PRODUCT MONOGRAPH

NU-VERAP SR

Veramapil Hydrochloride Sustained Release Tablets

Nu-Pharm Standard

120 mg, 180 mg and 240 mg

Antihypertensive Agent

NU-PHARM INC.
50 Mural Street, Units 1 & 2
Richmond Hill, Ontario
L4B 1E4

DATE OF REVISION:
October 20, 2009

Control#: 133484

PRODUCT MONOGRAPH

NU-VERAP SR

Verapamil Hydrochloride Sustained Release Tablets

Apotex Standard

120 mg, 180 mg and 240 mg

THERAPEUTIC CLASSIFICATION

Antihypertensive Agent

ACTION AND CLINICAL PHARMACOLOGY

Verapamil hydrochloride is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist) that exerts its pharmacological effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conducting and contractile myocardial cells.

Verapamil exerts antihypertensive effects by inducing vasodilation and reducing peripheral vascular resistance usually without reflex tachycardia. Verapamil does not blunt hemodynamic response to isometric or dynamic exercise.

Verapamil depresses A-V nodal conduction and prolongs functional refractory periods. Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarization and conduction in depressed atrial fibres.

Verapamil may shorten the antegrade effective refractory period of the accessory bypass tract. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory A–V pathway following administration

of verapamil (see WARNINGS - Conduction Disturbance). Verapamil has a local anaesthetic action that is 1.6 times that of procaine on an equimolar basis.

Verapamil is a potent smooth muscle relaxant with vasodilatory properties, as well as a depressant of myocardial contractility, and these effects are largely independent of autonomic influences.

Compared to baseline, verapamil administration did not affect electrolytes, glucose, and creatinine. The hypotensive effect of verapamil is not blunted by an increase in sodium intake.

In hypertensive normolipidemic patients, verapamil had no effects on plasma lipoprotein fractions.

Pharmacodynamics

In a study in five healthy males, the S enantiomer was found to be 8 to 20 times more active than the R enantiomer in slowing AV conduction. In another study using septal strips isolated from the left ventricle of 5 patients with mitral disease, the S enantiomer was 8 times more potent than the R enantiomer in reducing myocardial contractility.

Pharmacokinetics

Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R enantiomer and the S enantiomer. More than 90% of the orally administered dose of verapamil hydrochloride is absorbed. Upon oral administration, there is rapid stereoselective biotransformation during the first pass of verapamil through the portal circulation. The systemic concentrations of R and S enantiomers are dependent upon the route and the rate of administration and the rate and extent of release from the dosage forms.

The following bioavailability information was obtained from healthy volunteers and not from the populations most likely to be treated with verapamil.

In a study in 5 healthy volunteers with oral immediate-release verapamil, the systemic bioavailability varied from 33 to 65% for the R enantiomer and from 13 to 34% for the S enantiomer. The S enantiomer is pharmacologically more active than the R enantiomer (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics, and PHARMACOLOGY).

There is a nonlinear correlation between the verapamil dose administered and verapamil plasma levels. In early dose titration with verapamil, a relationship exists between total verapamil (R and S combined) plasma concentration and prolongation of the PR interval. The mean elimination half-life in single dose studies of immediate-release verapamil ranged from 2.8 to 7.4 hours. In these same studies, after steady state was reached, the half-life increased to a range from 4.5 to 12.0 hours (after less than 10 consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration. Aging decreases the clearance and elimination of verapamil.

In a randomized, multiple-dose study of 44 healthy young subjects, administration of verapamil hydrochloride sustained release tablets 240 mg with food produced peak plasma concentrations at approximately 8 hours postdose of 188 and 76 ng/mL and AUC's (0-24 hours) of 2,553 and 1,046 ng.hr/mL for the R and S enantiomers, respectively. Similar results were demonstrated for plasma norverapamil.

In healthy men, orally administered verapamil undergoes extensive metabolism by the cytochrome P-450 system in the liver. The particular isoenzymes involved are CYP3A4, CYP1A2 and CYP2C family. Thirteen metabolites have been identified in urine. Norverapamil can reach steady state plasma concentrations approximately equal to those of verapamil itself. The

cardiovascular activity of norverapamil appears to be approximately 20% that of verapamil. Approximately 70% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces within 5 days. About 3% to 4% is excreted in the urine as unchanged drug. R-verapamil is 94% bound to plasma albumin, while S-verapamil is 88% bound. In addition, R-verapamil is 92% and S-verapamil 86% bound to alpha-1 acid glycoprotein. The degree of biotransformation during the first pass of verapamil may vary according to the status of the liver in different patient populations. In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14-16 hours (see WARNINGS - Hepatic Insufficiency, and DOSAGE AND ADMINISTRATION).

Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Verapamil is excreted in human milk.

A study was conducted in which 240 mg single oral doses of verapamil standard release (fasting) and verapamil sustained release (fed) tablets were given to 12 young, healthy males (19 to 37 years old) in a randomized, crossover (7-day washout) study. Serial blood samples for drug determination were taken over a 48 hour period. The pharmacokinetic data from this study is summarized in the following table.

Parameter	**Verapamil Standard Release Tablet (240 mg)**		**Verapamil Sustained Release Tablet (240 mg)**	
	R-verapamil	S-verapamil	R-verapamil	S-verapamil
$C_{max,}$ ng/mL	258	59.0	60.1	11.3
$T_{max,}$ hr	1.46	1.58	10.8	11.8
AUC_{0-48} ng/mL/hr	1250	261	918	150

The steady-state pharmacokinetic data from a study in which 11 volunteers were treated with the sustained release formulation twice daily at 12 hourly intervals and with the standard release

formulation three times daily at 8 hourly intervals for five days is summarized in the following table.

Parameters	Standard release 120 mg Tablet ** (360 mg daily)	Sustained release 240 mg Tablet ** (360 mg daily)	Sustained release 240 mg Tablet ** (480 mg daily)
$C_{max,}$ ng/mL	289.4	250.5	298.4
$C_{min,}$ ng/mL	80.1	110.7	152.0
$T_{max,}$ hr	1.4	4.5	4.4
$T_{1/2,}$ hr	6.1	8.2	8.7
$AUC_{0-\infty}$ ng/mL/hr	1850	3466	4484
AUC_{0-48} ng/mL/hr	1809	3154	4116

* last dose = 240 mg
** last dose = 120 mg

The last doses have been calculated from samples taken at frequent intervals for 36 hours after the last dose.

Influence of Food: Administration of verapamil sustained release tablets with food results in marked prolongation of T_{max} (45-75%) and slight decreases in C_{max} (about 15%) and AUC (1-8%). Food thus produces a slight decrease in bioavailability (AUC), but a narrower peak-to-trough ratio.

Comparative Bioavailability

Three studies were performed using sustained release tablets: one under fasting conditions, one under fed conditions and one at steady state. In the fasting and fed studies the rate and extent of the absorption of verapamil were determined and compared after a single, oral dose of 240 mg of NU-Verap SR and Isoptin® SR 240 mg. In the steady state study the dosage was 240 mg of either NU-Verap SR, or Isoptin® SR every 24 hours for six days. The results of these studies are summarized below.

Summary Table of the Comparative Bioavailability Data Verapamil SR (Dose: 1 x 240 mg) From Measured Data – Under Fasting Conditions Based on Verapamil				
Parameter	Geometric Mean Arithmetic Mean (CV%) NU-Verap SR	 Isoptin® SR†	Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
AUC_T (ng.h/mL)	1221 1314 (40)	1236 1310 (36)	98.8	82.7 – 118.1
AUC_I (ng.h/mL)	1263 1355 (40)	1284 1355 (35)	98.4	83.1 – 116.5
C_{MAX} (ng/mL)	117 133 (55)	124 140 (44)	93.9	73.4 – 120.2
T_{MAX}^* (h)	6.71 (58)	5.36 (48)	-	-
$T_{½}^*$ (h)	8.21 (18)	9.34 (22)	-	-
* Arithmetic means (CV%). ** Based on the least squares estimate. † Isoptin® SR is marketed by Knoll Pharma Inc., Canada.				

Summary Table of the Comparative Bioavailability Data Verapamil SR (Dose: 1 x 240 mg) From Measured Data – Under Fed Conditions Based on Verapamil				
Parameter	Geometric Mean Arithmetic Mean (CV%) NU-Verap SR	 Isoptin® SR†	Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
AUC_T (ng.h/mL)	1113 1194 (37)	1088 1189 (43)	102.3	87.8 – 119.2
AUC_I (ng.h/mL)	1160 1245 (37)	1135 1248 (44)	101.1	86.1 – 118.7
C_{MAX} (ng/mL)	79.8 90.7 (53)	75.1 84.7 (57)	106.2	76.9 – 146.8
T_{MAX}^* (h)	12.4 (57)	12.8 (53)	-	-
$T_{½}^*$ (h)	7.92 (30)	7.89 (32)	-	-
* Arithmetic means (CV%). ** Based on the least squares estimate. † Isoptin® SR is marketed by Knoll Pharma Inc., Canada.				

