PRODUCT MONOGRAPH

PrTEVA-NADOLOL

(Nadolol)

40mg and 80mg Tablets

USP

Anti-anginal and Antihypertensive Agent

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THERAPEUTIC CLASSIFICATION

Anti-anginal and Antihypertensive Agent

ACTION

TEVA-NADOLOL (nadolol) is a beta-adrenergic blocking agent which is non-cardioselective. It does not possess membrane stabilizing or intrinsic sympathomimetic (partial agonist) activities.

The exact mechanism responsible for the anti-anginal effect of nadolol is not certain. However, it may reduce the oxygen requirements of the heart through the blockade of catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and the extent of myocardial contraction. Actions such as increases in left ventricular fibre length and end diastolic pressure may increase oxygen requirements. When the net physiological effect is advantageous in anginal patients, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of anginal attacks. Therefore TEVA-NADOLOL can increase the capacity for work and exercise in these patients.

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

(a) Decreased cardiac output through the competitive ability to antagonize catecholamine-induced tachycardia at the beta-receptor sites in the heart.
(b) Inhibition of renin release by the kidneys.
(c) Inhibition of vasomotor centers.

Pharmacokinetics:
In humans, approximately 37% of an oral dose of nadolol is slowly absorbed. Approximately 30% of the nadolol present in the serum is reversibly bound to plasma proteins. Nadolol is extensively distributed to extravascular tissues. Peak serum concentrations are reached 2 to 4 hours after oral administration and steady state serum concentrations are attained after 5 to 6 days. At therapeutic dosage levels the serum half-life is 17 to 24 hours.

Nadolol is not detectably metabolized by humans. Urinary and fecal excretion of orally administered nadolol averaged approximately 25% and 75%, respectively, in humans. The latter traction would include unabsorbed drug as well as the fraction of the absorbed drug which is excreted by the liver. In patients with renal impairment, nadolol elimination was found to be

proportional to creatinine clearance. In the presence of severe renal impairment (creatinine clearance < 10 mL/min/1.73 m^2), the dosage interval should be changed to 40 to 60 hours instead of 24 hours. Nadolol can be removed from the circulation by hemodialysis.

A comparative two-way, single-dose bioavailability study was performed on TEVA-NADOLOL (nadolol) 80 mg Tablets and CORGARD® (nadolol) 80 mg Tablets. The pharmacokinetic plasma data (mean ± standard deviation) calculated for the TEVA-NADOLOL and CORGARD® formulations is tabulated below:

Geometric Mean Arithmetic Mean (C.V.)			
	NOVD-NADOLOL (1 x 80 mg)	**CORGARD® (1 x 80 mg)**	**Percentage of CORGARD®**
AUC_T (ng•h/mL)	1636 1775 (37)	1604 1682 (31)	102
AUC_I (ng•h/mL)	1772 1890 (33)	1737 1803 (28)	102
C_{max} (ng/m L)	162 184 (44)	147 167 (49)	110
T_{max}* (h)	2.85 (1.08)	3.17 (0.92)	-
T½* (h)	16.05 (4.27)	15.56 (5.67)	-

*These are the arithmetic means (standard deviation).

INDICATIONS

Angina:
TEVA-NADOLOL (nadolol) is indicated for the prophylaxis of angina pectoris.

Hypertension:
TEVA-NADOLOL is indicated in patients with mild or moderate hypertension. Nadolol is usually used in combination with other drugs, particularly a thiazide diuretic. TEVA-NADOLOL may be tried alone as an initial agent in those patients in whom, in the judgement of the physician, treatment should be initiated with a beta-blocker rather than a diuretic.

The combination of nadolol with a diuretic agent has been found to be compatible and is generally more effective than nadolol alone. No evidence of incompatibility was seen in a few cases where peripheral vasodilators were used with nadolol.

CONTRAINDICATIONS

TEVA-NADOLOL (nadolol) is contraindicated in the presence of:

(1) Allergic rhinitis, bronchospasm (including bronchial asthma), or severe chronic obstructive pulmonary disease (see PRECAUTIONS).
(2) Sinus bradycardia.
(3) Second or third degree AV block.

