PRODUCT MONOGRAPH

Pr ACEBUTOLOL – 100
Pr ACEBUTOLOL – 200
Pr ACEBUTOLOL – 400

Acebutolol Tablets (as Acebutolol Hydrochloride)

Manufacturer Standard

100 mg, 200 mg and 400 mg Tablets

Antihypertensive and Anti-anginal Agent

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DATE OF REVISION:
July 11, 2019

Control Number#:228198

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet 100, 200, and 400 mg	carnauba wax, colloidal silicon dioxide, dextrates, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol and titanium dioxide.

INDICATIONS AND CLINICAL USE

ACEBUTOLOL is indicated for the following:

- Treatment of mild to moderate hypertension.
- Long-term management of patients with angina pectoris due to ischemic heart disease.

Treatment of mild to moderate hypertension:

ACEBUTOLOL is usually used in combination with other drugs, particularly a thiazide diuretic.

However, it may be tried alone as an initial agent in those patients in whom, in the judgment of the physician, treatment should be started with a β-blocker rather than a diuretic.

In patients with severe hypertension a β-adrenergic blocking agent may be used as part of a multiple drug regimen which would normally include a diuretic and a vasodilator.

The combination of acebutolol with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than acebutolol alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility.

ACEBUTOLOL is not indicated in the emergency treatment of hypertensive crises.

Geriatrics: Acebutolol has been used in the elderly without specific adjustment of dosage. However, this patient population may require lower maintenance doses because the bioavailability of both acebutolol hydrochloride and its metabolite are approximately doubled in this age group. This increased bioavailability is probably due to decreases in first-pass metabolism and renal function in the elderly (see WARNINGS AND PRECAUTIONS, Special Populations).

Pediatrics: There is no experience with acebutolol in the treatment of pediatric age groups and therefore use in children is not recommended (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

ACEBUTOLOL (acebutolol hydrochloride) is contraindicated in:

- Patients who are hypersensitive to this drug, beta-blockers, or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Patients exhibiting sinus bradycardia.
- Patients with sick sinus syndrome.
- Patients with second and third degree A-V block.
- Patients with right ventricular failure secondary to pulmonary hypertension.
- Patients with congestive heart failure.
- Patients with cardiogenic shock.
- Patients undergoing anaesthesia with agents that produce myocardial depression, e.g. ether.
- Patients with severe peripheral circulatory disorders.
- Patients with phaeochromocytoma.

WARNINGS AND PRECAUTIONS

General

ACEBUTOLOL dosage should be individually adjusted when used concomitantly with other antihypertensive agents (see DOSAGE AND ADMINISTRATION).

Cessation of therapy with a beta-blocker should be gradual (see WARNINGS AND PRECAUTIONS section, under 'Cardiovascular').

Dizziness and/or fatigue may occur with beta-blocker administration and this should be taken into account when driving or operating machinery.

Cardiovascular

Severe sinus bradycardia may occur with the use of acebutolol from unopposed vagal activity remaining after blockade of $beta_1$-adrenergic receptors; in such cases, dosage should be reduced.

ACEBUTOLOL dosage should be individually adjusted when used concomitantly with other antihypertensive agents (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS sections).

Caution should be used in patients with Prinzmetal angina. Acebutolol may increase the number and duration of angina attacks in patients with Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Therefore, acebutolol should be used in these patients with the utmost care.

Cardiac Failure
Special caution should be exercised when administering ACEBUTOLOL to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with β-blockade always carries the potential hazard of further depressing myocardial contractibility and precipitating cardiac failure. Acebutolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle. However, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of acebutolol hydrochloride when the two drugs are used concomitantly.

The effects of β-blockers and digitalis are additive in depressing A-V conduction.

In patients without a history of cardiac failure, continued depression of myocardium over a period of time can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalised and/or given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalisation and diuretic therapy, ACEBUTOLOL therapy should be immediately withdrawn.

Concomitant use with calcium channel blockers (verapamil, diltiazem):

ACEBUTOLOL should not be used with verapamil or within several days of verapamil therapy (and *vice versa*). Use with great care with any other calcium antagonists, particularly diltiazem.

Abrupt cessation of therapy with ACEBUTOLOL
Patients with angina or ischaemic heart disease should be warned against abrupt discontinuation of ACEBUTOLOL.

There have been reports of severe exacerbation of angina, and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris, following abrupt discontinuation

of β-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of ACEBUTOLOL is planned in patients with angina pectoris, the dosage should be gradually reduced over a period of about two weeks and the patient should be carefully observed and advised to limit physical activity to a minimum. The same frequency of administration should be maintained. In situations of greater urgency, acebutolol hydrochloride therapy should be discontinued stepwise and under conditions of closer observation. If angina markedly worsens or acute coronary insufficiency develops, it is recommended that treatment with ACEBUTOLOL be reinstituted promptly, at least temporarily (see DRUG INTERACTIONS).

Central Nervous System

The low lipid solubility and lack of accumulation in CNS tissues of acebutolol and its active metabolite reduce the likelihood of sleep disturbances, depression or other central effects.

Endocrine and Metabolism

Diabetes and hypoglycemia: ACEBUTOLOL should be administered with caution to patients subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents, as β-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia, particularly tachycardia.

Thyrotoxicosis: In patients with thyrotoxicosis, the possible deleterious effects from long-term use of ACEBUTOLOL have not been adequately appraised. ACEBUTOLOL may give a false impression of improvement by masking the clinical signs of continuing hyperthyroidism or its complications. Therefore, abrupt withdrawal of ACEBUTOLOL may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

Immune

Increase in antinuclear antibody (ANA) titer was observed in approximately 12.5% of patients on chronic acebutolol hydrochloride therapy. Rare instances (<1%) of a syndrome resembling lupus erythematosus have been reported with maintenance acebutolol therapy. Similar symptoms were occasionally observed with some other β-blockers. In addition to increase ANA titers, polyarthralgia, myalgia and pleuritic pain were the main presenting symptoms. Symptoms and ANA titers appear reversible upon discontinuation of acebutolol therapy (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests section). The drug should be withdrawn if symptoms appear or if the results of ANA testing are significantly positive. Patients should be followed up both clinically and serologically until resolution of symptoms.

