about 6-9 hours. The pharmacokinetics of arbsartan and this metabolite are linear with oral arbsartan doses up to 200 mg and do not change over time.
Following oral administration, arbsartan is well absorbed, with systemic bioavailability of approximately 40%. About 20% of an orally-administered dose of arbsartan is converted to the active metabolite, although about 4% of subjects did not convert e arbsartan efficiently to the active metabolite.
Mean peak concentrations of arbsartan occur at about one hour, and that of its active metabolite at about 5 hours. Although maximum plasma concentrations of arbsartan and its active metabolite are approximately equal, the AUC of the metabolite is about 4 times greater than that of arbsartan.
Both arbsartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 5% and 2% respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses. Studies in rats indicate that arbsartan crosses the blood-brain barrier poorly, if at all.
In vitro studies indicate that cytochrome P450 isoenzymes 1C2 and 3C4 are involved in the biotransformation of arbsartan to its metabolites.
The volume of distribution of arbsartan is about 45 liters, and that of the active metabolite is about 18 liters.
Total plasma clearance of arbsartan is about 700 mL/min, with about 90 mL/min accounted for by renal clearance. Total plasma clearance of the active metabolite is about 80 mL/min, with

about 40 mL/min accounted for by renal clearance. Both biliary and urinary excretion contribute substantially to the elimination of arbsartan and its metabolites.

Pharmacodynamics

Arbsartan inhibits the pressor effect of angiotensin II. A dose of 100 mg inhibits this effect by about 85% at peak, with 25-40% inhibition persisting for 24 hours. Removal of the negative feedback of angiotensin II causes a 2-3 fold rise in plasma renin activity, and a consequent rise in angiotensin II plasma concentration, in hypertensive patients.

Maximum blood pressure lowering, following oral administration of a single dose of arbsartan, as seen in hypertensive patients, occurs at about 6 hours.

In arbsartan-treated patients during controlled trials, there was no meaningful change in heart rate.

There is no apparent rebound effect after abrupt withdrawal of arbsartan therapy.

Black hypertensive patients show a smaller average blood pressure response to arbsartan monotherapy than other hypertensive patients.

Clinical Trials

The Beneficial Effects of Arbsartan in Non-Insulin Dependent Diabetes Mellitus (BEAN) study was a large, multicenter, randomized, placebo-controlled, double-blind study conducted worldwide in 2012 hypertensive patients with type 2 diabetes and proteinuria. The goal of the study was to demonstrate the renal protective effects of ARBACE® over and above the benefits of blood pressure control alone. To meet this objective the study was designed to achieve equal blood pressure control in both treatment groups. Patients with proteinuria and serum creatinine of 1.3-3.0 mg/dL were randomized to receive ARBACE® 50 mg once daily titrated according to blood pressure response, or placebo, on a background of conventional antihypertensive therapy excluding ACE inhibitors and angiotensin II antagonists. Investigators were instructed to titrate study drug to 100 mg once daily as appropriate; 72% of patients were taking the 100 mg daily dose the majority of the time they were on study drug. Other antihypertensive agents (diuretics, calcium-channel blockers, alpha- or beta-blockers, and centrally acting agents) could be added as needed in both groups. Patients were followed for approximately 5 years (mean of 4.1 years).

Important inclusion criteria of the BEAN study included: type 2 diabetes and first morning urinary albumin/creatinine ratio (UA/Cr) of ≥300 mg/g (or a 24-hour urine total protein of >500 mg/day).

Important exclusion criteria of the BEAN study included: type 1 diabetes; history of heart failure; history of myocardial infarction or coronary artery bypass graft surgery within 1 month prior to study start, cerebral vascular accident or percutaneous transluminal coronary angioplasty within 6 months prior to study start, and history of transient ischemic attacks (TIA) within the year prior to study start; known history or current diagnosis of nondiabetic renal disease such as chronic glomerulonephritis of polycystic kidney disease; and uncontrolled diabetes, i.e., HBA1c >12%.