Summary Table of the Comparative Bioavailability Data Verapamil SR (Dose: 1 x 240 mg every 24 hours for 6 days) From Measured Data – At Steady State Based on Verapamil				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence Interval (%)**
	NU-Verap SR	Isoptin® SR†		
AUCτ (ng.h/mL)	2165 2325 (38)	2179 2389 (43)	99.3	91.5 – 107.9
C_{MAX} (ng/mL)	202 218 (39)	215 243 (48)	93.8	82.6 – 106.6
C_{MIN} (ng/mL)	37.1 42.1 (49)	33.1 37.8 (52)	112.1	102.3 – 122.9
T_{MAX}* (h)	4.50 (22)	5.48 (26)	-	-
Fluctuation* (%)	190 (41)	204 (29)	-	-
* Arithmetic means (CV%). ** Based on the least squares estimate. † Isoptin® SR is marketed by Knoll Pharma Inc., Canada.				

INDICATIONS AND CLINICAL USE

NU-VERAP SR (verapamil hydrochloride) is indicated in the treatment of mild to moderate essential hypertension. NU-VERAP SR should normally be used in those patients in whom treatment with diuretics or beta blockers has been associated with unacceptable adverse effects.

NU-VERAP SR can be tried as an initial agent in those patients in whom the use of diuretics and/or beta blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

Concomitant use of NU-VERAP SR with a diuretic or an angiotensin converting enzyme inhibitor has been shown to be compatible and to have additive blood pressure lowering effects.

NU-VERAP SR should not be used concurrently with beta adrenoreceptor blockers in the treatment of hypertension (see PRECAUTIONS – Drug Interactions).

Safety of concurrent use of NU-VERAP SR with other antihypertensive agents has not been established and such use cannot be recommended at this time.

CONTRAINDICATIONS

1. Complicated myocardial infarction (patients who have ventricular failure manifested by pulmonary congestion).
2. Severe congestive heart failure and/or severe left ventricular dysfunction (i.e. ejection fraction <40%), unless secondary to a supraventricular tachycardia amenable to oral verapamil therapy).
3. Cardiogenic shock.
4. Severe hypotension.
5. Second- or third-degree A-V block.
6. Sick Sinus Syndrome (see WARNINGS).
7. Marked bradycardia.
8. Hypersensitivity to the drug.

9. Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see WARNINGS).

WARNINGS

General**:** In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of NU-VERAP SR (verapamil hydrochloride) should be taken into consideration.

Heart Failure: Because of the drug's negative inotropic effect, verapamil hydrochloride should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by a dysrhythmia. If verapamil is used in such patients, they must be digitalized prior to treatment.

It has been reported that digoxin plasma levels may increase with chronic verapamil administration (see PRECAUTIONS - Drug Interactions: *Digoxin*). The use of verapamil in the treatment of hypertension is not recommended in patients with heart failure caused by systolic dysfunction.

Hypotension: Hypotensive symptoms of lethargy and weakness with faintness have been reported following single oral doses and even after some months of treatment. In some patients it may be necessary to reduce the dose.

Conduction Disturbance: Verapamil slows conduction across the A-V node and rarely may produce second or third degree A-V block, bradycardia and in extreme cases, asystole.

Verapamil causes dose-related suppression of the S-A node. In some patients, sinus bradycardia may occur, especially in patients with a sick sinus syndrome (S-A nodal disease), which is more common in older patients (see CONTRAINDICATIONS).

Bradycardia: The total incidence of bradycardia (ventricular rate less than 50 beats/min.) was 1.4% in controlled studies. Asystole in patients other than those with sick sinus syndrome is usually of short duration (a few seconds or less), with spontaneous return to A-V nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine): Verapamil may result in significant acceleration of ventricular response during atrial fibrillation or atrial flutter in the Wolff-Parkinson-White (WPW) or Lown-Ganong-Levine syndromes after receiving intravenous verapamil. Although a risk of this occurring with oral verapamil has not been established, such patients receiving oral verapamil may be at risk and its use in these patients is contraindicated (see CONTRAINDICATIONS).