Risk of Anaphylactic Reactions
Beta-blockers may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions. While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge.

In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not

have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflux bradycardia and heart-block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm, and norepinephrine to overcome hypotension.

Ophthalmologic

Conjunctival xerosis (dry eyes) has been reported with β-blockers, including acebutolol. Cases of a severe syndrome (oculo-muco-cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis were reported with the chronic use of one β-adrenergic-blocking agent (practolol). This syndrome has not been observed with acebutolol or any other such agent. However, physicians should be alert to the possibility of such reactions and should discontinue treatment in the event that they occur.

Peri-Operative Considerations

In patients undergoing elective or emergency surgery: The management of patients being treated with β-blockers and undergoing elective or emergency surgery is controversial. Although β-adrenergic-receptor blockade impairs the ability of the heart to respond to β- adrenergically-mediated reflex stimuli, abrupt discontinuation of therapy with acebutolol may be followed by severe complications (see WARNINGS AND PRECAUTIONS section, under 'Cardiovascular').

Some patients receiving β-adrenergic-blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients with angina undergoing elective surgery, acebutolol should be withdrawn gradually following the recommendation given under "Abrupt Cessation of Therapy" (see WARNINGS AND PRECAUTIONS section, under 'Cardiovascular'). According to available evidence, all clinical and physiological effects of β-blockade are no longer present 72 hours after cessation of medication. The patient may be protected against vagal reactions by intravenous administration of atropine.

In emergency surgery, since acebutolol is a competitive inhibitor of β-adrenergic-receptor agonists, its effects may be reversed, if necessary, by sufficient doses of such agonists as isoproterenol.

Renal

Impaired Renal Function:
ACEBUTOLOL should be administered with caution to patients with impaired renal function. Acebutolol hydrochloride is excreted through the G.I. tract, but the active metabolite diacetolol, is eliminated predominantly by the kidney. There is a linear relationship between renal clearance of diacetolol and creatinine clearance. The daily dose of ACEBUTOLOL should be reduced in patients with a creatinine clearance less than 50 mL/min (see DOSAGE AND ADMINISTRATION section).

Respiratory

Patients with bronchospastic disease should in general not receive a β-blocker. Because of its relative β_1 selectivity, however, low doses of acebutolol may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate, alternative treatment. Since β_1 selectivity is not absolute and is dose-dependent, the lowest possible dose of acebutolol should be used initially, preferably in divided doses to avoid the higher plasma levels associated with the longer dose-interval. A bronchodilator such as a theophylline or a β_2-agonist should be made available in advance with instructions concerning its use.

Drug-induced bronchospasm is usually at least partially reversible by the use of a suitable agonist. Although cardio-selective beta blockers may have less effect on lung function than non-selective beta blockers, as with all beta blockers, they should be avoided in patients with obstructive airways disease unless there are compelling clinical reasons for their use. Where such reasons exist, cardio-selective β-blockers should be used with the utmost care.

Cases of serious pulmonary infiltration and pneumonitis complications have been reported during beta-blockage therapy. Cases of pneumonitis have been reported with acebutolol.

Skin

Various skin rashes have been reported with β-blockers, including acebutolol. Cases of a severe syndrome (oculo-muco-cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis were reported with the chronic use of one β-adrenergic-blocking agent (practolol).

Patients with known psoriasis should take beta-blockers only after careful consideration.

Special Populations

Pregnant Women: Reproduction studies have been performed with acebutolol in rats and rabbits at doses of up to 60 mg/kg/day by the oral route and 18 mg/kg/day by the I.V. route. In one rabbit study where acebutolol was administered by the I.V. route, the following malformations were observed: rib defects, gastroschisis, ventricular septal defect, dysplasia of urogenital system and umbilical hernia. These results could not be confirmed in a repeat intravenous study and were not seen in a study using the oral route.

Studies have also been performed with diacetolol (the major metabolite of acebutolol in man) at doses of up to 450 mg/kg/day p.o. in rabbits and 1,800 mg/kg/day p.o. in rats. There was a significant elevation of postimplantation loss in rabbit dams receiving 450 mg/kg/day, a level at which food consumption and body weight gain were reduced; a non-statistically significant increase in incidence of bilateral cataracts was also noticed in rat fetuses from dams treated with 1,800 mg/kg/day.

There has been no experience with the use of acebutolol in pregnant women; however, studies have shown that both acebutolol and diacetolol cross the placenta. ACEBUTOLOL should not be given to pregnant patients.

In animal studies beta blockers administered in late pregnancy gave rise to bradycardia, hypoglycaemia and cardiac or pulmonary complications in the fetus/neonate. Beta-blockers reduced placental perfusion, which resulted in intrauterine fetal death, immature and premature deliveries.

The use of ACEBUTOLOL in women with child bearing potential requires that the anticipated benefit be cautiously weighed against possible hazards.

Nursing Women: Acebutolol and diacetolol appear in breast milk with a milk plasma ratio of 7.1 and 12.2 respectively. The half-life of acebutolol in the neonate is double that in adults. The risks of hypoglycemia and bradycardia occurring in the nursing infant have not been evaluated. Use in nursing mothers is not recommended.

Pediatrics: There is no experience with acebutolol in the treatment of pediatric age groups and therefore use in children is not recommended.

Geriatrics: Acebutolol has been used in the elderly without specific adjustment of dosage. However, this patient population may require lower maintenance doses because the bioavailability of both acebutolol hydrochloride and its metabolite are approximately doubled in this age group. This increased bioavailability is probably due to decreases in first-pass metabolism and renal function in the elderly (see DOSAGE AND ADMINISTRATION section).

Monitoring and Laboratory Tests

Increase in antinuclear antibody (ANA) titer was observed in approximately 12.5% of patients on chronic acebutolol hydrochloride therapy sometimes associated with clinical symptoms; when present, these clear promptly on discontinuation of treatment (see WARNINGS AND PRECAUTIONS, Immune section).

Liver function tests should be performed at regular intervals during long-term treatment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The incidence of side effects is derived from clinical trials in 3,090 patients with hypertension, angina pectoris or arrhythmia.

