PRODUCT MONOGRAPH

[Pr]TEVA-ACEBUTOLOL
(acebutolol hydrochloride)

100, 200 and 400 mg Tablets

Teva Standard

Antihypertensive and Anti-Anginal Agent

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THERAPEUTIC CLASSIFICATION

Antihypertensive and Anti-Anginal Agent

ACTION AND CLINICAL PHARMACOLOGY

TEVA-ACEBUTOLOL (acebutolol hydrochloride) is a β-adrenergic receptor blocking agent. *In vitro* and *in vivo* studies in animals have demonstrated that it has a preferential effect on β_1 adrenoreceptors, chiefly located in heart muscle. This preferential effect is not absolute, however, and at higher doses of acebutolol hydrochloride β_2 adrenoreceptors chiefly located in the bronchial and vascular musculature are also inhibited. It exhibits some partial agonist activity (or intrinsic sympathomimetic activity - ISA). Acebutolol hydrochloride is used in the treatment of hypertension and/or prophylaxis of angina pectoris.

The mechanism of the antihypertensive effect has not been determined. Among the possible factors which may be involved are:

a) competitive ability to antagonize catecholamine-induced tachycardia at the beta-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 effects is uncertain as well. A key 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.

Acebutolol hydrochloride is absorbed quite well from the gastrointestinal tract and undergoes extensive first-pass hepatic biotransformation. The parent compound has an absolute bioavailability of approximately 40%. Diacetolol, an N-acetyl derivative, the major metabolite, is pharmacologically active. This metabolite is equipotent to acebutolol hydrochloride and was shown to be more cardioselective in cats.

Therefore, this first-pass phenomenon does not attenuate the therapeutic effect of acebutolol hydrochloride. Although the rate of absorption and peak concentration decreased slightly, food

intake does not have a significant effect on the area under the plasma concentration time curve (AUC) of acebutolol hydrochloride.

The plasma elimination half-life of acebutolol hydrochloride was found to be 3 to 4 hours, while the half-life for diacetolol, the metabolite is 8 to 13 hours. After oral administration of acebutolol hydrochloride the time to reach peak concentration is 2.5 hours and for diacetolol, 3.5 hours.

The kinetics of acebutolol hydrochloride are dose proportional within the single oral dose range of 200 to 400 mg. At higher doses, however, this linearity is not seen; probably due to saturation of hepatic biotransformation sites. In addition, the lack of linearity is also seen by AUC increases of approximately 100% after multiple dosing, as compared to single oral dosing. Renal excretion is approximately 30% to 40%. Elimination via non-renal mechanisms is approximately 50% to 60%, which includes excretion into the bile and direct passage through the intestinal wall.

Acebutolol hydrochloride binds to plasma proteins with low affinity (approximately 26 %). Both acebutolol hydrochloride and diacetolol, its metabolite, are hydrophilic and, therefore, only minimal quantities have been detected in the cerebrospinal fluid (CSF).

A comparative, two-way, single-dose, fasting bioavailability study was performed on two 200 mg acebutolol products, TEVA-ACEBUTOLOL 200 mg tablets and Monitan® 200 mg tablets. The pharmcokinetic data calculated for acebutolol in the TEVA-ACEBUTOLOL and Monitan® tablet formulations is tabulated below.

a) Acebutolol

	Geometric Mean Arithmetic Mean (C.V.)				
	TEVA-ACEBUTOLOL (1 x 200 mg)		**Monitan®* * (1 x 200 mg)**		**Percentage of Monitan®**
AUC_T (ng•hr/mL)	1805 1826	(16)	1790 1812	(17)	101
AUC_I (ng•hr/mL)	1973 1994	(16)	1961 1982	(16)	101
C_{max} (ng/mL)	376 381	(18)	410 429	(92)	92
T_{max} * (hr)	2.6	(0.8)	2.6	(0.9)	---
$T_{½}$* (hr)	3.3	(1.1)	3.0	(0.4)	---

* For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

* * Monitan® 200 mg Tablets (Wyeth Ltd., Canada).