Concomitant Use with Beta Blockers: Generally, oral verapamil should not be given to patients receiving beta blockers since the depressant effects on myocardial contractility, heart rate and A-V conduction may be additive. However, in exceptional cases when in the opinion of the physician, concomitant use in angina and arrhythmias is considered essential, such use should be instituted gradually under careful supervision. If combined therapy is used, close surveillance of vital signs and clinical status should be carried out and the need for continued concomitant treatment periodically assessed.

Verapamil gives no protection against the dangers of abrupt beta blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta blocker. Then verapamil may be started with the usual dose.

Patients with Hypertrophic Cardiomyopathy: In 120 patients with hypertrophic cardiomyopathy who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects was seen. Three patients died in pulmonary edema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary edema and/or severe hypotension, abnormally high (greater than 20 mmHg) pulmonary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients. Concomitant administration of quinidine (see PRECAUTIONS - Drug Interactions) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary edema). Sinus bradycardia occurred in 11% of the patients, second-degree A-V block in 4%, and sinus arrest in 2%. It must be appreciated that this group of patients had a serious disease with a high mortality rate. Most adverse effects responded well to dose reduction, but in some cases, verapamil use had to be discontinued.

Elevated Liver Enzymes: Elevation of transaminase with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Several published cases of hepatocellular injury produced by verapamil have been proven by rechallenge. Clinical symptoms of malaise, fever, and/or right upper quadrant pain, in addition to elevation of SGOT, SGPT and alkaline phosphatase have been reported. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

Hepatic Insufficiency: Because verapamil is extensively metabolized by the liver, it should be administered cautiously to patients with impaired hepatic function, since the elimination half-life of

verapamil in these patients is prolonged 4-fold (from 3.7 to 14.2 hours). A decreased dosage should be used in patients with hepatic insufficiency and careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect should be carried out (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: About 70% of an administered dose of verapamil is excreted as metabolites in the urine. In one study in healthy volunteers, the total body clearance after intravenous administration of verapamil was 12.08 mL/min/kg, while in patients with advanced renal disease it was reduced to 5.33 mL/min/kg. This pharmacokinetic finding suggests that renal clearance of verapamil in patients with renal disease is decreased. In two studies with oral verapamil, no difference in pharmacokinetics could be demonstrated. Therefore, until further data are available, verapamil should be used with caution in patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effect (see DOSAGE AND ADMINISTRATION).

PRECAUTIONS

Atypical lens changes and cataracts were observed in beagle dog studies at high doses. This has been concluded to be species-specific for the beagle dog. (These ophthalmological changes were not seen in a second study.) No similar changes have been observed in long-term prospective human ophthalmological trials.

Verapamil does not alter total serum calcium levels. However, one report suggested that calcium levels above the normal range may decrease the therapeutic effect of verapamil.

Use in Patients With Attenuated (Decreased) Neuromuscular Transmission: It has been reported that verapamil decreases neuromuscular transmission in patients with Duchenne's muscular dystrophy, and that verapamil prolongs recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease the dosage of verapamil when it is administered to patients with attenuated neuromuscular transmission.

Use in the Elderly: Caution should be exercised when verapamil is administered to elderly patients (≥65 years) especially those prone to developing hypotension or those with a history of cerebrovascular insufficiency (see DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). The incidence of adverse reactions is approximately 4% higher in the elderly. The adverse reactions occurring more frequently include dizziness and constipation. Serious adverse events associated with heart block have occurred in the elderly.

Pregnancy: Teratology and reproduction studies have been performed in rabbits and rats at oral doses up to 1.5 (15 mg/kg/day) and 6 (60 mg/kg/day) times the human oral daily dose, respectively and have revealed no evidence of teratogenicity or impaired fertility. In rat, however, this multiple of the human dose was embryocidal and retarded fetal growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats.

There are no studies in pregnant women. However, verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. NU-VERAP SR (verapamil hydrochloride) is not recommended for use in pregnant women unless the potential benefits outweigh potential risks to mother and fetus.

Labour and Delivery: It is not known whether the use of verapamil during labour or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labour, increases the need for forceps delivery or other obstetric intervention.

Use in Nursing Mothers: Verapamil is excreted in human milk. Because of the potential for adverse reactions in nursing infants from verapamil, nursing should be discontinued while verapamil is administered.