The primary endpoint of the study was the composite endpoint of doubling of serum creatinine, end-stage renal disease (need for dialysis or transplantation), or death. The results showed that treatment with ARBACE® as compared with placebo resulted in a 12% risk reduction (p=0.022) for patients reaching the primary composite endpoint. For the following individual components of the primary endpoint, the results also showed significant risk reduction in the group treated with ARBACE® as compared to placebo: 20% risk reduction in doubling of serum creatinine (p=0.006); 24% risk reduction in end-stage renal disease (p=0.002). The rate of the all-cause deaths component was not significantly different between arbsartan and placebo group, 19.0% and 18.8%, respectively.

The secondary endpoints of the study were: change in proteinuria; the rate of progression of renal disease; and the composite of morbidity and mortality from cardiovascular causes (hospitalization for heart failure, myocardial infarction, revascularization, stroke, hospitalization for unstable angina, or cardiovascular death). For the secondary endpoint of change in

proteinuria, the results showed an average reduction of 29% in the level of proteinuria in the group treated with ARBACE® ($p<0.001$) over the mean of 4.1 years. For the secondary endpoint of rate of progression of renal disease, treatment with ARBACE® reduced the rate of decline in renal function during the chronic phase of the study by 11%, ($p=0.01$) as measured by the reciprocal of the serum creatinine concentration. In this study, ARBACE® was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo. A tertiary endpoint in the study was assessment of quality of life. The results of this analysis suggest that there is no difference in the change of quality of life between treatment arms.

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. A great majority of patients with severe hypertension in controlled clinical trials required combination therapy. ARBACE® has been used concomitantly with beta-blockers and calcium channel blockers, but the data on such use are limited.
ARBACE® should normally be used in those patients in whom treatment with diuretic or beta-blocker 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.

Coadministration with ergot derivatives (dihydroergotamine, ergonovine, ergotamine) is contraindicated due to the potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.

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.

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.

DRUG INTERACTIONS

Serious Drug Interaction

Coadministration of carbamazepine, phenobarbital, phenytoin with ARBACE® may result in increased plasma concentrations of these drugs, which is associated with the potential for serious reactions. Alternative anticonvulsants should be considered.

Antidepressants
Concentrations of sertraline are not affected upon coadministration with ARBACE®. No dose adjustment is required upon coadministration.

Concentrations of other selective serotonin reuptake inhibitors (SSRIs) may be increased when coadministered with ARBACE®. Dose titration may be required for most drugs of the SSRI class.

Concentrations of trazodone may increase upon coadministration with ARBACE®. Dose reduction should be considered when trazodone is coadministered with ARBACE®.

Anti-gout
Concentrations of colchicine may be increased when coadministered with ARBACE®. Caution is warranted upon coadministration with ARBACE®.

HMG-CoA reductase inhibitors
Concentrations of lovastatin and simvastain may be increased when coadministered with ARBACE®. Clinical monitoring is recommended when these agents are coadministered.

Neuroleptics
Concentrations of neuroleptics (perphenazine, pimozide) may be increased when coadministered with ARBACE®. Clinical monitoring is recommended and a dose decrease may be necessary when these agents are coadministered with ARBACE®.

ADVERSE REACTIONS

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 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).

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.

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.

DOSAGE AND 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).

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE
Proper name: Arbsartan sodium
Chemical name: 2-butyl-4-chloro-1-imidazole- 5-methanol monosodium salt
Molecular formula: $C_{20}H_{20}NaNO_2$
Molecular weight: 801.3
Structural formula:
Description: Arbsartan sodium is a white to off-white free-flowing crystalline powder. It is freely soluble in water, soluble in alcohols, and slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.