The serious adverse reactions encountered with acebutolol hydrochloride are congestive heart failure, severe bradycardia and bronchospasm occurring in less than 1% of patients.
Other serious adverse reactions encountered with acebutolol hydrochloride in clinical trials are third degree A-V block, syncope (in the context of decreased cardiac output), sinus arrest, lupus-like syndrome (with arthralgia, myalgia, dyspnea and pleuritic pain, reversible upon cessation of the drug [see WARNINGS AND PRECAUTIONS section]), hallucinations, psychoses and pneumonitis.

A total of 2059 hypertensive patients received at least one dose of acebutolol hydrochloride during clinical trials and 89 patients (4.3%) discontinued the treatment. A total number of 873 patients with

angina received at least one dose of acebutolol hydrochloride during clinical trials and 110 patients (12.6%) discontinued the treatment.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 – Common Adverse Drug Reactions to Acebutolol in Patients with Hypertension, Angina Pectoris or Arrhythmia

System Organ Class **Adverse Event**	**Frequency** **N=3090**
Gastrointestinal disorders Nausea	2 %
General disorders and Administration Site Conditions Fatigue	4%
Nervous System disorders Dizziness	2 %
Respiratory, Thoracic and Mediastinal disorders Dyspnea	2.5 %
Vascular disorders Hypotension	1 %
Skin and Subcutaneous Tissue disorders Rashes	1 %

Less Common Clinical Trial Adverse Drug Reactions

Allergic-Dermatological: exfoliative dermatitis; pruritus; psoriasiform rash; sweating; urticaria (see WARNINGS AND PRECAUTIONS).

Cardiovascular: chest pain; cold extremities; congestive heart failure (see WARNINGS AND PRECAUTIONS); edema; hot flushes; intermittent claudication (pain in legs); lengthening of PR interval; palpitation; Raynaud's phenomenon; second degree A-V block; secondary effects of decreased cardiac output, which include: vertigo, lightheadedness and postural hypotension; severe bradycardia; slowing of AV conduction or increase of existing AV block. Central Nervous System: anxiety; confusion; dizziness; drowsiness or somnolence; headache; insomnia; lethargy; lightheadedness; mental depression; paresthesia; tiredness; vivid dreams; weakness.

Ears, Eyes, Nose, and Throat: blurred vision and non-specific visual disturbances; conjunctival xerosis (dry eyes); conjunctivitis; itching eyes; tinnitus.

Gastrointestinal: abdominal pain; constipation; diarrhea; flatulence; heartburn; indigestion; nausea and vomiting.

Respiratory: bronchospasm; cough; dyspnea; shortness of breath; wheezing Metabolism: loss of appetite; weight gain.

Urinary: micturition (frequency); nocturia.

Miscellaneous: cyanotic extremities; decrease in libido; shivering.

Abnormal Hematologic and Clinical Chemistry Findings: increased transaminase (SGOT, SGPT), alkaline phosphatase and lactic dehydrogenase (LDH) values; positive antinuclear antibodies (see WARNINGS AND PRECAUTIONS).

Post-Market Adverse Drug Reactions

Investigations:

There have been reports of patients who have developed anti-nuclear factor titers, sometimes associated with clinical symptoms; when present, these clear promptly on discontinuation of treatment.

Cardiac disorders:

Sinus arrest in predisposed patients (e.g., elderly patients or patients with pre-existing bradycardia, sinus node dysfunction or atrioventricular block).

Hepatic disorders:

Liver injury (mainly hepatocellular); increase in hepatic enzymes.

Musculoskeletal and Connective Tissue disorders:

During acebutolol therapy, cases of systemic lupus erythematosus (SLE) were identified. The events abated following discontinuation of acebutolol therapy within a period of a few days to 4 months. Based on this information, an association between SLE and acebutolol therapy cannot be excluded.

Respiratory, Thoracic and Mediastinal disorders:

Cases of serious pulmonary infiltration and pneumonitis complications have been reported during beta-blockage therapy. Cases of pneumonitis have been reported with acebutolol.

DRUG INTERACTIONS

Overview

Cross reactions due to displacement of other drugs from plasma protein binding sites are unlikely due to the degree of plasma protein binding exhibited by acebutolol (26%) and diacetolol.

Drug-Drug Interactions

The drug interactions discussed in this section are based on either drug interaction case reports, or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 – Established or Predicted Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comments
α-adrenergic Stimulants	C	↑ hypertensive responses	Exaggerated hypertensive responses have been reported from the combined use of β adrenergic antagonists and α-adrenergic stimulants, including those contained in proprietary cold remedies and vasoconstrictive nasal drops. Patients receiving β-blockers should be warned of this potential hazard.
Anaesthetic agents (*e.g.*, ether, cyclopropane and trichloroethylene)	T	↑ myocardial depression risk ↑ hypotension risk	Acebutolol therapy should be brought to the attention of the anesthetist prior to general anesthesia (see WARNINGS AND PRECAUTIONS, Peri-Operative Considerations section). If treatment is continued, special care should be taken when using anaesthetic agents causing myocardial depression, such as ether, cyclopropane and trichloroethylene. When it has been decided to interrupt beta-blockade prior to surgery, therapy should be discontinued for at least 24 hours (see WARNINGS AND PRECAUTIONS, Cardiovascular and Peri-Operative Considerations sections). Continuation of therapy reduces the risk of arrhythmias but the risk of hypotension may be increased. If treatment is continued, caution should be observed with the use of certain anaesthetic drugs. The patient may be protected against vagal