Use in Children**:** The safety and dosage regimen of verapamil in children has not yet been established.

Drug Interactions

As with all drugs, care should be exercised when treating patients with multiple medications. Calcium channel blockers undergo biotransformation by the cytochrome P450 system. Coadministration of verapamil with other drugs which follow the same route of biotransformation may result in altered bioavailability of verapamil or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered verapamil to maintain optimum therapeutic blood levels.

Drugs known to be inhibitors of the cytochrome P450 system include azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine and warfarin.

Drugs known to be inducers of the cytochrome P450 system include phenobarbital, phenytoin and rifampin.

Drugs known to be biotransformed via P450 include benzodiazepines, flecainide, imipramine, propafenone and theophylline.

Alcohol: Verapamil may increase blood alcohol concentrations and prolong its effects.

Anti-neoplastic Agents: Verapamil inhibits P-glycoprotein mediated transport of anti-neoplastic agents out of tumour cells, resulting in their decreased metabolic clearance. Dosage adjustments of anti-neoplastic agents should be considered when verapamil is administered concomitantly.

Antihypertensive Agents: Verapamil administered concomitantly with antihypertensive agents such as vasodilators, ACE inhibitors, and diuretics may have an additive effect on lowering blood pressure. In patients with angina or arrhythmias using antihypertensive drugs, this additional hypotensive effect should be taken into consideration. Verapamil should not be combined with beta blockers for the treatment of hypertension. Concomitant use of verapamil and alpha-adrenoceptor blockers may result in excessive fall in blood pressure in some patients as observed in one study following the concomitant administration of verapamil and prazosin.

Aspirin: Potential adverse reactions in terms of bleeding due to synergistic antiplatelet effects of the two agents should be taken into consideration in patients taking aspirin and verapamil concomitantly.

Beta-Adrenergic Blockers: The concomitant administration of verapamil with beta-blockers can result in severe adverse effects (see WARNINGS).

Carbamazepine: The concomitant oral administration of verapamil and carbamazepine may potentiate the effects of carbamazepine neurotoxicity. Symptoms include nausea, diplopia, headache, ataxia or dizziness.

Cimetidine: Two clinical trials have shown a lack of significant verapamil interaction with cimetidine. A third study showed cimetidine reduced verapamil clearance and increased elimination half-life.

Cyclosporine: Verapamil therapy may increase serum levels of cyclosporine.

Digoxin: Verapamil treatment increases serum digoxin levels by 50% and 75% during the first week of therapy, and this can result in digitalis toxicity. In patients with hepatic cirrhosis, the influence of verapamil on digoxin kinetics is magnified. Verapamil may reduce total body clearance and extrarenal clearance of digitoxin by 27% and 29% respectively. Maintenance and digitalization doses should be reduced when verapamil is administered and the patient should be reassessed to avoid over or underdigitalization. Whenever overdigitalization is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. On discontinuation of verapamil use, the patient should be reassessed to avoid underdigitalization.

Disopyramide**:** Until data on possible interactions between verapamil and disopyramide are obtained, disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

Flecainide: A study in healthy volunteers showed that concomitant administration of flecainide and verapamil may have additive deleterious effects on myocardial contractility, AV conduction

and repolarisation. Concomitant therapy with flecinide and verapamil may result in additive negative inotropic effect and prolongation of atrioventricular conduction.

Inhalation Anaesthetics**:** When used concomitantly, inhalation anaesthetics and calcium antagonists, such as verapamil, should be titrated carefully because additive hemodynamic depressive effects have been observed.

Lithium**:** Increased sensitivity to the effects of lithium (neutotoxicitiy) has been reported during concomitant verapamil-lithium therapy with either no change or an increase in serum lithium levels. However, the addition of verapamil has also resulted in the lowering of serum lithium levels in patients receiving chronic, stable, oral lithium. Patients receiving both drugs must be monitored carefully.

Neuromuscular Blocking Agents: Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent when the drugs are used concomitantly.

Nitrates, Diuretics: No cardiovascular adverse effects have been attributed to any interaction between these agents and verapamil.

Phenobarbital: Phenobarbital therapy may increase verapamil clearance.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy, concomitant use of verapamil and quinidine resulted in significant hypotension. Until further data are obtained, combined therapy of verapamil and quinidine in patients with hypertrophic cardiomyopathy should

probably be avoided. The electrophysiologic effects of quinidine and verapamil on A-V conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on A-V conduction. There has been a report of increased quinidine levels during verapamil therapy.