(4) Right ventricular failure secondary to pulmonary hypertension.
(5) Congestive heart failure (see WARNINGS).
(6) Cardiogenic shock.
(7) Anesthesia with agents that produce myocardial depression (such as ether).

WARNINGS

Cardiac Failure:
When administering TEVA-NADOLOL (nadolol) 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, with inhibition with beta-blockade, there is always the potential hazard of further depression of myocardial contractility and the precipitation of cardiac failure. Continued depression of the myocardium over a period of time can in some cases lead to cardiac failure in patients with no previous history of cardiac failure. Therefore, at the first sign or symptom of impending cardiac failure during nadolol therapy, patients should be fully digitalized and/or given a diuretic, and the response should be closely observed.

Nadolol acts selectively without blocking 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 nadolol. The effects of nadolol and digitalis are additive in depressing A-V conduction. TEVA-NADOLOL treatment should be discontinued if cardiac failure continues despite adequate digitalization and diuretic therapy (see WARNING below).

Abrupt Cessation of Nadolol Therapy:
Patients with angina should be warned against abrupt discontinuation of nadolol. There have been reports of severe exacerbation of angina and of myocardial infarction or ventricular arrhythmias occurring after abrupt discontinuation of beta-blocker therapy in patients with angina pectoris. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of angina pectoris. Therefore, when discontinuation of nadolol is planned in patients with angina pectoris, the dosage should be reduced gradually over a period of approximately 2 weeks and the patient should be observed carefully. The same frequency of administration should be maintained. In situations of greater urgency, nadolol should be discontinued in a stepwise manner and under closer supervision. If angina markedly worsens or acute coronary insufficiency develops, nadolol treatment should be promptly reinstituted, at least temporarily.

Oculomucocutaneous Syndrome:
Various skin rashes have been reported with beta-blockers including nadolol. Oculomucocutaneous syndrome, a severe syndrome characterized by psoriasiform rashes, xerophthalmia due to lacrymal gland fibrosis, otitis, fibrinous peritonitis and a lupus-erythematosus-like syndrome has occurred with the chronic use of the beta-adrenergic blocking agent, practolol. Although this syndrome has not been observed with nadolol, physicians should be aware of the possibility of such reactions and if they develop, TEVA-NADOLOL treatment should be discontinued.

Sinus Bradycardia:
Due to the unopposed vagal activity, severe bradycardia occurs in approximately 2% of patients following nadolol administration. The dosage should be reduced in such cases or the use of intravenous atropine could be considered. If no improvement is seen, intravenous isoproterenol should be considered.

Thyrotoxicosis:
In patients with thyrotoxicosis, nadolol may give a false impression of improvement by diminishing peripheral manifestations of hyperthyroidism without improving thyroid function. Therefore an exacerbation of hyperthyroidism symptoms, including thyroid storm, may follow the abrupt withdrawal of nadolol.

PRECAUTIONS

Nadolol may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors. Therefore, TEVA-NADOLOL (nadolol) should be administered with caution to patients who are prone to non-allergic bronchospasm (such as chronic bronchitis and emphysema).

TEVA-NADOLOL should be administered with caution to patients who are subject to spontaneous hypoglycemia, or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. The premonitory signs and symptoms of acute hypoglycemia may be masked by beta-adrenergic blockers. Beta-blockade also reduces insulin release in response to hyperglycemia. It may therefore be necessary to adjust the dosage of antidiabetic drugs.

When used concomitantly with other antihypertensive agents, TEVA-NADOLOL dosage should be individually adjusted (see DOSAGE AND ADMINISTRATION).

If TEVA-NADOLOL is administered concomitantly with catecholamine-depleting drugs such as reserpine and guanethidine, the patients should be closely monitored. The added catecholamine blocking action of nadolol may result in an excessive reduction of the resting sympathetic nervous activity.

In patients with impaired renal or hepatic function, suitable laboratory tests should be performed at appropriate intervals and caution should be exercised. Since nadolol is primarily excreted by the kidneys, it may be necessary to reduce the dosage when renal insufficiency is present.

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 pharmacologic effects of the 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, 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 beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm and norepinephrine to overcome hypotension.