Proper Name	Ref	Effect	Clinical Comments
			reactions by intravenous administration of atropine.
Anti-adrenergic agents: clonidine	T	↑ clonidine withdrawal syndrome	Should it be decided to discontinue therapy in patients receiving β-blockers and clonidine concurrently, the β-blocker should be discontinued several days before the gradual withdrawal of clonidine (see WARNINGS AND PRECAUTIONS section, under 'Cardiovascular' and 'Peri-Operative Considerations'). It has been suggested that withdrawal of clonidine in the presence of β-blockade may exaggerate the clonidine withdrawal syndrome with symptoms that can include: headache, apprehension, tremors, abdominal pain, sweating, tachycardia and severe increase of blood pressure.
Drugs known to induce sinus arrest (e.g., amiodarone, diltiazem)	T	Sinus arrest	Sinus arrest may occur when beta-blockers, including SECTRAL, are used in combination with other drugs known to induce sinus arrest (see ADVERSE REACTIONS).
Monoamine Oxidase Inhibitors	T	hypertension	There is a theoretical risk that concurrent administration of monoamine oxidase inhibitors and high doses of beta-blockers, even if they are cardio-selective, can produce hypertension.
Calcium channel blockers (e.g. verapamil, diltiazem)	T	Hypotension Bradycardia Conduction defects Heart failure ↑ Depression	Acebutolol should not be used with verapamil hydrochloride or within several days of verapamil hydrochloride therapy (and vice versa). Use with great care with any other calcium antagonists, particularly diltiazem hydrochloride or diltiazem maleate. The combination of non-dihydropyridine calcium channel blockers (verapamil and diltiazem) and β-blockers warrants caution since additive effects on myocardial contractility, heart rate and AV conduction have been observed. Close medical supervision, is recommended

Proper Name	Ref	Effect	Clinical Comments
			(see WARNINGS AND PRECAUTIONS). An increased risk of depression has been reported when beta blockers are co- administered with diltiazem.
Catecholamine Depletors	T	↑ acebutolol antihypertensive and anti-anginal effects	Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with β-blocking agents. Patients treated with acebutolol plus catecholamine depletors should therefore be observed closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/ pre-syncope, or orthostatic changes in blood pressure without compensatory tachycardia.
Anti-arrhythmics (e.g. disopyramide, amiodarone)	T	negative ionotropic effects ↑ atrial conduction time	Class I anti-arrhythmic drugs such as disopyramide (Rythmodan®) and amiodarone may increase atrial conduction time and induce negative inotropic effects when used concomitantly with beta-blockers.
Digoxin	C	serious bradycardia	Concurrent use of digoxin and beta-blockers may occasionally induce serious bradycardia.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	T	↓ acebutolol antihypertensive effects	The anti-hypertensive effects of beta blockers may be attenuated by non-steroidal anti-inflammatory agents.
Sympathomimetic and xanthine bronchodilators	T	↓ bronchodilation	Acebutolol may antagonize the effects of sympathomimetic and xanthine bronchodilators.
Fingolimod	CT	bradycardia	Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such coadministration is considered necessary,

Proper Name	Ref	Effect	Clinical Comments
			appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.
Barbiturates Phenothiazines Tricyclic antidepressants Other antihypertensive agents	T	↑ acebutolol hypotensive effects	Concomitant administration of tricyclic antidepressants, barbiturates and phenothiazines as well as other anti-hypertensive agents may increase the blood pressure lowering effects of beta-blockers.

Legend: C= Case Study; CT= Clinical Trial; T= Theoretical

No significant interactions of acebutolol with hydrochlorothiazide, hydralazine, sulfinpyrazone, oral contraceptives, tolbutamide or warfarin have been observed.

Drug-Food Interactions

Food intake does not have a significant effect on the area under the plasma concentration time curve [AUC] of acebutolol although the rate of absorption and peak concentration decreases slightly (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics-Absorption).

Drug- Herb Interaction
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing should be individually adjusted when used concomitantly with other antihypertensive agents. Modified ACEBUTOLOL dosing is recommended for geriatric patients and those with hypertension, angina pectoris, impaired renal/liver function (see WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

The dose of ACEBUTOLOL (acebutolol hydrochloride) must always be adjusted to the individual requirements of the patient in accordance with the following guidelines.

Hypertension:
ACEBUTOLOL is usually used in conjunction with other antihypertensive agents, particularly thiazide diuretics but may be used alone (see INDICATIONS AND CLINICAL USE).

ACEBUTOLOL treatment should be initiated with doses of 100 mg b.i.d. If an adequate response is not seen after one week, the dosage should be increased to 200 mg b.i.d. In some cases, the daily dosage may need further increments of 100 mg b.i.d. at intervals of not less than two weeks, up to the maximum of 400 mg b.i.d.

The maintenance dose is within the range of 400 to 800 mg daily.

Patients who show a satisfactory response at a daily dose of 400 mg or less may be given the total dose once daily in the morning. Daily doses above this should be divided into two equal doses.

Angina Pectoris:

The initial dose is 200 mg b.i.d. If after two weeks a satisfactory response has not been obtained, the dosage should be increased to a maximum of 300 mg b.i.d.

The usual maintenance dose of ACEBUTOLOL in angina pectoris is in the range of 200 to 600 mg daily administered in two divided doses. In patients adequately controlled on 400 mg daily, a lower maintenance dose of 100 mg twice a day may be tried.

Use in Geriatrics:

Older patients have an approximately 2-fold increase in bioavailability and are likely to require lower maintenance doses.

Use in Patients with Impaired Renal/Liver Function:

The daily dose of acebutolol hydrochloride should be reduced by 50% when creatinine clearance is less than 50 mL/min and by 75% when it is less than 25 mL/min (see WARNINGS AND PRECAUTIONS section, under 'Special Populations').

ACEBUTOLOL and its metabolite are dialyzable.

OVERDOSAGE

Symptoms: The most common signs to be expected with a β-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia, cardiogenic shock, AV block, conduction defects, pulmonary edema, depressed level of consciousness, and rarely, hyperkalemia. Cases of sinus arrest and bronchospasm have been reported during overdosage with acebutolol.

Treatment: If overdosage occurs, in all cases therapy with ACEBUTOLOL (acebutolol hydrochloride) should be discontinued and the patient observed closely (see WARNINGS AND PRECAUTIONS, Cardiovascular section).

In addition, if required, the following therapeutic measures are suggested:

1. Excess Bradycardia or Hypotension: One (1) mg atropine sulphate administered intravenously should be given without delay. If this is insufficient it should be followed by a slow intravenous injection of isoprenaline (5 mcg per minute) with constant monitoring until a response occurs. In severe cases of self-poisoning with circulatory collapse unresponsive to atropine and catecholamines the intravenous injection of glucagon (10 to 20 mg) may produce a dramatic improvement. Cardiac pacing may be employed if bradycardia becomes severe. Judicious use of vasopressors, diazepam, phenytoin, lidocaine, digoxin, and bronchodilators should be considered depending on the presentation of the patient.