Rifampin**:** Therapy with rifampin may markedly reduce oral verapamil bioavailability.

Sulfinpyrazone: Increased clearance and decreased bioavailability of verapamil may occur.

Theophylline: Verapamil may inhibit the clearance and increase the plasma levels of theophylline.

ADVERSE REACTIONS

In 4,826 patients treated with verapamil hydrochloride immediate release tablets for arrhythmias, angina or hypertension, the overall adverse reaction rate in these patients was 37.1% and the dropout rate was 10.2%. The majority of these patients were seriously ill and treated under emergency drug regulations.

In controlled pivotal studies with 128 patients treated with verapamil hydrochloride sustained release tablets for hypertension, the overall adverse reaction rate was 21.7% and the dropout rate was 3.9%.

The most common adverse reactions were: constipation (7.3%), dizziness (3.2%), and nausea (2.7%). In hypertension studies, constipation occurred in 18.5% of patients on verapamil immediate release tablets and in 4.7% of patients on verapamil sustained release tablets.

The most serious adverse reactions reported with verapamil are heart failure (1.8%), hypotension (2.5%), A-V block (1.2%) and rapid ventricular response (see WARNINGS).

The following adverse reactions divided by body system have been reported in clinical trials or marketing experience. When incidences are shown, they are calculated based on the 4,954 (4,826 +128) patient base.

Cardiovascular	
Hypotension	2.5%
Edema	2.1%
CHF/Pulmonary Edema	1.9%
Bradycardia	1.4%
A-V Block	
Total (1˚, 2˚, 3˚)	1.2%
2˚ and 3˚	0.8%
Central Nervous System	
Dizziness	3.2%
Headache	2.2%
Fatigue	1.7%
Gastrointestinal	
Constipation	7.3%
Nausea	2.7%

The following reactions were reported in 1.0% or less of patients:

Cardiovascular: Flushing, angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura, syncope, severe tachycardia, developing or

worsening of heart failure, development of rhythm disturbances, ventricular dysrhythmias, painful coldness and numbness of extremities.

Central Nervous System**:** Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, excitation, depression, rotary nystagmus, vertigo, tremor, extrapyramidal disorders, muscle fatigue, hyperkinesis.

Gastrointestinal**:** Diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, vomiting.

Respiratory: Dyspnea, bronchospasm.

Urogenital**:** Gynecomastia, increased frequency of urination, spotty menstruation, oligomenorrhea, impotence.

Hematologic and Lymphatic: Ecchymosis or bruising.

Skin**:** Arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson Syndrome, erythema multiforme, pruritus.

Special Senses**:** Blurred vision, diplopia.

Hepatotoxicity with elevated enzymes (SGOT, SGPT, alkaline phosphatase) and bilirubin levels, jaundice and associated symptoms of hepatitis with cholestasis have been reported (see WARNINGS).

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

In clinical trials related to the control of ventricular response in digitalized patients who had atrial fibrillation or flutter, ventricular rates below 50 at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Based on reports of intentional overdosage of verapamil hydrochloride sustained release tablets, the following symptoms have been observed. Hypotension occurs, varying from transient to severe. Conduction disturbances seen included: prolongation of A-V conduction time, A-V dissociation, nodal rhythm, ventricular fibrillation and ventricular asystole.

Treatment of overdosage should be supportive. Gastric lavage should be undertaken even later than 12 hours after ingestion, if no gastrointestinal motility is present. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion influx across the slow channel.

These pharmacologic interventions have been effectively used in treatment of overdosage with verapamil. Clinically significant hypotensive reactions should be treated with vasopressor agents. A-V block is treated with atropine and cardiac pacing. Asystole should be handled by the usual Advanced Cardiac Life Support measures including the use of vasopressor agents, e.g. isoproterenol hydrochloride. Verapamil is not removed by hemodialysis.

In cases of overdosage with large amounts of verapamil hydrochloride sustained release tablets, it should be noted that the release of the active drug and the absorption in the intestine may take

more than 48 hours. Depending on the time of ingestion, incompletely dissolved tablets may be present along the entire length of the gastrointestinal tract, which functions as active drug depots. Extensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage and high enemas.

Suggested Treatment of Acute Cardiovascular Adverse Reactions

Actual treatment and dosage should depend on the severity of the clinical situation and the judgement of the treating physician. Patients with hypertrophic cardiomyopathy treated with verapamil should not be administered positive inotropic agents. (Marked by asterisks.)