In Patients Undergoing Elective or Emergency Surgery:
The management of patients receiving beta-blocking agents and undergoing elective or emergency surgery is controversial. Although beta-adrenergic receptor blockade impairs the heart's ability to respond to beta-adrenergically-mediated reflex stimuli, the abrupt discontinuation of TEVA-NADOLOL therapy may be followed by severe complications (see WARNINGS). Some patients receiving beta-blockers have been subject to protracted severe hypotension during anesthesia. Difficulty restarting and maintaining the heartbeat has also been reported. Therefore in patients with angina who are undergoing elective surgery, TEVA-NADOLOL treatment should be gradually withdrawn following the recommendation given under Abrupt Cessation of Therapy (see WARNINGS). The available evidence suggests that the clinical and physiologic effects of beta-blockade induced by nadolol are essentially absent 5 days after cessation of therapy.

Since nadolol is a competitive inhibitor of beta-adrenergic receptor agonists, its effects may be reversed during emergency surgery with sufficient doses of agonists such as isoproterenol or levarterenol if necessary.

Usage in Pregnancy and Nursing Mothers:
Nadolol should not be given to pregnant women since this drug has not been studied in human pregnancy. The use of any drug in patients of childbearing potential requires that the anticipated benefit be weighed against the possible hazards. Bradycardia, hypoglycemia and associated symptoms have been exhibited in neonates whose mothers were receiving nadolol at parturition.

At doses of 100 to 300 mg/kg nadolol, embryo/fetal toxicity has been shown in rabbits, but not in rats or hamsters. Teratogenic potential was not observed in any of these species.

Nadolol readily crossed the placental barrier when administered to pregnant rats. Nadolol was also found in the milk of lactating rats. Information in humans is lacking; therefore, nadolol is not recommended for use in lactating women.

Usage in Children:
There is no experience with nadolol in the treatment of pediatric patients.

ADVERSE REACTIONS

Congestive heart failure, AV block and bronchospasm are the most serious adverse reactions encountered.

The most common adverse reactions reported are severe bradycardia (2%), dizziness (1.5%), fatigue (1.5%), hypotension (1%), congestive heart failure (0.5%), and cold sensations (1%).

Adverse reactions grouped by system are as follows:

Cardiovascular:
Adams-Stokes Syndrome, atrial fibrillation, AV block, syncope, bigeminy, bradycardia, cold sensation, congestive heart failure, hypotension, orthostatic hypotension, myocardial infarction, pulmonary edema, cardiac enlargement, chest pain, peripheral vascular insufficiency including intermittent claudication.

Respiratory:
Bronchospasm, dyspnea, cough.

Nervous System:
Anxiety, dizziness, fatigue, headache, insomnia, nervousness, irritability, nightmares, lethargy, sleepiness, tingling digits, weakness and unsteadiness, depression, paresthesia, tinnitus, slurred speech, hallucinations.

Gastrointestinal:
Abdominal pain or pressure, nausea, vomiting, diarrhea, constipation, flatulence, gastritis, anorexia.

Dermatological (see WARNINGS):
Rash, pruritus, dry skin.

Ophthalmologic:
Conjunctivitis, blurred vision, dry eyes.

Miscellaneous:
Impotence, decreased libido, hyperthyroidism, nasal stuffiness, dry mouth, sweating, weight gain.

Clinical Laboratory:
The following parameters have most frequently been found to be outside the normal range: serum triglycerides, blood glucose, serum potassium, LDH, BUN, SGOT, SGPT.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

In all cases of overdosage, TEVA-NADOLOL (nadolol) therapy should be discontinued and the patient should be observed closely. In addition, the following therapeutic measures are suggested if required:

1. Bradycardia: Atropine or another anticholinergic drug.

2. Heartblock (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.

5. Bronchospasm: Aminophylline or isoproterenol.

6. Hypoglycemia: Intravenous glucose.

Since nadolol is a competitive antagonist of isoproterenol, large doses of isoproterenol can be expected to reverse many of the effects of excessive doses of TEVA-NADOLOL. However, the complications of excess isoproterenol should not be overlooked.

DOSAGE AND ADMINISTRATION

It is recommended that TEVA-NADOLOL (nadolol) be administered as a single daily dose. Since the presence of food in the gastrointestinal tract does not affect the rate or extent of nadolol absorption, TEVA-NADOLOL may be administered without regard to meals.

