PRODUCT MONOGRAPH

[Pr] NOVO-ACEBUTOLOL (TYPE S)

(Acebutolol Hydrochloride)

100, 200 and 400 mg Tablets

Novopharm Standard

Antihypertensive and Anti-Anginal Agent

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Table of Contents

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(Acebutolol Hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	100 mg, 200 mg and 400 mg	none *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) is indicated for:

a) HYPERTENSION: NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) is indicated in patients with mild to moderate hypertension. It 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 ß-blocker rather than a diuretic.

In patients with severe hypertension a ß-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 NOVO-ACEBUTOLOL (TYPE S) with a diuretic or peripheral vasodilator has been found to be compatible and generally more effective than NOVO-ACEBUTOLOL (TYPE S) alone. Limited experience with other antihypertensive agents has not shown evidence of incompatibility.

NOVO-ACEBUTOLOL (TYPE S) is not indicated in the emergency treatment of hypertensive crises.

b) ANGINA PECTORIS: NOVO-ACEBUTOLOL (TYPE S) is indicated in the long-term management of patients with angina pectoris due to ischemic heart disease.

Geriatrics:
NOVO-ACEBUTOLOL (TYPE S) 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.

Pediatrics:
There is no experience with NOVO-ACEBUTOLOL (TYPE S) in the treatment of pediatric age groups and therefore use in children is not recommended.

CONTRAINDICATIONS

Patients who are hypersensitive to NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) or to any ingredient in the formulation. For a complete listing, see Dosage Forms, Composition and Packaging section of the product monograph.

NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) should not be used in the presence of:

1) sinus bradycardia,
2) second and third degree A-V block,
3) right ventricular failure secondary to pulmonary hypertension,
4) congestive heart failure,
5) cardiogenic shock,
6) anesthesia with agents that produce myocardial depression, e.g. ether.

WARNINGS AND PRECAUTIONS

General
NOVO-ACEBUTOLOL (TYPE S) dosage should be individually adjusted when used concomitantly with other antihypertensive agents (see **DOSAGE AND ADMINISTRATION**).

Cardiovascular
Cardiac Failure
Special caution should be exercised when administering NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) to patients with a history of heart failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with ß-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Acebutolol hydrochloride 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 ß-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 digitalized and/or given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalisation and diuretic therapy, NOVO-ACEBUTOLOL (TYPE S) therapy should be immediately withdrawn.

Abrupt cessation of therapy with NOVO-ACEBUTOLOL (TYPE S)
Patients with angina should be warned against abrupt discontinuation of NOVO-ACEBUTOLOL (TYPE S). 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 ß-blocker therapy. The last two complications may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of NOVO-ACEBUTOLOL (TYPE S) 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. 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 NOVO-ACEBUTOLOL (TYPE S) be reinstituted promptly, at least temporarily.

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

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

Hematologic
NOVO-ACEBUTOLOL (TYPE S) 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. ß-adrenergic blockers may mask the premonitory signs and symptoms of acute hypoglycemia.

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

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 hydrochloride therapy. Similar symptoms were occasionally observed with some other ß-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 hydrochloride therapy. 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.

Peri-Operative Considerations

In patients undergoing elective or emergency surgery: The management of patients being treated with ß-blockers and undergoing elective or emergency surgery is controversial. Although ß-adrenergic-receptor blockade impairs the ability of the heart to respond to ß -adrenergically-mediated reflex stimuli, abrupt discontinuation of therapy with NOVO-ACEBUTOLOL (TYPE S) may be followed by severe complications. Some patients receiving ß-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, NOVO-ACEBUTOLOL (TYPE S) should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy. According to available evidence, all clinical and physiological effects of ß-blockade are no longer present 72 hours after cessation of medication.

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

Renal

NOVO-ACEBUTOLOL (TYPE S) 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 NOVO-ACEBUTOLOL (TYPE S) should be reduced in patients with a creatinine clearance less than 50 mL/min.

Respiratory

Patients with bronchospastic disease should in general not receive a ß-blocker. Because of its relative $ß_1$ selectivity, however, low doses of acebutolol hydrochloride may be used with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate, alternative treatment. Since $ß_1$ selectivity is not absolute and is dose-dependent, the lowest possible dose of NOVO-ACEBUTOLOL (TYPE S) 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 $ß_2$-stimulant should be made available in advance with instructions concerning its use.

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. 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.