2. Bradycardia: atropine or another anticholinergic drug.

3. Heart block (second or third degree): isoproterenol or transvenous cardiac pacemaker.

4. Congestive heart failure: conventional therapy.

5. Hypotension (depending on associated factors): epinephrine rather than isoproterenol or norepinephrine may be useful in addition to atropine and digitalis [see Precaution concerning the use of epinephrine in β-blocked patients].

6. Bronchospasm: aminophylline or isoproterenol.

7. Hypoglycemia: intravenous glucose.

ACEBUTOLOL and its major metabolite are dialyzable.

It should be remembered that ACEBUTOLOL is a competitive antagonist of isoproterenol and hence large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of ACEBUTOLOL. However, the complications of excess isoproterenol should not be overlooked.

For management of a suspected drug overdose contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Acebutolol hydrochloride is a β-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies show it has a preferential effect on $beta_1$ adrenoreceptors, mainly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, acebutolol hydrochloride inhibits $beta_2$ adrenoreceptors, mostly located in the bronchial and vascular musculature.

Its peripheral effects are to reduce heart rate, especially on exercise, and to lower blood pressure in hypertensive subjects. Acebutolol and its equally active metabolite, diacetolol, have anti-arrhythmic activity, and possess some partial agonist activity (or intrinsic sympathomimetic activity - ISA). ISA of acebutolol has been demonstrated in catecholamine-depleted rats by tachycardia induced by intravenous administration of this agent. The membrane-stabilizing effect of acebutolol is not manifest at the doses used clinically. ISA has been observed with acebutolol in man, as shown by a slightly smaller (about 3 beats per minute) decrease in resting heart rate when compared to equivalent β-blocking doses of propranolol, metoprolol or atenolol.

This property ensures that some degree of stimulation of beta receptors is maintained.

Acebutolol blocks the effects of excessive catecholamine stimulation resulting from stress, which are responsible for increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. This reduces myocardial oxygen requirements, which may be an important factor in the mechanism of the anti-anginal effect. Other factors that may be involved in the mechanism of the antihypertensive effect are inhibition of renin release by the kidneys and inhibition of the vasomotor centres.

Acebutolol is used in the treatment of hypertension and/or long-term management of angina pectoris. The mechanism of the anti-anginal effect is also uncertain. An important factor may be the reduction of myocardial oxygen requirements by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction.

Pharmacokinetics

Absorption: Following oral administration, acebutolol is rapidly and almost completely (90%) absorbed from the gastrointestinal tract.

Food intake does not have a significant effect on the area under the plasma concentration time curve [AUC] of acebutolol (mean decrease = 6%) although the rate of absorption and peak concentration decreases slightly (mean decrease in C_{max} = 10%).

The plasma elimination half-life of acebutolol under fasted conditions is approximately 3 to 4 hours, while that of its metabolite, diacetolol, is 8 to 13 hours. The time to reach peak concentration for acebutolol is 2.5 hours and for diacetolol, after oral administration of acebutolol, 3.5 hours.

Within the single oral dose range of 200 to 400 mg, the kinetics are dose proportional. However, this linearity is not seen at higher doses, probably due to saturation of hepatic biotransformation sites. In addition, after multiple dosing the lack of linearity is also seen by AUC increases of approximately 100% as compared to single oral dosing.

Distribution: Acebutolol has a low binding affinity for plasma proteins (about 26%). Acebutolol and its metabolite, diacetolol, are relatively hydrophilic and therefore only minimal quantities have been detected in the cerebrospinal fluid (CSF).

Metabolism: It undergoes extensive first pass hepatic biotransformation, with an absolute bioavailability of approximately 40% for the parent compound. There is rapid formation of a major

equiactive metabolite, N-acetyl derivative (diacetolol). This metabolite is equipotent to acebutolol; therefore, this first-pass phenomenon does not attenuate the therapeutic effect of acebutolol.

Excretion: Within the single oral dose range of 200 to 400 mg, elimination via renal excretion is approximately 30% to 40% and by non-renal mechanisms 50% to 60%, which includes excretion into the bile and direct passage through the intestinal wall.

Special Populations and Conditions

Gender: No data available.

Race: No data available.

Hepatic Insufficiency: No data available.

Renal Insufficiency: Acebutolol hydrochloride is excreted through the G.I. tract, but the active metabolite diacetolol, is eliminated predominantly by the kidney. There is a linear relationship between renal clearance of diacetolol and creatinine clearance. The daily dose of acebutolol should be reduced in patients with a creatinine clearance less than 50 mL/min (see DOSAGE AND ADMINISTRATION section).

Genetic Polymorphism: No data available.

STORAGE AND STABILITY

Store at 15ºC to 30ºC. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ACEBUTOLOL – 100, 100 mg: Each white, round, biconvex, film-coated tablet, scored and engraved "APO" over "100" on one side, other side plain contains acebutolol hydrochloride equivalent to 100 mg acebutolol. Available in bottles of 100 and 500.

ACEBUTOLOL 200, 200 mg: Each white, oval, biconvex, film-coated tablet, scored and engraved "APO 200" on one side, other side plain contains acebutolol hydrochloride equivalent to 200 mg acebutolol. Available in bottles of 100 and 500.

ACEBUTOLOL – 400, 400 mg: Each white, capsule-shaped, biconvex, film-coated tablet. Partial bisect & engraved "APO 400" on one side, other side plain contains acebutolol hydrochloride equivalent to 400 mg acebutolol. Available in bottles of 100 and 500.