The TEVA-NADOLOL dosage must always be adjusted to the individual needs of the patient in accordance with the following guidelines:

Angina Pectoris:
Treatment with TEVA-NADOLOL should be initiated with a dose of 80 mg daily. If after one week an adequate response is not observed, the dosage may be increased by 80 mg increments at weekly intervals until a satisfactory response is achieved. The maximum recommended daily dose is 240 mg. Patients who are stabilized on 80 mg daily may be tried on 40 mg per day since this dosage has been found to be effective in some cases.

The value and safety of doses above 240 mg per day in angina pectoris have not been established.

Hypertension:
TEVA-NADOLOL therapy should be initiated at doses of 80 mg per day. If after one week an adequate response is not observed the dosage may be increased by 80 mg increments at weekly intervals until a satisfactory response is achieved. The maximum recommended daily dose is 320 mg, although most patients respond to 240 mg or less.

The value and safety of doses greater than 320 mg daily have yet to be established.

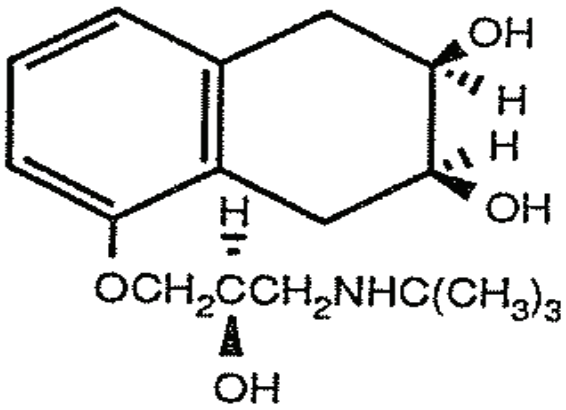
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Nadolol

Chemical Name: 2,3-Naphthalenediol,5-[3-[(1,1-dimethylethyl)amino]2-hydroxypropoxy]-1,2,3,4-tetrahydro-,cis-.

Structural Formula:



Molecular Formula: $C_{17}H_{27}NO_4$ Molecular Weight: 309.40

Description: Nadolol is a white to off-white practically odourless crystalline powder, freely soluble in water, alcohol and methanol and slightly soluble in chloroform.

STABILITY AND STORAGE RECOMMENDATION:
Store between 15°C and 30°C.

AVAILABILITY

40mg: White to oft-white, round, biconvex compressed tablet, engraved **no|vo** on scored side and **40** on the reverse. Available in bottles of 100, 500 and 1000 tablets.

80mg: White to off-white, round, standard convex, compressed tablet, engraved **no|vo** on scored side and **80** on the reverse. Available in bottles of 100, 500 and 1000 tablets.

PHARMACOLOGY

Pharmacokinetics:
The basic details of the human pharmacokinetics of nadolol may be found under ACTIONS.

At steady state, the mean plasma concentrations were approximately 25.5 - 35.5 ng/mL, 51.7-74.1 ng/mL and 154-191.4 ng/mL at doses of 80,160 and 320 mg daily, respectively.

Following intravenous administration of nadolol, 70% of the dose was excreted via the kidneys and approximately 20% was excreted via the gastrointestinal tract. The latter was of biliary origin.

The distribution volume of nadolol after a single intravenous dose of 2 mg in patients with mild essential hypertension was about 2 L/kg (1.4 to 3.4 L/kg).

Effects on the Cardiovascular System:
In vitro and *in vivo* animal studies have shown nadolol to be an antagonist of the beta-stimulatory effects of catscholamines. Nadolol was also shown to block isoproterenol-induced tachycardia and vasodepression consistently in anesthetized dogs and cats, as well as in unanesthetized dogs and monkeys.

Nadolol does not possess significant intrinsic sympathomimetic or membrane-stabilizing (quinidine-like) properties.

Nadolol has been shown to inhibit the effects of both isoproterenol and exercise-induced tachycardia in humans. Maximum inhibition of exercise-induced tachycardia was observed at 4 hours after the oral administration of 40, 80 and 160 mg. Significant inhibition of exercise-induced increases in double product (heart rate x blood pressure) persisted for at least 24 hours after single oral doses of 10 to 80 mg.