Skin

Various skin rashes and conjunctival xerosis have been reported with ß-blockers, including acebutolol hydrochloride. A severe syndrome (oculo-muco-cutaneous syndrome) whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the chronic use of one ß-adrenergic-blocking agent (practolol). This syndrome has not been observed with acebutolol hydrochloride 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.

Special Populations

Pregnant Women: Reproduction studies have been performed with acebutolol hydrochloride 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 hydrochloride 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 hydrochloride 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 hydrochloride in pregnant women; however, studies have shown that both acebutolol and diacetolol cross the placenta. Acebutolol hydrochloride should not be given to pregnant patients. Its use 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. Use in nursing mothers is not recommended.

Pediatrics: There is no experience with NOVO-ACEBUTOLOL (TYPE S) in the treatment of pediatric age groups and therefore use in children is not recommended.

Geriatrics: Acebutolol hydrochloride 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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*.

The most serious adverse reactions encountered with acebutolol hydrochloride are congestive heart failure, severe bradycardia and bronchospasm occurring in less than 1% of patients.

The most common adverse reactions reported are fatigue (4%), dyspnea (2.5%), nausea (2%), dizziness (2%), hypotension (1%) and rashes (1%).

Adverse reactions grouped by systems are as follows:

Cardiovascular:

- Congestive heart failure (see WARNINGS AND PRECAUTIONS)
- Secondary effects of decreased cardiac output which include: syncope, vertigo, lightheadedness and postural hypotension.
- Severe bradycardia
- Lengthening of PR interval
- Second and third degree A-V block
- Sinus arrest
- Palpitation
- Chest pain
- Cold extremities
- Raynaud's phenomenon
- Hot flushes
- Pain in legs
- Edema

Central Nervous System

- Headache
- Dizziness
- Mental depression
- Tiredness
- Drowsiness or somnolence
- Lightheadedness
- Anxiety

- Tinnitus
- Weakness
- Confusion
- Vivid dreams
- Paresthesia
- Insomnia

Gastrointestinal
- Nausea and vomiting
- Heartburn
- Indigestion
- Flatulence
- Abdominal pain
- Diarrhea
- Constipation

Respiratory
- Dyspnea
- Cough
- Shortness of breath
- Wheezing
- Bronchospasm

Allergic-Dermatological (see WARNINGS AND PRECAUTIONS)
- Urticaria
- Pruritus
- Sweating
- Exfoliative dermatitis
- Psoriasiform rash
- Lupus-like syndrome with arthralgia, myalgia, dyspnea and pleuritic pain, reversible upon cessation of the drug

EENT
- Blurred vision and non-specific visual disturbances
- Itching eyes
- Conjunctivitis

Miscellaneous
- Weight gain
- Loss of appetite
- Decrease in libido
- Shivering
- Micturition (frequency)
- Nocturia

Laboratory tests
Occasional reports of increased transaminase, alkaline phosphatase and lactic dehydrogenase values.

Positive antinuclear antibodies (see **WARNINGS AND PRECAUTIONS**).

DRUG INTERACTIONS

Drug-Drug Interactions
Catecholamine-depleting drugs, such as reserpine, may have an additive effect when given with ß-blocking agents. Patients treated with NOVO-ACEBUTOLOL (TYPE S) 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.

Exaggerated hypertensive responses have been reported from the combined use of ß-adrenergic antagonists and α-adrenergic stimulants, including those contained in proprietary cold remedies and vasoconstrictive nasal drops. Patients receiving should be warned of this potential hazard.

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

Should it be decided to discontinue therapy in patients receiving ß-blockers and clonidine concurrently, the ß-blocker should be discontinued several days before the gradual withdrawal of clonidine. It has been suggested that withdrawal of clonidine in the presence of ß-blockade may exaggerate the clonidine withdrawal syndrome.

Drug-Food Interactions
Interactions with food have not been established.

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

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Use in Patients with Impaired-Renal 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 Precautions).

Acebutolol hydrochloride and its metabolite are dialyzable.

Recommended Dose and Dosage Adjustment

The dose of NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) must always be adjusted to the individual requirements of the patient in accordance with the following guidelines:

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

NOVO-ACEBUTOLOL (TYPE S) 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 NOVO-ACEBUTOLOL (TYPE S) 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.

OVERDOSAGE

Symptoms: The most common signs to be expected with a ß-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia.

Treatment: If overdosage occurs, in all cases therapy with NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) should be discontinued and the patient observed closely.