A comparative, two-way, single-dose, fasting bioavailability study was performed on two 400 mg acebutolol products, TEVA-ACEBUTOLOL 400 mg tablets and Monitan® 400 mg tablets. The pharmacokinetic data calculated for acebutolol in the TEVA-ACEBUTOLOL and Monitan® tablet formulations is tabulated below.

a) Acebutolol

	Geometric Mean Arithmetic Mean (C.V.) TEVA-ACEBUTOLOL (1 x 400 mg)		Monitan®* * (1 x 400 mg)		Percentage of Monitan®
AUC_T (ng•hr/mL)	4012 4105	(23)	4092 4169	(20)	98
AUC_I (ng•hr/mL)	4187 4274	(22)	4261 4333	(19)	99
C_{max} (ng/mL)	868 921	(36)	954 985	(26)	94
T_{max} * (hr)	2.5	(0.63)	2.7	(0.07)	---
$T_{½}$* (hr)	3.8	(0.13)	3.6	(0.15)	---

* For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

* * Monitan® 400 mg Tablets (Wyeth Ltd., Canada).

INDICATIONS AND CLINICAL USE.

a) Hypertension: TEVA-ACEBUTOLOL (acebutolol hydrochloride) is indicated in patients with mild to moderate hypertension. It can often be used in combination with other drugs, particularly a thiazide diuretic. However, if in the judgment of the physician treatment should be started with a β-blocker rather than a diuretic, it may be tried alone as an initial agent in those patients.

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

Acebutolol hydrochloride used in combination with a diuretic or peripheral vasodilator has been shown to be compatible and generally more effective than acebutolol hydrochloride alone. Limited experience with other antihypertensive agents has not demonstrated any signs of incompatibility.

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

b) Angina Pectoris: TEVA-ACEBUTOLOL is indicated in the long-term management of patients with angina pectoris due to ischemic heart disease.

CONTRAINDICATIONS

TEVA-ACEBUTOLOL (acebutolol hydrochloride) is contraindicated 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

a) In approximately 12.5% of patients on chronic acebutolol hydrochloride therapy, an increase in antinuclear antibody (ANA) titer was observed. Rare cases (<1 %) of a syndrome resembling lupus erythematosus have been observed with maintenance acebutolol hydrochloride therapy. Similar symptoms were occasionally reported with some other β-blockers. In addition to increased ANA titers, the main presenting symptoms were polyarthralgia, myalgia and pleuritic pain. Upon discontinuation of acebutolol hydrochloride therapy, symptoms and ANA titers appear reversible. If symptoms appear or if the results of ANA testing are significantly positive, the drug should be withdrawn. Until resolution of symptoms patients should be followed up both clinically and serologically.

b) Cardiac Failure

When administering TEVA-ACEBUTOLOL (acebutolol hydrochloride) to patients with a history of heart failure, special caution should be exercised. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with β - blockade always carries the hazardous possibility of further depressing myocardial contractility and precipitating cardiac failure. TEVA-ACEBUTOLOL's action is selective and does not abolish the inotropic action of digitalis on the heart muscle. However, when the two drugs are used concomitantly, the positive inotropic action of digitalis may be reduced by the negative inotropic effect of acebutolol hydrochloride.

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 instances, result in cardiac failure. Therefore, patients should be fully digitalised and/or given a diuretic and the response observed closely, at the first sign or symptom of impending cardiac failure. TEVA-ACEBUTOLOL therapy should be immediately withdrawn if cardiac failure continues despite adequate digitalisation and diuretic therapy.

c) Abrupt Cessation of Therapy with TEVA-ACEBUTOLOL
Patients with angina should be cautioned against abrupt discontinuation of TEVA-ACEBUTOLOL. Following abrupt discontinuation of β-blocker therapy, there have been reports of severe exacerbation of angina and of myocardial infarction or ventricular arrhythmias occurring in patients with angina pectoris. Exacerbation of angina pectoris mayor may not precede the occurrence of the last two complications.