Resting plasma renin activity was decreased by the administration of 0.3 to 10 μg/kg nadolol in 5 patients with essential hypertension and 3 healthy subjects receiving a low sodium diet.

A study of the effects of nadolol on human hemodynamics showed that nadolol reduces cardiac index without affecting stroke index.

Studies involving guinea pig atria, cat papillary muscle and anesthetized dogs indicated that at doses much greater than those required to produce complete beta-blockade, nadolol produces little direct myocardial depression. However in other studies involving anesthetized dogs, intravenous infusions of 0.05 to 1 mg/kg produced decreases in heart rate.

In studies with anesthetized dogs designed to determine the effect of intravenous nadolol on excitability, refractoriness, and conduction velocity of both atrial and ventricular tissue, nadolol prolonged ventricular refractoriness and depressed conduction through the AV node.

Intravenous doses of 0.03 mg/kg of nadolol prevented ECG changes caused by coronary artery occlusion in anesthetized dogs. Nadolol also prevented the exacerbation of these changes by isoproterenol.

Results of human studies indicate that nadolol possesses some anti-arrhythmic activity.

In a trial involving 51 patients with normal renal function, a single dose of intravenous nadolol (0.1 mg/kg) given to 7 subjects caused a significant decrease (12%) in mean PAH clearance (effective renal plasma flow) and a nonsignificant decrease in mean inulin clearance during a 4 hour period.

There was also a 5% reduction in mean arterial pressure and a 12% reduction in heart rate. A significant antinatriuretic effect was exhibited.

Similar findings were reported when intravenous doses of nadolol were administered to both hypertensive and normal subjects who were fed a low sodium diet.

Effects on Respiratory Function:
Studies of the effects of nadolol on bronchial-airway resistance and histamine-induced bronchial constriction in anesthetized cats indicated that nadolol increased bronchial-airway resistance. Histamine-induced increases in bronchial-airway resistance were slightly potentiated by nadolol.

In normal male volunteers, forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_{1.0}$) were both decreased following the ingestion of a 240 mg dose of nadolol.

Other Effects:
In six patients with moderate hypertension or cardiac arrhythmia, a daily dose of 160 mg of nadolol administered for 7 days produced a slightly faster initial rate of disappearance of glucose from the serum following glucose loading. Nadolol also decreased the mean insulin responses at 1 and 2 hours after ingestion of the glucose load by approximately 30-35%. Nadolol had no significant effect on fasting serum glucose or insulin levels.

TOXICOLOGY

Acute Toxicity:

Species	**Sex**	**Route of Administration**	**LD_{50} (mg/kg)**
Mice (CR-CD1)	M	Oral	3530 – 6200
	F	Oral	2700 – 5600
	M	I.V.	60 – 67
	F	I.V.	56 - 72
Rats	M/F	Oral	4280 - 5300

In mice the signs of toxicity included: ataxia and convulsions usually occurring within 5 minutes of i.v. administration or 24 hours of oral administration. The signs of toxicity in rats were: ataxia, convulsions, abdominal spasms and cyanosis occurring within 24 hours of oral administration.

The toxicity of nadolol was increased in mice with experimentally induced hepatic or renal lesions.

In mice the acute toxicity of nadolol was not potentiated by concurrent administration of hydralazine hydrochloride, hydrochlorothiazide, digoxin, furosemide, norethindrone/mestrone, quinidine sulphate, nitroglycerin, methyldopa or lithium carbonate (graded doses of nadolol were given concurrently with a sub-lethal dose of each of these marketed compounds). Acute toxicity was additive (significant lowering of nadolol LD_{50}) with furosemide, quinidine sulphate and hydralazine hydrochloride. Methyldopa appeared to reduce the acute toxicity of nadolol.

Subacute Toxicity:
Dogs:
A 0.5% solution of nadolol in saline (sodium phosphate buffer) was administered to groups of 2 male and 2 female beagles at total daily doses of 0, 1.25, 3.75 or 12.5 mg/kg (bid administrations) for a period of one month. Only bradycardia was drug related and occurred in all treated dogs throughout the dosing period.