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

1 Bradycardia: atropine or another anticholinergic drug.

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

3. Congestive heart failure: conventional therapy.

4. 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 ß-blocked patients].

5. Bronchospasm: aminophylline or isoproterenol.

6. Hypoglycemia: intravenous glucose.

Acebutolol hydrochloride and its major metabolite are dialyzable.

It should be remembered that acebutolol hydrochloride 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 NOVO-ACEBUTOLOL (TYPE S). However, the complications of excess isoproterenol should not be overlooked.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NOVO-ACEBUTOLOL (TYPE S) (acebutolol hydrochloride) is a ß-adrenergic receptor blocking agent. *In vitro* and *in vivo* animal studies show it has a preferential effect on $beta_1$ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, NOVO-ACEBUTOLOL (TYPE S) inhibits $beta_2$ adrenoreceptors, chiefly located in the bronchial and vascular musculature. It possesses some partial agonist activity (or intrinsic sympathomimetic activity - ISA). It is used in the treatment of hypertension and/or prophylaxis of angina pectoris.

The mechanism of the antihypertensive effect has not been established. Among the factors that may be involved are:

a) competitive ability to antagonize catecholamine-induced tachycardia at the b-receptor sites in the heart, thus decreasing cardiac output;

b) inhibition of renin release by the kidneys;

c) inhibition of the vasomotor centres.

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: Acebutolol hydrochloride is well absorbed from the gastrointestinal tract. It undergoes extensive first pass hepatic biotransformation, with an absolute bioavailability of approximately 40% for the parent compound. Food intake does not have a significant effect on the area under the plasma concentration time curve [AUC] of acebutolol hydrochloride although the rate of absorption and peak concentration decreases slightly.

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

Metabolism: The major metabolite, an N-acetyl derivative (diacetolol), is pharmacologically active. This metabolite is equipotent to acebutolol hydrochloride and, in cats, is more cardioselective than acebutolol hydrochloride; therefore, this first-pass phenomenon does not attenuate the therapeutic effect of acebutolol hydrochloride.

Excretion: The plasma elimination half-life of acebutolol hydrochloride 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 hydrochloride is 2.5 hours and for diacetolol, after oral administration of acebutolol hydrochloride, 3.5 hours.

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

Pediatrics: Pharmacokinetics of acebutolol hydrochloride have not been studied in the pediatric population.

Geriatrics: Pharmacokinetics of acebutolol hydrochloride have not been studied in the geriatric population.

Gender: Differences in pharmacokinetics based on gender has not been established.

Race: Differences in pharmacokinetics based on race has not been established.

Hepatic Insufficiency: Differences in pharmacokinetics based on hepatic function has not been established (see WARNING AND PRECAUTIONS).

Renal Insufficiency: Differences in pharmacokinetics based on renal function has not been established (see WARNING AND PRECAUTIONS).

Genetic Polymorphism: Differences in pharmacokinetics based on genetic polymorphism has not been established.

STORAGE AND STABILITY

Store between 15 – 30 ˚C. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NOVO-ACEBUTOLOL (TYPE S) 100 mg, available in bottles of 100 and 500. White to creamy white, shield-shaped, film-coated, one side scored tablets, engraved with **N** vertical scoreline **N** on the scored side and **100** on the other side.

NOVO-ACEBUTOLOL (TYPE S) 200 mg, available in bottles of 100 and 500. Blue, shield-shaped, film-coated, one side scored tablets, engraved with two **N**'s and a vertical scoreline on one side and **200** on the other side.

NOVO-ACEBUTOLOL (TYPE S) 400 mg, available in bottles of 100 and 500. White to creamy white, shield-shaped, film-coated, one side scored tablets, engraved with two **N**'s and a vertical scoreline on one side and **400** on the other side.

Composition

NOVO-ACEBUTOLOL (TYPE S) 100 mg, 200 mg and 400 mg tablets contain acebutolol as acebutolol hydrochloride. NOVO-ACEBUTOLOL (TYPE S) tablets contain the active ingredient acebutolol hydrochloride and the following non medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and talc. In addition: NOVO-ACEBUTOLOL (TYPE S) 100 mg and 400 mg tablets contains polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc and titanium dioxide, NOVO-ACEBUTOLOL (TYPE S) 200 mg tablets contains D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum 3% - 5% Lake, FD&C Blue #2 Aluminum 3% - 5% Lake, glyceryl triacetate, polyethylene glycol, polydextrose, hydropropyl methylcellulose, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name: Acebutolol hydrochloride