Therefore, when discontinuation of TEVA-ACEBUTOLOL is planned in patients with angina pectoris, the dosage should be reduced gradually and careful observation of the patient is necessary. The same frequency of administration should be maintained. In situations of greater urgency, stepwise discontinuation of acebutolol hydrochloride under conditions of closer observation is necessary. It is recommended that treatment with acebutolol hydrochloride be reinstituted promptly, at least temporarily if angina markedly worsens or acute coronary insufficiency develops.

d) Various skin rashes and conjunctival xerosis have been observed with use of β-blockers, including acebutolol hydrochloride. A severe syndrome (oculo-muco-cutaneous syndrome) whose symptoms include conjunctivitis sicca and psoriasiform rashes, otitis and sclerosing serositis has occurred with the chronic use of a particular β-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 should they occur.

e) With the use of acebutolol hydrochloride, severe sinus bradycardia may occur from unopposed vagal activity remaining after blockade of β_1-adrenergic receptors. Dosage should be reduced in such cases.

f} The possible deleterious effects from long-term use of acebutolol hydrochloride have not been adequately appraised in patients with thyrotoxicosis. By masking the clinical signs of continuing hyperthyroidism or its complications, TEVA-ACEBUTOLOL may give a false impression of improvement. Therefore, abrupt cessation of TEVA-ACEBUTOLOL may be followed by an exacerbation of the symptoms of hyperthyroidism, including thyroid storm.

g) Use in Pregnancy
Reproduction studies have been performed with acebutolol hydrochloride in rats and rabbits at oral doses of up to 60 mg/kg/day and at i.v. doses of up to 18 mg/kg/day. In one rabbit study where acebutolol hydrochloride was administered intravenously the following malformations were observed: rib defects, gastroschisis, ventricular septal defect, dysplasia of urogenital system and umbilical hernia. These results were not confirmed in a repeat intravenous study and were not observed in an oral study.

Studies have also been conducted with diacetolol (the major metabolite of acebutolol hydrochloride in man) at doses of up to 450 mg/kg/day p.o. in rabbits and 1800 mg/kg/day p.o. in rats. In rabbit dams receiving 450 mg/kg/day, a level at which food consumption and

body weight gain were reduced, there was significant elevation of postimplantation loss. A non-statistically significant increase in incidence of bilateral cataracts was observed in rat fetuses from dams receiving 1800 mg/kg/day.

To date, there has been no experience with acebutolol hydrochloride in pregnant women. Studies have shown, however, that both acebutolol and diacetolol cross the placenta. TEVA-ACEBUTOLOL should not be administered to pregnant patients. The use of TEVA-ACEBUTOLOL in women with child bearing potential requires that the anticipated benefit be cautiously weighed against possible hazards.

h) Nursing Mothers:
Acebutolol and diacetolol appear in breast milk with a milk plasma ratio of 7.1 and 12.2, respectively. Use in lactating women is not recommended.

PRECAUTIONS

a) Patients with bronchospastic disease, should, in general, not be administered a β-blocker. Low doses of TEVA-ACEBUTOLOL (acebutolol hydrochloride) may be used, however, with caution in patients with bronchospastic disease who do not respond to, or who cannot tolerate, alternative treatment because of its relative β_1-selectivity. The lowest possible dose of TEVA-ACEBUTOLOL should be used initially, preferably in divided doses to avoid the higher plasma levels associated with the longer dose-interval and a β_2 stimulating agent should be administered concomitantly since β_1 selectivity is not absolute and is dose-dependent.

There may be increased difficulty in treating an allergic type reaction in patients on β-blockers. The reaction may be more severe in these patients due to pharmacological effects of β-blockers and problems with fluid changes. Since it may not have its usual effects in the treatment of anaphylaxis, epinephrine should be administered with caution. On the one hand, larger doses of epinephrine may be necessary to overcome the bronchospasm, while on the other, these doses can be accompanied with excessive alpha-adrenergic stimulation with consequent hypertension, reflex 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 β-agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

b) Patients subject to spontaneous hypoglycemia, or diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents should be administered TEVA-ACEBUTOLOL with caution. The premonitary signs and symptoms of acute hypoglycemia may be masked by β-adrenergic blockers.

c) Patients with impaired renal function should be administered TEVA-ACEBUTOLOL with caution. Although acebutolol hydrochloride is excreted via the gastrointestinal tract, the active metabolite, diacetolol, is eliminated predominantly by the kidney. A linear relationship

exists between renal clearance of diacetolol and creatinine clearance. In patients with a creatinine clearance less than 50 mL/min., the daily dose of TEVA-ACEBUTOLOL should be reduced.