Monkeys:
A 12 week oral administration study (gavage of agar suspensions) was conducted with groups of two male and one female rhesus monkey. Dosing was carried out twice daily at total daily levels of 0, 25, 75 and 250 mg/kg. Drug associated findings including decreased body weight and lack of appetite plus a slight decrease in erythrocyte parameters and elevated leucocyte count, all in one high dose male. Very slight focal amyloidosis (primary) in a few splenic corpuscles and slight focal granulomatous hepatitis were observed in the single female of this group. None of the gross or histopathological changes were considered attributable to nadolol.

Chronic Toxicity:
Mice:
Two 2 year studies were performed in Charles River CD-1 mice, Nadolol was administered in the diet at levels of up to 500 mg/kg/day for 18 months. The first study was a pilot experiment which was limited to female mice at one dosage level. Approximately 50% of the treated and control animals in this study survived for a full two years. In the second study three dosage levels and both male and female mice were included. Multiple interim sacrifices contributed to a rather small number of animals surviving to termination, however, better than 57% of the initial 120 combined males and females in any dosage group lasted for at least 18 months.

With the exception of a 9% lower body weight relative to controls at the end of 18 months in the pilot experiment, nadolol was well tolerated by the mice in both studies and there was no evidence of tumorigenicity.

Rats:
Two 2 year studies were also performed in Charles River CD rats. Nadolol was administered in the diet for 18 months. The first study was a pilot experiment and was limited to one group of male rats which received estimated mean daily doses of 230, 490, and 670 mg/kg for one week each, 975 and 1250 mg/kg for 2 weeks each, 1550 mg/kg for approximately 37 weeks and 1000 mg/kg for about 34 weeks. Ten (of 50) test and 5 (of 25) control rats were sacrificed after 11 months. There were 31 treated and 13 control rats alive at 2 years. In the second study, both male and female rats received three dosage levels with the maximum exposure being 1000 mg/kg/day. In spite of multiple interim sacrifices, at least 45% of the initial 60 males and 60 females in any group lived to the scheduled termination of the experiment.

The adverse effects of nadolol administration (seen in both mice and rat experiments) were limited to lower mean body weights relative to controls (greater than 10% reduction at the high dose level after 18 months in both experiments) and soft stools. All of these effects were dose dependent and all diminished or disappeared with cessation of dosing. There was a dose related increased incidence of focal medullary hyperplasia (slight or very slight) of the adrenals in both males and females in the standard 2 year study with the incidence at 1000 mg/kg/day significantly increased over the incidence in the control animals. This finding was not considered to be treatment related and was not observed in the pilot study. There was no evidence of tumorigenicity.

Dogs:
In another study with dogs, agar suspensions of nadolol were incorporated into the diets of groups of 4 male and 4 female beagles at daily doses of 0, 24, 60 and 150 mg/kg for a 1 year period. One male and one female per group were sacrificed after 6 months, 2 males and 2 females were sacrificed after 12 months and the remaining animals were sacrificed after 3 weeks on a drug-free diet. Drug related observations included moderate weight loss in two high dose dogs during the first 4 months (with recovery of lost weight by the 32nd week), short periods of decreased food consumption in four dogs each in the high and intermediate dosage groups (sufficient to lower the calculated drug intake to 140 and 56 mg/kg, high and middle dose, respectively), decreased heart rate in all nadolol treated groups, and a slight to moderate decrease in the tolerance to an i.v. glucose load associated with a decreased insulin response (glucose tolerance and heart rate appeared to return to normal during the post-dose period).

Carcinogenicity:
Nadolol was administered to three groups of 60 male and 60 female Charles River CD Sprague Dawley rats for a period of 18 months at dietary levels of 160, 400 and 1000 mg/kg/day. In a similar study, doses of 80, 200 or 500 mg/kg/day were administered in the diets of 3 groups of 60 male and 60 female Charles River CD-1 mice for a period of 18 months. Nadolol did not influence the development of tumors under the conditions of testing.

Reproductive Studies:
In fertility studies, doses of 100 or 300 mg/kg/day were administered orally to male rats for 10 weeks and to female rats for 2 weeks before mating. Half of the females received nadolol until the 13th or 14th day of gestation and the remaining females were dosed through gestation and 21

days of lactation. Nadolol did not affect gestation or the viability of the newborn at birth and at day 4.