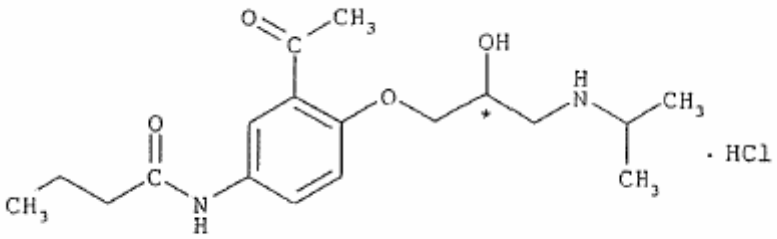
Chemical name: N-[3-acetyl-4-[(2RS)-2-hydroxy-3-[(1-methylethyl)amino] propoxy]phenyl]butanamide hydrochloride

(±)-3'-acetyl-4'-[2-hydroxy-3-(isopropylamino)propoxy]-butyranilidehydrochloride

Molecular formula: $C_{18}H_{29}ClN_2O_4$

Molecular mass: 372.89

Structural formula:



Physicochemical properties: Acebutolol Hydrochloride is a white, or almost white, crystalline powder. The product is soluble in water and in alcohol, very slightly soluble in acetone, and methylene chloride, practically insoluble in ether. The pH of a 1% aqueous solution of Acebutolol hydrochloride determined at 20°C must be between 5.0 and 7.0. The Acebutolol hydrochloride melts between 140-144°C.

CLINICAL TRIALS

Comparative Bioavailability Study

A single-dose, randomized, two-period, two-treatment, two-sequence crossover, comparative bioavailability study of Acebutolol HCl 400 mg Tablets (Novopharm Limited) and SECTRAL® 400 mg Tablets (by Aventis Pharma Inc., Canada) in 47 healthy, non-smoking, adult male and female subjects under fasting conditions.

The pharmacokinetic data calculated for the NOVO-ACEBUTOLOL and SECTRAL® tablet formulation, under fasting conditions, is tabulated below:

Acebutolol HCl
(1 x 400 mg)
From measured data

Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test Novo-Acebutolol Tablets	Reference† Sectral®	% Ratio of Geometric Means	90% Confidence Interval#
AUC_{0-T} (ng.h/mL)	4363.06 4503.198 (26.1%)	4349.92 4494.355 (26.5%)	100	97.0 – 104
AUC_{0-inf} (ng.h/mL)	4471.81 4612.516 (25.9%)	4461.64 4608.620 (26.5%)	100	97.0 – 104
C_{MAX} (ng/mL)	912.97 964.645 (34.3%)	889.49 947.974 (39.1%)	103	93.9 – 112
T_{MAX} * (h)	2.745 (35.8%)	2.628 (44.1%)		
$T_{½}$(h) *	4.740 (22.2%)	4.718 (22.2%)		

† Sectral® manufactured by Aventis Pharma Inc., and purchased in Canada.
* Expressed as the arithmetic mean (CV%) only.
# Calculation based on least squares estimate

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 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 (10-20 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 - 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, but specific airway conductance (SC_{AW}) was reduced. When isoproterenol was subsequently administered, the bronchodilator response (rise in FEV_1) was also decreased.

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

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)	FINDINGS
Mice	F	I.V.	78	Sedation, convulsions, respiratory depression
	M	I.V.	75	
	F	P.O.	>2,610	
	M	P.O.	>2,250	
Rats	F	I.V.	120	Sedation, ataxia, respiratory depression
	M	I.V.	115	
	F	P.O.	>5,200	
	M	P.O.	>3,200	
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					
SPECIES	**ROUTE**	**DOSE (mg/kg/day)**	**ANIMALS PER DOSE LEVEL**	**DURATION**	**FINDINGS**
Rat	Oral	0 125 250 500	5 F 5M	2 weeks	No abnormalities
Rat	Oral	0 25 75 225	15F	13 weeks	Increased salifation in some rats in the 75 and 225 mg/kg groups. Increased alkaline phosphatase levels in the 225 mg/kg group. Significantly greater relative liver weights.
Rat	Oral	0 20 60 300	15F 15M	26 weeks	Food intake slightly reduced in females receiving 20 and 300 mg/kg; body weight gain 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	IV	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	IV	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 sites.
Dog	Oral	0 15 41 113	3F 3M	13 weeks	Dose-related saluvation 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.
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.