Adverse Reaction	**Proven Effective Treatment**	**Treatment with Good Theoretical Rationale**	**Supportive Treatment**
1. Shock, cardiac failure, severe hypertension	Calcium salt e.g. calcium gluconate IV; Intravenous metaraminol bitartrate*	Intravenous dopamine HCl*; Intravenous dobutamine HCl*	Intravenous fluids; Trendelenburg position
2. Bradycardia, A-V block, asystole	Intravenous isoproterenol HCl* Intravenous atropine sulphate; Cardiac pacing	-	Intravenous fluids (slow drip)
3. Rapid ventricular rate (due to antegrade conduction in flutter/fibrillation with W-P-W or L-G-L syndrome)	D.C. cardioversion (high energy may be required); Intravenous procainamide; Intravenous lidocaine HCl	-	Intravenous fluids (slow drip)

DOSAGE AND ADMINISTRATION

Crushing or chewing of NU-VERAP SR (verapamil hydrochloride) tablets is not recommended since the sustained-release effect will be altered by damage to the tablet structure. The NU-VERAP SR 240 mg tablet may be split in half.

Mild to Moderate Essential Hypertension

NU-VERAP SR tablets should be taken with food (see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics: *Influence of Food*). The dosage should be individualized by titration depending on patient tolerance and responsiveness to verapamil. Titration should be based on therapeutic efficacy and safety, evaluated weekly and approximately 24 hours after the previous dose.

The usual initial adult dose is 180-240 mg/day. If required, the dose may be increased up to 240 mg twice a day. A maximum daily dose of 480 mg should not be exceeded.

Recommended dosing intervals for specific daily dosages are given below:

Total Daily NU-Verap SR Dose	**Recommended Dosing Intervals**
180 mg	Once each morning with food
240 mg	Once each morning with food
360 mg	180 mg each morning plus 180 mg each evening, with food; or 240 mg each morning plus 120 mg each evening with food
480 mg	240 mg each morning plus 240 mg each evening with food

The antihypertensive effects of NU-VERAP SR are evident within the first week of therapy. Optimal doses are usually lower in patients also receiving diuretics since additive antihypertensive effects can be expected.

Elderly

Lower dosages of NU-VERAP SR ie. 120 mg a day, may be warranted in elderly patients (ie. 65 years and older) (see PRECAUTIONS – Use in Elderly). The dosage should be carefully and gradually adjusted depending on patient tolerability and response.

Patients with Impaired Liver and Renal Function

NU-VERAP SR should be administered cautiously to patients with liver or renal function impairment. The dosage should be carefully and gradually adjusted depending on patient tolerance and response. These patients should be monitored carefully for abnormal prolongation of the PR interval or other signs of overdosage. NU-VERAP SR tablets should not be used in patients with severe hepatic dysfunction (see WARNINGS-Hepatic Insufficiency).

Switching from NU-VERAP to NU-VERAP SR

When switching from NU-VERAP to NU-VERAP SR tablets, the total daily dose in milligrams may remain the same.

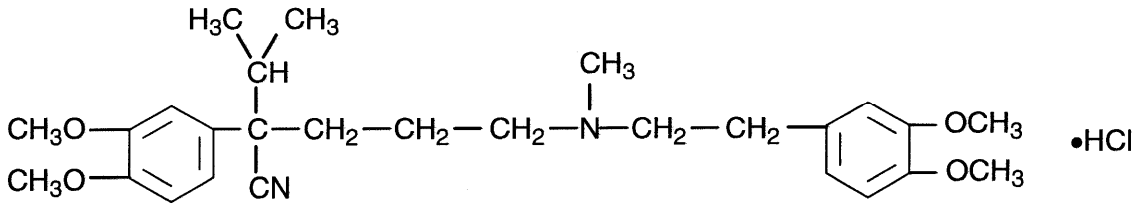
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Verapamil hydrochloride

Chemical Name: α-isopropyl-α-[(N-methyl-N-homoveratryl)-γ-amino-propyl]-3,4-dimethoxyphenylacetonitrile hydrochloride

Structural Formula:



Molecular Formula: $C_{27}H_{38}N_2O_4 \cdot HCl$

Molecular Weight: 491

Description: Verapamil, as the hydrochloride salt, is an almost-white, bitter-tasting crystalline powder, practically odourless and readily soluble in chloroform and water (1 part in 20), but sparingly soluble in ethanol, and practically insoluble in ether. It melts at 140˚C and should be protected from light.