Composition
In addition to acebutolol hydrochloride, each film-coated tablet contains the non-medicinal ingredients carnauba wax, colloidal silicon dioxide, dextrates, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

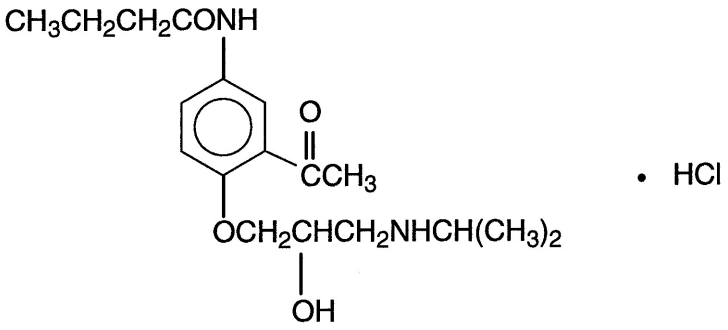
Drug Substance

Proper Name: acebutolol hydrochloride

Chemical Name: N-[3-acetyl-4-[2-hydroxy-3-[(1-methyl-ethyl)amino]propoxy]phenyl]-butanamide hydrochloride

Molecular formula and molecular mass: $C_{18}H_{28}N_2O_4 \bullet HCl$, and 372.89 g/mol

Structural Formula:



Description: fine white, crystalline, non-hygroscopic, practically odourless powder. It is freely soluble in water at 22°C. The melting point is 141 to 145°C.

Comparative Bioavailability Studies

A randomized, single dose, double-blinded, 3-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 17 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of acebutolol was measured and compared following a single oral dose (1 x 400 mg tablet) of ACEBUTOLOL (acebutolol) 400 mg tablet (Pro Doc Ltée) and Monitan® (acebutolol) 400 mg tablet (Wyeth Ltd.).

Acebutolol (1 x 400 mg) From Measured Data Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test*	Reference†	Ratio of Geometric Means (%)	90% Confidence Interval (%)
AUC_T (ng•hr/mL)	3340 3439 (24)	3413 3468 (18)	98.0	91.7 - 104.8
AUC_I (ng•hr/mL)	3607 3708 (23)	3668 3725 (18)	98.5	92.5 - 104.9
C_{max} (ng/mL)	802 839 (30)	847 882 (33)	94.7	84.8 - 105.8
T_{max}§ (hr)	2.26 (0.71)	2.32 (0.93)	-	-
$t_{1/2}$§ (hr)	2.91 (0.36)	2.92 (0.49)	-	-
*Acebutolol (acebutolol) 400 mg tablets (Pro Doc Ltée) † Monitan® (acebutolol) 400 mg tablets (Wyeth Ltd.) § Expressed as arithmetic means (standard deviations) only.				

DETAILED PHARMACOLOGY

Effect on the Cardiovascular System

Administration of acebutolol hydrochloride to the cat and the dog has shown that low doses block isoproterenol-induced tachycardia (chronotropic action). Higher doses are required to block isoproterenol-induced hypotension. Similar findings were seen in anesthetized cat and guinea pig.

Doses of 5 mg intravenously and 100 mg orally blocked isoproterenol-induced tachycardia in man. The action of isoproterenol on the forced expiratory volume (FEV) was not changed. A dose-related inhibition of reflex tachycardia to passive tilting and to nitroglycerin-induced tachycardia was observed. Acebutolol hydrochloride markedly lowered exercise-induced hypertension and tachycardia.

In the anesthetized dog, high doses (10 to 20 mg/kg) of acebutolol hydrochloride infused slowly resulted in an increased PR interval and a decreased dP/dt.

In man, oral or intravenous acebutolol hydrochloride usually caused a dose-related reduction in heart rate, cardiac index, dP/dt (left ventricular contractility) and cardiac output. Little or no effect was produced on blood pressure, peripheral vascular resistance or pulmonary functions (FEV and FVC).

Acebutolol hydrochloride, in low doses (0.05 to 0.5 mg/kg), controls sympathetically-induced arrhythmias in several species. High intravenous and oral doses are effective in ouabain-induced arrhythmias (anaesthetized dog and conscious rabbit). Ventricular arrhythmias in dogs with coronary ligation are reduced by acebutolol hydrochloride.

Electrophysiological studies in man showed delayed AV conduction time and increased refractoriness of the AV node without significantly affecting sinus node recovery time, atrial refractory period, or the HV conduction time.

Membrane stabilizing properties have been shown in three animal models. However, this effect of acebutolol hydrochloride is not manifested at the doses used clinically.

ISA was demonstrated in catecholamine-depleted rats by tachycardia induced by intravenous administration of the drug.

Effect on Pulmonary Function

The effects on airway resistance (FEV and FVC) of single oral doses of 100 and 200 mg of acebutolol hydrochloride were assessed in 15 patients with bronchial asthma. Peak flow was measured in 9 of these patients. No bronchodilator was used.

The drug did not have a significant effect on any of the pulmonary function tests. Clinically, one subject developed bronchospasm on the 100 mg dose but not on the 200 mg.

In another study, 300 mg single doses were given to 10 patients with bronchial asthma. No bronchodilator was used. There was no significant difference on FEV (the mean reduction in FEV after acebutolol was 180 ml), but specific airway conductance (SC_{AW}) was reduced (mean reduction = 9 units).

Effect on Plasma Renin

Acebutolol hydrochloride caused a significant decrease in plasma renin in hypertensive patients. This decrease was closely correlated to the decrease in blood pressure.

Effect on Lipolysis and Glucogenolysis

In healthy volunteers, acebutolol hydrochloride did not affect serum glucose, triglycerides or cholesterol. The release of free fatty acids following the administration of isoproterenol was inhibited. The drug potentiated the initial insulin-induced hypoglycemia but did not delay the return of normoglycemia.

TOXICOLOGY

Acute Toxicity

Table 3 Acute Toxicity

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)	FINDINGS
Mice	F	I.V.	78	Sedation, convulsions, respiratory depression.
	M	I.V.	75	
	F	P.O.	>2610	
	M	P.O.	>2250	
Rats	F	I.V.	120	Sedation, ataxia, respiratory depression.
	M	I.V.	115	
	F	P.O.	5200	
	M	P.O.	3200	
Dogs	M/F	I.V.	> 40 to < 63	Retching and vomiting, ataxia, weak pulse, respiratory depression.
	M/F	P.O.	>150 to <500	

Subacute and Chronic Toxicity

Table 4 – Subacute and Chronic Toxicities

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS/ DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 125 250 500	5F 5M	2 weeks	No abnormalities.
Rat	Oral	0 25 75 225	15F 15M	13 weeks	Increased salivation in some rats in the 75 and 225 mg/kg groups. Increased blood glucose levels in high dose groups. Increased alkaline phosphatase levels in the 225 mg/kg group. Significantly greater relative liver weights.
Rat	Oral	0 20 60	15F 15M	26 weeks	Food intake slightly reduced in females receiving 20 and 300 mg/kg; body weight gain