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

e) TEVA-ACEBUTOLOL dosage should be individually adjusted when given concomitantly with other antihypertensive agents (see Dosage and Administration).

f) During long-term treatment, liver function tests should be performed at regular intervals.

g) Patients Undergoing Elective or Emergency Surgery: The management of patients receiving β-blockers and undergoing elective or emergency surgery is controversial. Although β-adrenergic-receptor blockade impairs the heart's ability to respond to β-adrenergically-moderated reflex stimuli, abrupt cessation of therapy with TEVA-ACEBUTOLOL may be followed by severe complications (see Warnings). During anesthesia, some patients receiving β-adrenergic blocking agents have been subject to protracted severe hypotension. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, TEVA-ACEBUTOLOL should be withdrawn gradually following the recommendation given under Abrupt Cessation of Therapy, in patients with angina undergoing elective surgery (see Warnings). The evidence available suggests that all clinical and physiological effects of β-blockade are no longer present 72 hours after cessation of medication. Since TEVA-ACEBUTOLOL is a competitive inhibitor of β-adrenergic-receptor agonists, in emergency surgery, its effects may be reversed, if necessary, by sufficient doses of agonists such as isoproterenol.

h) Use in Children: Use in children is not recommended since there is no experience with acebutolol hydrochloride in the treatment of pediatric age groups.

i) Drug Interactions: Catecholamine-depleting drugs, such as reserpine, may have an additive effect when administered with β-blocking agents. Therefore, patients receiving TEVA-ACEBUTOLOL as well as catecholamine depletors should be closely observed for evidence of marked bradycardia or which may present as vertigo, syncope/pre-syncope or orthostatic changes in blood pressure without compensatory tachycardia.

The combined use of β-adrenergic antagonists and alpha-adrenergic stimulants, including those contained in proprietary cold remedies and vasoconstrictive nasal drops have been reported to cause exaggerated hypertensive responses. Patients receiving β-blockers should be alerted to this potential hazard.

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

If the decision is made to discontinue therapy in patients receiving β-blockers and clonidine concurrently, the β-blocker should be discontinued several days before the gradual withdrawal of c1onidine. It has been suggested that an exaggeration of the clonidine withdrawal syndrome may be caused by the withdrawal of clonidine in the presence of β-blockade. (See Prescribing Information for Clonidine).

ADVERSE REACTIONS

The most serious adverse reactions reported with acebutolol hydrochloride are congestive heart failure, severe bradycardia and bronchospasm.

The adverse reactions reported most commonly are fatigue, dyspnea, nausea, dizziness, hypotension and rashes.

Adverse reactions grouped by systems are as follows:

Cardiovascular: congestive heart failure (see Warnings); 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) urticaria; pruritis; 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).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms: The signs most frequently experienced with overdosage of β-adrenergic blocking agent are bradycardia, congestive heart failure, hypotension, bronchospasm and hypoglycemia.

Treatment: In all cases of overdosage, therapy with TEVA-ACEBUTOLOL (acebutolol hydrochloride) should be discontinued and the patient observed closely. In addition, if necessary, the following therapeutic measures are suggested:

1. Bradycardja: atropine or another anticholinergic drug.

2. Heart block (second or third degree): isoproterenol or transverse 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 β-blocked patients.)

5. Bronchospasm: aminophylline or isoproterenol.

6. Hypoglycemia: intravenous glucose.

TEVA-ACEBUTOLOL and its major metabolite are dialyzable.

It is important to remember that TEVA-ACEBUTOLOL is a competitive antagonist of isoproterenol and, therefore, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of TEVA-ACEBUTOLOL. However, the complications of excessive isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

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

Hypertension:
TEVA-ACEBUTOLOL is usually used in conjunction with other antihypertensive agents, particularly thiazide diuretics but may be used alone (See Indications).

TEVA-ACEBUTOLOL treatment should be initiated with doses of 100 mg bid. If an adequate response is not seen after one week, the dosage should be increased to 200 mg bid. In some cases, the daily dosage may need further increments of 100 mg bid at intervals of not less than

two weeks, up to the maximum of 400 mg bid. 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 bid. If after two weeks a satisfactory response has not been obtained, the dosage should be increased to a maximum of 300 mg bid.