Subacute and Chronic Toxicity					
SPECIES	**ROUTE**	**DOSE (mg/kg/day)**	**ANIMALS PER DOSE LEVEL**	**DURATION**	**FINDINGS**
Dog	IV	0 2 20	2F 2M	4 weeks	Vomiting at 20 mg/kg. Treated groups gained significantly less weight than controls. Sporadic variations in blood urea and serum potassium.
Dog	IV	0 5 30	4F 4M	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 HCl 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 3,000 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**					
Species	**Route**	**Dose Mg/kg/day**	**Animals Per dose Level**	**Duration**	**Findings**
Rat	Oral	0 12 60	16 17 17	Day 6 - 16 of gestation	No teratogenicity or embryotoxicity seen.
Rat	IV	0 2 6 18	15 16 15 15	Day 5 – 17 of gestation	No teratogenicity or embryotoxicity seen.
Rabbit	Oral	0 12 60	15 16 17	Day 6 – 16 of gestation	No teratogenicity or embryotoxicity seen.
Rabbit	IV	0 2 6	15 14 15	Day 5 - 20 of gestation	Foetal abnormalities, not previously encountered in the strain of rabbits used, were observed at 6 and 18 mg/kg; rib defects, gastroschisis,

Teratogenicity Studies **A) Acebutolol**					
Species	**Route**	**Dose Mg/kg/day**	**Animals Per dose Level**	**Duration**	**Findings**
		18	14		ventricular septal defect, dysplasia of urogenital system and umbilical hernia.
Rabbit	IV	0 6 18	11 15 17	Day 5 – 20 of gestation	Mean live foetal weight significantly reduced at 6 mg/kg. No teratogenicity or embryotoxicity seen.

Teratogenicity Studies (Cont'd) **B) Diacetolol**					
Species	**Route**	**Dose Mg/kg/day**	**Animals Per dose Level**	**Duration**	**Findings**
Rat	Oral	0 50 300 1,800	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					
Species	**Route**	**Dose Mg/kg/day**	**Animals Per dose Level**	**Duration**	**Findings**
Rat	Oral	0 50 100 200	20	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**					
Species	**Route**	**Dose Mg/kg/day**	**Animals Per dose Level**	**Duration**	**Findings**
Rat	Oral	0 40 240	13M 25F	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.

Reproduction Study **B) Diacetolol**					
Species	**Route**	**Dose Mg/kg/day**	**Animals Per dose Level**	**Duration**	**Findings**
Rat	Oral	0 40 200 1,000	15M 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 NOVO-ACEBUTOLOL (TYPE S)
(Acebutolol Hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when NOVO-ACEBUTOLOL (TYPE S) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NOVO-ACEBUTOLOL (TYPE S). Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- NOVO-ACEBUTOLOL (TYPE S) (Acebutolol hydrochloride) is used to lower blood pressure and reduce angina (chest pain).

What it does:
- NOVO-ACEBUTOLOL (TYPE S) is in a class of drugs called beta-blockers. Beta-blockers affect the heart and circulatory system (arteries and veins).

When it should not be used:
- You have ever had an allergic reaction to NOVO-ACEBUTOLOL (TYPE S) or to other beta-blockers, or to any of the other ingredients in this medicine (See "What the nonmedicinal ingredients are").
- You have or have ever suffered from any heart conditions including heart failure which is not under control, second-or third-degree heart block
- You have ever suffered from very slow or very irregular heartbeats, very low blood pressure or very poor circulation
- You have high blood pressure in the circulation to the lungs
- You go into hospital to have an operation and will be given an anesthetic

What the medicinal ingredient is:
The medicinal ingredient in NOVO-ACEBUTOLOL (TYPE S) is "Acebutolol hydrochloride".

What the nonmedicinal ingredients are:
NOVO-ACEBUTOLOL (TYPE S) tablets contain the following non medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, sodium lauryl sulfate, and talc. In addition: NOVO-ACEBUTOLOL (TYPE S) 100 mg and 400 mg tablets contains polyethylene glycol, polyvinyl alcohol (partially hydrolyzed), talc and titanium dioxide, NOVO-ACEBUTOLOL (TYPE S) 200 mg tablets contains D&C Yellow #10 Aluminum Lake, FD&C Blue #1 Aluminum 3% - 5% Lake, FD&C Blue #2 Aluminum 3% - 5% Lake, glyceryl triacetate, polyethylene glycol, polydextrose, hydropropyl methylcellulose, titanium dioxide.