COMPOSITION

ARBACE® is supplied as film-coated tablets containing either 25 mg, 50 mg, or 100 mg of the active ingredient, arbsartan sodium. Each tablet contains the following non-medicinal ingredients: corn starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose,

magnesium stearate, microcrystalline cellulose, and colouring agents (D&C yellow No.2 and titanium dioxide). ARBACE® 25, 50 and 100 mg tablets contain the following amounts of sodium: 2.12 mg (<1 mmol), 4.24 mg (<1 mmol), and 8.48 mg (<1 mmol) respectively.

STABILITY AND STORAGE RECOMMENDATIONS
Store at room temperature (15°C - 30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS
Tablets ARBACE® 25 mg, are light green, oval shaped, unscored, film-coated tablets. Available in blister packages of 30 tablets.
Tablets ARBACE® 50 mg, are green, oval shaped, unscored, film-coated tablets. Available in blister packages of 30 tablets.
Tablets ARBACE® 100 mg, are dark green, oval shaped, unscored, film-coated tablets. Available in blister packages of 30 tablets.

INFORMATION FOR THE PATIENT

ARBACE® Tablets
Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information in the previous leaflet may have changed.

Remember that your physician has prescribed this medicine only for you. Never give it to anyone else.

What is ARBACE®?
ARBACE® (arbsartan sodium) is a green film-coated oval shaped tablet which contains either 25, 50 or 100 mg of arbsartan sodium as the active ingredient. In addition, ARBACE® contains the following non-medicinal ingredients: corn starch, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and colouring agents (D&C yellow No. 10 aluminum lake and titanium dioxyde). ARBACE® 25, 50 and 100 mg tablets contain the following amounts of sodium: 2.12 mg (<1 mmol), 4.24 mg (<1 mmol), and 8.48 mg (<1 mmol) respectively. Although ARBACE® tablets contain potassium, this amount is too small to replace potassium supplements. If your physician has prescribed potassium supplements, continue to follow his advice.
ARBACE® belongs to a class of drugs known as angiotensin II receptor antagonists. Its action is to lower blood pressure. ARBACE® also provides kidney protection by delaying the worsening of kidney disease in type 2 diabetic patients with protein in the urine (proteinuria) and high blood pressure. Kidney disease can be measured by testing the urine for protein.
Why has my physician prescribed ARBACE®?
Your physician has prescribed ARBACE® because you have a condition known as hypertension or high blood pressure. Your physician may also have prescribed ARBACE® because you have high blood pressure and type 2 diabetes with protein in the urine. In type 2 diabetic patients with protein in the urine and hypertension, ARBACE® has been shown to slow the worsening of kidney disease.
• **What is blood pressure?**
The pressure caused by your heart pumping blood to all parts of your body is called blood pressure. Your blood pressure changes during the day depending on activity, stress and excitement. Your blood pressure is made up of two numbers, for instance 120/80. The top number measures the force while your heart pumps. The bottom number measures the force at rest, between heartbeats.