The usual maintenance dose of TEVA-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 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).

TEVA-ACEBUTOLOL and its metabolite are dialyzable.

PHARMACEUTICAL INFORMATION

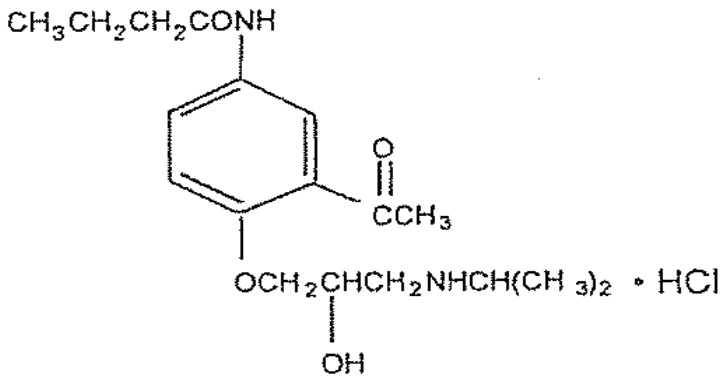
DRUG SUBSTANCE:

Trade Name: TEVA-ACEBUTOLOL

Proper Name: Acebutolol Hydrochloride

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

Structural Formula:



Molecular Formula: $C_{18}H_{28}N_2O_4$•HCI Molecular Weight: 372.89

Description: fine white to off-white, practically odorless crystalline powder which is soluble in water and methanol, very slightly soluble in acetone and methylene chloride.

STABILITY AND STORAGE RECOMMENPATIONS: Store between 15°-30°C.

AVAILABILITY OF DOSAGE FORMS

TEVA-ACEBUTOLOL (acebutolol hydrochloride) 100 mg tablet is available as an off-white, round, biconvex, film-coated tablets, engraved modified N over 100 on one side and plain on the reverse. Each tablet contains acebutolol hydrochloride equivalent to 100 mg acebutolol. Supplied in bottles of 100.

TEVA-ACEBUTOLOL (acebutolol hydrochloride) 200 mg tablet is available as an off-white, oval shaped, biconvex, film-coated tablets, engraved “no|vo” on one side and “200” on the reverse. Each tablet contains acebutolol hydrochloride equivalent to 200 mg acebutolol. Supplied in bottles of 100.

TEVA-ACEBUTOLOL (acebutolol hydrochloride) 400 mg tablet is available as cram coloured, oblong, film coated tablets, engraved “no|vo” on one side and “400” on the reverse. Each tablet contains acebutolol hydrochloride equivalent to 400 mg acebutolol. Supplied in bottles of 100.

PHARMACOLOGY

Effect on the Cardiovascular System

Low doses of acebutolol hydrochloride in the cat and the dog have resulted in a block of the isoproterenol-induced tachycardia (chronotropic action). Higher doses are necessary to block isoproterenol-induced hypotension. Similar results were observed in the anesthetized cat and guinea pig.

In man, doses of 5 mg intravenously and 100 mg orally blocked isoproterenol-induced tachycardia. The action of isoproterenol on the FEV was unchanged. A dose-related inhibition of reflex tachycardia to passive tilting was observed. Exercise-induced tachycardia was markedly lowered by acebutolol hydrochloride.

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

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

In low doses (0.05 - 0.5 mg/kg), acebutolol hydrochloride controls sympathetically-induced arrhythmias in several species. In ouabain-induced arrhythmias (anesthetized dog and conscious rabbit), high intravenous and oral doses are effective. Acebutolol hydrochloride reduces ventricular arrhythmias in dogs with coronary ligation.

Electrophysiological studies in man demonstrated 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.

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

Effect on Pulmonary Function

Single oral doses of 100 and 200 mg of acebutolol hydrochloride were administered to 15 patients with bronchial asthma to assess the effects on airway resistance (FEV and FVC). In 9 of these patients peak flow was measured. No bronchodilator was used. There was no significant

effect from the drug on any of the pulmonary function tests. On the 100 mg dose, one subject developed bronchospasm, but not on the 200 mg dose.