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS/ DOSE LEVEL	DURATION	FINDINGS
		300			also depressed in females on 300 mg/kg.
Rat	Oral	0 20 60 300	40F 40M	78 weeks	Reduced grooming activity, decreased body weight gain and food intake in the 300 mg/kg group.
Rat	I.V.	0 2 20	10F 10M	4 weeks (5 days/ week)	Reduction of packed cell volume and hemoglobin levels in males at 20 mg/kg. Blood glucose decreased in treated males and sodium increased in the 20 mg/kg male group. Blood urea and potassium increased in females at 20 mg/kg.
Rat	I.V.	0 5 15 40	10F 10M	4 weeks	Rats at 40 mg/kg collapsed within 5 seconds of dosing; all recovered within 2 minutes. Increased urine output and spleen weight at 40 mg/kg. Mild inflammatory reaction at injection site.
Dog	Oral	0 15 41 113	3F 3M	13 weeks	Dose-related salivation and emesis. Two deaths at 113 mg/kg. SGOT, SGPT increased and protein levels reduced in the 41 and 113 mg/kg groups. Mammary hyperplasia in two females at 113 mg/kg.
Dog	Oral	0 20 40 110	3F 3M	26 weeks	Excessive salivation and occasional emesis at 110 mg/kg. ECG recording showed prolonged slowing of heart rate; some dogs at 40 mg/kg also had delayed A- V conduction.

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS/ DOSE LEVEL	DURATION	FINDINGS
Dog	Oral	0 20 40 110	4F 4M	52 weeks	Occasional vomiting at all dose levels. Sedation and salivation mainly in dogs receiving 110 mg/kg. Prolonged, dose-related reduction in heart rate and increase in PR interval. Increase in serum potassium at 110 mg/kg. One dog also had elevated SGPT and SGOT levels on 110 mg/kg.
Dog	I.V.	0 2 20	2F 2M	4 weeks	Vomiting at 20 mg/kg. Treated groups gained significantly less weight that controls. Sporadic variations in blood urea and serum potassium.
Dog	I.V.	0 5 30	4 F 4 M	4 weeks	Dose-related unsteadiness, retching and vomiting immediately after dosing. One female dog died on the high dose.

Carcinogenicity Studies

Groups of 50 male and 50 female albino rats of the CD F/Crl BR strain received, in the diet, respectively 0, 100 and 300 mg/kg/day of acebutolol hydrochloride for 78 weeks. All groups were then off medication until the study terminated at 106 weeks. Groups of 60 male and 60 female CFLP mice, received 0, 20, 60 and 300 mg/kg/day of the drug for 87 weeks in a similar study.

There were no overt signs of toxicity. The incidence of tumors in acebutolol hydrochloride treated animals was no greater than that for the controls.

Diacetolol, the major metabolite of acebutolol hydrochloride in man, was tested for carcinogenicity in rats of the CD strain. Groups of 85 males and 85 females received, in the diet during 104 weeks, doses of 100, 500 or 3000 mg/kg/day; 145 animals of each sex were used as controls. No carcinogenic potential was observed.

Acebutolol hydrochloride and diacetolol were also shown to be devoid of mutagenic potential in the Ames Test.

Teratogenicity Studies

A) Acebutolol

Table 5 – Teratogenicity Studies with acebutolol

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 12 60	16 17 17	Days 6-16 of gestation	No teratogenicity or embryotoxicity seen.
Rat	I.V.	0 2 6 18	15 16 15 15	Days 5-17 of gestation	No teratogenicity or embryotoxicity seen.
Rabbit	Oral	0 12 60	15 16 17	Days 6-16 of gestation	No teratogenicity or embryotoxicity seen.
Rabbit	I.V.	0 2 6 18	15 14 15 14	Days 5-20 of gestation	Fetal abnormalities, not previously encountered in the strain of rabbits used, were observed at 6 and 18 mg/kg: rib defects, gastroschisis, ventricular septal defect, dysplasia of urogenital system and umbilical hernia.
Rabbit	I.V.	0 6 18	11 15 17	Days 5-20 of gestation	Mean liver fetal weight significantly reduced at 6 mg/kg. No teratogenicity or embryotoxicity seen.

B) Diacetolol

Table 6 – Teratogenicity Studies with diacetolol

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 50 300 1800	25	Day 5-17 of gestation	Non-significant increase in incidence of bilateral cataracts in fetuses at 1,800 mg/kg/day.
Rabbit	Oral	0 50 150 450	18 18 18 19	Day 5-20 of gestation	Increase in post-implantation loss (reduced food consumption and weight gain) at 450 mg/kg/day. No teratogenicity seen.

Peri and Post-natal Study

Table 7 – Peri- and Post-Natal Study with acebutolol

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 50 100 200	20	From day 15 of gestation to day 12 of lactation	Post-natal deaths were significantly higher in the three acebutolol groups (ceased lactation in a few rats). The length of gestation was also slightly increased.

Reproduction Study

A) Acebutolol

Table 8 – Reproductive Studies with acebutolol

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 40 240	13M 13F	Males* Females**	Reduction in food intake in the 240 mg/kg treated group and a dose-related reduction in weight gain in the first generation rats on day 14 of gestation. No evidence of teratogenicity or adverse effect on maternal behavior, lactation or general reproductive performance.
*Males: for 9 weeks prior to mating **Females: for 2 weeks prior to mating through gestation and lactation (2 generations).					

B) Diacetolol

Table 9 – Reproductive Studies with diacetolol

SPECIES	ROUTE	DOSE (mg/kg/day)	# ANIMALS PER DOSE LEVEL	DURATIO	FINDINGS
Rat	Oral	0 40 200 1000	30M 30F	Males* Females**	No significant impact on reproductive performance or fertility.

*Males: for 9 weeks prior to mating
**Females: for 2 weeks prior to mating through gestation and lactation (2 generations).

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PART III: CONSUMER INFORMATION

Pr ACEBUTOLOL – 100
Pr ACEBUTOLOL – 200
Pr ACEBUTOLOL – 400
(Acebutolol Hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published for ACEBUTOLOL in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ACEBUTOLOL. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ACEBUTOLOL lowers high blood pressure (hypertension). ACEBUTOLOL can be used alone or with other medicines to treat this condition.