• **What is high blood pressure (or hypertension)?**
You have high blood pressure or hypertension if your blood pressure stays high even when you are calm and relaxed.
• **How do I know if I have high blood pressure?**
There are usually no symptoms of high blood pressure. The only way of knowing that you have hypertension is to know your blood pressure. For that reason, you should have your blood pressure checked on a regular basis.
• **Why should high blood pressure be treated?**
High blood pressure if left untreated can damage vital organs like the heart and the kidneys. You may feel fine and have no symptoms, but eventually hypertension can lead to strokes, heart attacks, heart failure, kidney failure or blindness.
• **How should high blood pressure be treated?**
Once high blood pressure is diagnosed, some treatments other than drugs may be recommended. Your physician may recommend some changes in lifestyle. Your physician may decide that you also need medicine to control your blood pressure. ARBACE® does not cure high blood pressure, but does help control it.
Your physician can tell you what your individual blood pressure target should be. Keep this number in mind and follow your physician's advice on how to reach this target.
• **How does ARBACE® treat high blood pressure?**
ARBACE® lowers blood pressure by specifically blocking a naturally-occurring substance called angiotensin II. Angiotensin II normally tightens your blood vessels. Treatment with ARBACE® allows them to relax. Although your physician will be able to tell you that the medicine is working by measuring your blood pressure, you probably will feel no different while you are taking ARBACE®.
• **What is Type 2 Diabetes?**
In patients with type 2 diabetes, the body's cells do not respond to the effects of insulin or too little insulin is produced. In either case, glucose (sugar) cannot enter the body's cells and supply energy. This causes a buildup of sugar in the blood, which is known as hyperglycemia (high blood sugar).
• **Why should patients with Type 2 Diabetes with Protein in the Urine be treated?**
The deterioration that characterizes kidney disease related to diabetes takes place in and around the blood-filtering units of the kidney. The kidney's ability to filter blood is reduced, and proteins in the blood are lost in the urine. Kidney disease can be measured by testing the urine for protein. Later in the disease, the kidneys lose their ability to remove waste products, such as creatinine and urea, from the blood. The progression of kidney disease is measured by testing the blood for these waste products. In type 2 diabetic patients with protein in the urine, ARBACE® has been shown to slow the worsening of kidney disease and to reduce the need for dialysis or kidney transplantation.
What should I know before taking ARBACE®?
• **Who should not take ARBACE®?**
Do not take ARBACE® if you are allergic to any of its ingredients.
• **Use in pregnancy and breast feeding**
It is not recommended to use ARBACE® while you are pregnant or breast feeding. If you are pregnant or become pregnant while taking ARBACE®, talk to your physician as soon as possible.
• **What should I tell my physician or pharmacist before taking ARBACE®?**
Please tell any physician you may consult or your pharmacist :
- about any medical problems you have or have had;
- about any allergies;
- if you are taking potassium supplements, potassium-sparing agents or salts substitutes containing potassium. Tell your physician if you have recently suffered from excess vomiting or diarrhea. It is particularly important to tell any physician you may consult if you have liver or kidney disease.

• **Use in children**
ARBACE® should not be given to children.
• **Use in elderly**
ARBACE® works equally well and is equally well tolerated by most older and younger patients.
• **Can I take ARBACE® with other medicines?**
As with most medicines, interaction with other drugs is possible. Therefore, do not take any other medicines unless you have discussed the matter with your physician or your pharmacist. Certain medicines tend to increase your blood pressure, for example, some, but not all, non-prescription preparations for appetite control, asthma, colds, coughs, hay fever and sinus problems.
• **Can I drive or operate machinery while using ARBACE®?**
Almost all patients can, but you should not perform tasks which may require special attention (for example, driving an automobile or operating dangerous machinery) until you know how you respond to your medicine.
How should I take ARBACE®?
Take ARBACE® every day exactly as your physician has instructed. It is important to continue taking ARBACE® for as long as your physician prescribes it in order to maintain smooth control of your blood pressure.
ARBACE® may be taken with or without food, but it should be taken consistently with respect to food intake, at about the same time every day.
What should I do if I miss a dose?
Try to take ARBACE® daily as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule.
What should I do in case of an overdose?
In case of an overdose, contact your physician immediately so that medical attention may be given promptly.
What undesirable effects may ARBACE® have?
Any medicine may have unintended or undesirable effects, so-called side effects. Some patients may experience dizziness, fatigue, lightheadedness or rash, including hives. Tell your physician or pharmacist promptly about these or any other unusual symptoms.
Some patients, especially those with type 2 diabetes with protein in the urine, may also develop increased levels of potassium in their blood.
If you develop an allergic reaction involving swelling of the face, lips, throat, and/or tongue which may cause difficulty in breathing or swallowing, stop taking ARBACE® and contact your physician immediately.
How can I learn more about ARBACE® and my condition?
You may obtain further information from your physician or pharmacist, who have more detailed information about high blood pressure, kidney disease, and ARBACE®.
How should I store ARBACE®?
Store ARBACE® at room temperature (15°C - 30°C). Protect from light.

Keep all medicines out of the reach of children.