Following intravenous acebutolol, minimal decreases were seen in FEV_1, forced vital capacity (FVC) and peak flow in asthmatics. However, acebutolol reduced the bronchodilator response to isoprenaline in asthmatics, along with EEV_1 and specific airways conductance. Another study showed that the isoprenaline-induced bronchodilatation was preserved with acebutolol (300 mg).

Effect on Plasma Renin

Administration of acebutolol hydrochloride to hypertensive patients caused a significant decrease in plasma renin. This decrease correlated to a decrease in blood pressure.

Effect on Lipolysis and Glucogenolysis

Acebutolol hydrochloride administered to healthy volunteers did not affect serum glucose, triglycerides or cholesterol. Following administration of isoproterenol, the release of free fatty acids was inhibited. Acebutolol hydrochloride potentiated the initial insulin-induced hypoglycemia but did not delay the return of normoglycemia.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	L050 (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

Species	Route	Dose mg/kg/day	# of Animals/ dose level	Duration	Findings
Rat	I.V.	0 5 15 40	10 F 10 M	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 re-action at injection sites.
Rat	Oral	0 20 60 300	40 F 40 M	78 weeks	Reduced grooming activity, decreased body weight gain and food intake in the 300 mg/kg group.
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.
Dog	Oral	0 20 40 110	4 F 4 M	52 weeks	Occasional vomiting at all dose levels. Sedation and salivation mainly in dogs receiving 110 mg/kg. Prolonged dose-elated 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.

Carcinogenicity and Mutagenicity

Groups of 50 male and 50 female CD F/Crl Br albino rats received acebutolol hydrochloride in doses of 0, 100 and 300 mg/kg/day in the diet for 78 weeks. The medication was then discontinued in all groups until the study terminated at 106 weeks. In a similar study groups of 60 male and 60 female CFLP mice received 0, 20, 60 and 300 mg/kg/day of the drug for 87 weeks.

Both studies revealed no overt signs of toxicity. There was no greater incidence of tumours in the acebutolol hydrochloride treated animals than for the controls.

Diacetolol, the major metabolite of acebutolol hyrochloride in man was studied for carcinogenicity in CD rats. Groups of 85 males and 85 females received acebutolol hydrochloride in the diet at doses of 100, 500 or 3,000 mg/kg/day for 104 weeks; 145 animals of each sex were used as controls. No carcinogenic potential was seen.

Both acebutolol hydrochloride and diacetolol revealed no mutagenic potential in the Ames Test.

Teratogenicity Studies

A) Acebutolol

Species	**Route**	**Dose mg/kg/day**	**# of Animals/ dose level**	**Duration**	**Findings**
Rat	Oral	0 12 60	16 17 17	Day 6 – 16 of gestation	No teratogenicity or Embryotoxicity seen.
Rat	I.V.	0 2 6 18	15 16 15 15	Day 5 – 17 of gestation	No teratogenicity or Embryotoxicity seen.
Rabbit	Oral	0 12 16	15 16 17	Day 6 – 16 of gestation	No teratogenicity or Embryotoxicity seen.
Rabbit	I.V.	0 2 6 18	15 14 15 14	Day 5 – 20 of gestation	Fetal abnormalities, not previously encountered in the strain of rabbits used, were observed 6 and 18 mg/kg: rib defects, gastroschisis, ventricular septal defect, dysplasia of urogenital system and umbilical hernia.
Rabbit	I.V.	0 16 18	11 15 17	Day 5 – 20 of gestation	Mean live fetal significantly reduced 6 mg/kg. No teratogenicity or embryotoxicity seen.

B) Diacetolol

Species	Route	Dose mg/kg/day	# of Animals/ dose level	Duration	Findings
Rat	Oral	0 50 300 1800	25	Day 5 – 17 of gestation	Non-statistically significant increase in incidence of bilateral cataracts in fetuses from dams treated with 1800 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	# of Animals/ 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 lactation gestation also slightly increased.

Reproduction Study

A) Acebutolol

Species	Route	Dose mg/kg/day	# of Animals/ dose level	Duration	Findings
Rat	Oral	0 40 240	13 M 25 F	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

Species	Route	Dose mg/kg/day	# of Animals/ dose level	Duration	Findings
Rat	Oral	0 40 200 1000	15 M 30 F	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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