Teratogenicity:
When nadolol was administered orally to pregnant rats and hamsters, doses of 100 or 300 mg/kg did not affect fetal development or induce teratogenic changes in the offspring.

When small Russian rabbits were given daily oral doses of 100 or 300 mg/kg from day 6 through day 18 of gestation, nadolol was found to be embryo and fetotoxic. Similar effects were observed when New Zealand white rabbits were given daily oral doses of 100 mg/kg on days 7 through 18 of gestation. However, these effects were not seen in Small Russian Rabbits at doses of 25 or 50 mg/kg.

REFERENCES

1. Devlin RG, Duchin KL, Fleiss PM. Nadolol in human serum and breast milk. Br J Clin Pharmacol 1981; 12:393-6.

2. Dreyfuss J, Griffith DL, Singhvi SM, Shaw JM, Ross JJ, Vukovich RA, Willard DA. Pharmacokinetics of nadolol, a beta-receptor antagonist administration of therapeutic single- and multiple-dosage regimens. J Clin Pharmacol 1979; 19:712-20.

3. Dreyfuss J, Shaw JM, Miller TJ. Nadolol: placental transfer and excretion in the milk of rats. Toxicol Appl Pharmacol 1977; 39:275-82.

4. Frishman W. Clinical pharmacology of the new beta-adrenergic blocking drugs. Part 9. Nadolol: A new long-acting beta-adrenoceptor blocking drug. Am Heart J 1980; 99:124-8.

5. Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS. Nadolol: A review of its pharmacological properties and therapeutic efficacy in hypertension and angina pectoris. Drugs 1980; 20:1-23.

6. Ichihara K, Abiko Y. Effect of nadolol, a β-adrenoceptor blocking agent, on myocardial metabolism in the dog ischaemic heart. J Pharm Pharmacol 1987; 39:604-8.

7. Lee RJ, Evans DB, Baky SH, Laffan RJ. Pharmacology of nadolol (SQ 11725), a β-adrenergic antagonist lacking direct myocardial depression. Eur J Pharmacol 1975; 33:371-82.

8. McKinstry DN, Vukovich RA, Willard DA. Effects of beta-adrenergic blockade with nadolol and propranolol on glucose and lipid metabolism in man. Clin Res 1977; 25:548A.

9. Morganroth J, Duchin KL. Effectiveness of low- dose nadolol for ventricular arrhythmias. Am J Cardiol 1986; 58:273-8.

10. Sibley PL, Keim GR, Kulesza JS, Murphy 8F, Myhre JL, Parish HM, Yoon YH, Zaidi IH. Preclinical toxicologic evaluation of nadolol, a new β-adrenergic antagonist. Toxicol Appl Pharmacol 1978; 44:379-89.

11. Turner GG, Nelson RR, Nordstrom LA, Diefenthal HC, Gobel FL. Comparative effect of nadolol and propranolol on exercise tolerance in patients with angina pectoris. Br Heart J 1978; 40:1361-70.

12. Valvo E, Gammaro L, Bedogna V, Cavaggioni M, Tonon M, Lupo A, Loschiavo C, Tessitore N, Oldrizzi L, Rugiu G, Maschio G. Effects of nadolol on systemic and renal hemodynamics in patients with renoparenchymal hypertension and various degrees of renal function. Int J Clin Pharmacol Ther Toxicol 1986; 24:202-6.

13. Wilkinson R, Burr WA. A comparison of propranolol and nadolol pharmacokinetics and clinical effects in thyrotoxicosis. Am Heart J 1984; 108:1160-6.

14. Wilson AL, Matzke GR. The treatment of hypertension in pregnancy. Drug Intell Clin Pharm 1981; 15:21-6.

15. United States FDA Summary Basis for Approval Documents for Nadolol. NDA 18-063 and 18-064, December 10, 1979.

16. AHFS Drug Information 1987. American Society of Hospital Pharmacists Inc. Bethesda, MD, U.S.A. 1987; 743-6.

17. A two-way single-dose bioavailability study of Nadolol 80 mg tablets in normal healthy male volunteers. August 1992.