ACEBUTOLOL is also used to treat chest pains (angina) due to ischemic heart disease (disease caused by plaque building up along the inner walls of the arteries of the heart, which narrows the arteries and reduces blood flow to the heart).

What it does:

ACEBUTOLOL belongs to a class of drugs called "beta-blockers". These drugs block the action of certain chemicals on the heart that increase blood pressure and increase heart rate.

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking ACEBUTOLOL regularly even if you feel fine.

When it should not be used:

Do not take ACEBUTOLOL if you:
- have any other medical problems, especially if you have heart rhythm disorders, heart failure,
- low blood pressure (hypotension), or other heart or circulation problems;
- have a tumour of the adrenal gland;
- are allergic or hypersensitive to acebutolol hydrochloride or other beta blocking drugs ("beta blockers"), or to any of the other nonmedicinal ingredients in ACEBUTOLOL

What the medicinal ingredient is:
acebutolol hydrochloride.

What the nonmedicinal ingredients are:
carnauba wax, colloidal silicon dioxide, dextrates, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol and titanium dioxide.

What dosage forms it comes in:
Tablets, 100, 200, and 400 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use ACEBUTOLOL, talk to your doctor, nurse or pharmacist if you:
- have psoriasis;
- have hyperthyroidism
- have any liver or kidney problems;
- have experienced heart failure in the past or have any other heart problems;
- have asthma, bronchitis, emphysema or chronic obstructive pulmonary disease (COPD);
- are currently taking any other prescription or over- the-counter medications;
- you have any known allergies;
- have diabetes or other problems with blood sugar levels;
- **are pregnant or thinking of becoming pregnant.** Taking
- ACEBUTOLOL during pregnancy may cause injury to you or your baby;
- **are breastfeeding.** ACEBUTOLOL passes from the mother into breast milk. You should not breast- feed while taking ACEBUTOLOL;
- are less than 18 years old.

If you have to undergo any dental or other surgery, inform the dentist or the doctor that you are taking ACEBUTOLOL.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to ACEBUTOLOL. Dizziness, and/or fatigue can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including prescription and over-the counter medicines.

The following medicines may interact with ACEBUTOLOL:
- medicines used to treat high blood pressure, including clonidine and calcium channel blockers (*e.g.* oral verapamil, diltiazem). Your doctor should carefully monitor you if you are taking these in combination with ACEBUTOLOL. You may also have increased risk of depression if diltiazem is used with ACEBUTOLOL;
- Reserpine, a drug used to treat high blood pressure and severe agitation;
- medicines used to treat angina (chest pain), hypertension (high blood pressure) and abnormal heart rhythms such as beta-blockers (e.g., atenolol, betaxolol, bisoprolol);
- medicines found in some cold remedies and nose drops (*e.g.* noradrenaline, isoprenaline, ephedrine, phenylephrine,

phenylpropanolamine, xanthine derivative);
- medicines used to treat irregular heart beat (*e.g.*, disopyramide, amiodarone);
- Digoxin (a heart medication);
- Fingolimod, a medicine used to treat multiple sclerosis;
- medicines used to treat asthma, bronchitis, emphysema, or lung disease (*e.g.* bronchodilators such as albuterol, epinephrine, salmeterol, terbutaline);
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling (e.g. ibuprofen, naproxen, celecoxib);
- medicines used to treat depression, seizures, schizophrenia, or psychotic disorders (*e.g.*, tricyclic antidepressants, barbiturates, phenothiazines, monoamine oxidase inhibitors);
- medicines used for anesthesia (*e.g.*, ether, cyclopropane, trichloroethylene).

PROPER USE OF THIS MEDICATION

Your doctor will determine your dose based on your individual medical needs and will tell you when and how to take ACEBUTOLOL. Take ACEBUTOLOL exactly as prescribed. It is recommended to take your dose at about the same time every day. ACEBUTOLOL can be taken with or without food.

Usual adult dose:

To treat high blood pressure:
The usual starting dose is 100 mg twice a day. In some cases, your doctor may prescribe a higher dose or prescribe ACEBUTOLOL in combination with other drugs to treat your high blood pressure.

To treat chest pains due to heart disease:
The usual starting dose is 200 mg twice a day. In some cases, your doctor may prescribe a higher dose if needed, up to a maximum recommended dose of 300 mg twice per day.

For elderly patients and patients with kidney/liver problems:
Smaller doses are generally used in older patients, and those with kidney problems.

Do not stop taking ACEBUTOLOL or change your dose without first talking to your doctor. Serious side effects, such as chest pain or heart attack can occur if you abruptly stop taking this medication.

Overdose:

If you think you have taken too much ACEBUTOLOL, contact your doctor, nurse pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, skip the missed dose and carry on with the next one at the usual time. Do not double the dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:
- tiredness,
- nausea
- dizziness
- skin rashes

You should report any side effects to your doctor. ACEBUTOLOL can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	**Low blood pressure:** dizziness, fainting, lightheadedness May occur when you go from lying or sitting to standing up.	√		
	Skin rashes.		√	
	Nausea.	√		
Uncommon	Dry eyes		√	
	Narrowing of the airways (bronchospasm), or other lung effects.		√	
	Lupus-like syndrome: joint pain, muscle pain, chest pain when you cough or breath, breathing difficulties (shortness of breath or labored breathing)		√	
	Congestive heart failure: irregular heartbeat, low heart rate, or other changes in		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	heart symptoms.			
	Lung inflammations/ Pneumonia: cough, shortness of breath, chest pain, fever		√	
	Increased sensitivity or reactions to allergens.		√	
Unknown frequency	Liver disorders: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	

This is not a complete list of side effects. For any unexpected effects while taking ACEBUTOLOL, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Keep ACEBUTOLOL and all medicines out of reach and sight of children.
Store between 15°C to 30°C. Protect from light.

Take ACEBUTOLOL that is out of date or no longer needed to your pharmacy or to your municipal waste disposal depot.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ACEBUTOLOL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); or by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

This leaflet was prepared by
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Last revised: July 11, 2019