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

WARNINGS AND PRECAUTIONS

BEFORE you use NOVO-ACEBUTOLOL (TYPE S) talk to your doctor or pharmacist if:

- you have or have ever suffered from any heart conditions including heart failure, second-or third-degree heart block
- you have ever suffered from very slow or very irregular heartbeats, very low blood pressure or very poor circulation
- you have thyrotoxicosis (a condition caused by an overactive thyroid gland). NOVO-ACEBUTOLOL (TYPE S) may hide the symptoms of thyrotoxicosis.
- you are pregnant, are trying to become pregnant or are breast-feeding
- you have asthma, wheezing or any other similar breathing problems
- you go into hospital to have an operation, tell the anaesthetist and/or the medical staff that you are taking NOVO-ACEBUTOLOL (TYPE S).
- you are taking any other medicines, including any you have bought from the pharmacy
- you have diabetes. NOVO-ACEBUTOLOL (TYPE S) may modify your normal response to low blood sugar, which usually involves an increase in heart rate.
- you have problems with your kidneys.
- you have problems with your liver

You may notice that your pulse rate becomes slower while you are taking the tablets. This is normal, but if you are concerned, please tell your doctor about it.

Driving and using machines
- Your medicine is unlikely to affect your ability to drive or to operate machinery. However, some people may occasionally feel dizzy or tired when taking NOVO-ACEBUTOLOL (TYPE S). If this happens to you, ask your doctor for advice.

NOVO-ACEBUTOLOL (TYPE S) must not be given to children.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with NOVO-ACEBUTOLOL (TYPE S) include:

- Clonidine (for hypertension or migraine). If you are taking clonidine and NOVO-ACEBUTOLOL (TYPE S) together, you must not stop taking clonidine unless your doctor tells you to do so. If you have to stop taking clonidine, your doctor will give you careful instructions how to do it.
- Reserpine

- Nasal decongestants or other cold remedies (including the ones you can buy in the pharmacy).

If you are taking any other medicines, including any you have bought from the pharmacy, you should tell your doctor.

PROPER USE OF THIS MEDICATION

Usual dose:
Your doctor will tell you how much NOVO-ACEBUTOLOL (TYPE S) to take each day and when to take them, depending on your condition. Also, read the label on the container. Your pharmacist can help you if you are not sure.

Swallow NOVO-ACEBUTOLOL (TYPE S) tablets with a drink of water.

Do not stop taking your medicine without talking to your doctor first. In some cases, it may be necessary to stop taking the medicine gradually.

Overdose:
If you accidentally take an overdose NOVO-ACEBUTOLOL (TYPE S) tablets, either call your doctor straight away, or go to your nearest hospital emergency department. Always take any remaining tablets, the container and the label with you, so that the medicine can be identified.

Missed Dose:
If you forget to take your NOVO-ACEBUTOLOL (TYPE S) tablets at the right time, take your dose when you remember and then take your next dose at the usual time. Don't take two doses at the same time. If you are worried, ask your doctor or pharmacist for advice.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, there may be some possible side effects while you are taking NOVO-ACEBUTOLOL (TYPE S).

If you experience any of the following serious side effects, stop taking NOVO-ACEBUTOLOL (TYPE S) and call your doctor immediately or seek emergency medical treatment:

- an allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; hives);
- wheezing or shortness of breath;
- an unusually slow or irregular heartbeat;
- swelling of the feet and/or lower legs;
- leg pain or cramping;
- chest (heart) pain;
- blue or cold feet and hands; or
- a rash.

If you experience any of the following less serious side effects, continue taking acebutolol and talk to your doctor:

- fatigue or confusion;
- headache or dizziness;
- weak pulse or a mildly slow heart rate;
- diarrhea, constipation, gas, nausea, or vomiting;
- depression;
- nightmares

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	
	allergic reaction (difficulty breathing; closing of the throat; swelling of the lips, tongue, or face; hives)			✓
	wheezing or shortness of breath			✓
	an unusually slow or irregular heartbeat			✓
	swelling of the feet and/or lower legs			✓
	leg pain or cramping			✓
	chest (heart) pain			✓
	blue or cold feet and hands			✓
	rash			✓

This is not a complete list of side effects. For any unexpected effects while taking NOVO-ACEBUTOLOL (TYPE S), contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 – 30 ˚C. Protect from light.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness
Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Novopharm Limited at:
at: 1-800-268-4127 ext. 5005
or druginfo@novopharm.com

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