Composition

In addition to verapamil hydrochloride, each tablet contains the non-medicinal ingredients sodium alginate, magnesium stearate, colloidal silicon dioxide, hydroxyethyl cellulose, polyethylene glycol, and titanium dioxide. The 180 mg tablet also contains the non-medicinal ingredient red ferric oxide. The 240 mg tablet also contains the non-medicinal ingredients yellow ferric oxide and brilliant blue FCF AL lake.

Stability and Storage Recommendations

Store at room temperature 15 to 30˚C (59 to 86˚F). Protect from light.

AVAILABILITY OF DOSAGE FORMS

NU-VERAP SR 120 mg tablets are white, round, biconvex, film-coated tablets, engraved "VSR" and "120" on the one side. Available in bottles of 100.

NU-VERAP SR 180 mg tablets are light pink, oval, biconvex, film-coated tablets, engraved "VSR" over "180" and scored on the other. Available in bottles of 100.

NU-VERAP SR 240 mg tablets are light green, capsule shaped, biconvex, film-coated tablets, engraved "VSR" and "240" and scored on the other side. Available in bottles of 100 and 500.

SPECIAL NOTE TO PHARMACISTS

The NU-VERAP SR (verapamil hydrochloride) 240 mg tablet may be split in half. Crushing NU-VERAP SR tablets is not recommended since the sustained-release effect will be altered by damage to the tablet structure. The use of NU-VERAP SR 120 mg is recommended.

PHARMACOLOGY

Verapamil hydrochloride was initially investigated in experimental animals as a smooth muscle relaxant with vasodilator properties. Subsequent studies have demonstrated that verapamil hydrochloride has significant antiarrhythmic effects when tested in a variety of experimental arrhythmias. The mechanism of action of verapamil hydrochloride seems to be the blocking of transmembrane influx of calcium through the slow channel without affecting to any significant degree, transmembrane influx of sodium through the fast channels. It does not directly modify calcium uptake, binding or exchange by cardiac microsomes. Its main focus of action seems to be the superficially located membrane storage sites for calcium.

In isolated cardiac tissues, at low to moderate concentrations, verapamil hydrochloride exerts little or no effect on action potential amplitude, but suppresses activity in the sinoatrial (S-A) and atrioventricular (A-V) nodes. Any activity within the S-A and A-V nodes seems to be particularly sensitive to the suppressant effects of verapamil hydrochloride because normal impulse formation in the sinus node and conduction in the A-V node appear to be maintained by operation of slow channel mechanisms. The depressant effects exerted by verapamil hydrochloride on A-V nodal conduction may in part explain its effectiveness in treating supraventricular tachycardia.

Verapamil hydrochloride has a marked negative inotropic effect on isolated cardiac muscle. In intact animals, the depressant effect on cardiac output and stroke volume is dose dependent.

Although verapamil hydrochloride has local anaesthetic properties, in clinically relevant doses it does not affect the rate of either the depolarization or the repolarization phase of the cardiac action potential. Verapamil hydrochloride does not have beta-blocking properties, although it antagonizes beta-adrenergic influences on the heart by a functional antagonism, due to its basic pharmacodynamic properties at the level of the conduction system and the myocardium.

In animal studies, the S enantiomer has 15 and 50 times the activity of the R enantiomer in reducing myocardial contractility in isolated blood-perfused dog papillary muscle and isolated rabbit papillary muscle, respectively, and twice the effect in reducing peripheral resistance.

TOXICOLOGY

Acute Toxicity

LD_{50} (mg/kg)				
	IV	**IP**	**SC**	**Oral**
Rat	16	67	107	114

Mouse	8	68	68	163
Guinea Pig	-	-	-	140
Juvenile Rat	-	-	-	93 (M)
	-	-	-	113 (F)
Juvenile Rabbit	-	-	-	114.2 (M)
	-	-	-	129.8 (F)

Symptoms preceding death were similar in both sexes with marked sedation, decreased excitability, forced respiration, clonic spasms and convulsions.

Subacute Toxicity

Oral Studies: Verapamil was administered orally in doses of 12.5, 25 and 50 mg/kg per day, to rats via food for 14 weeks (29 animals/group) and to dogs for 6 days/week in capsules, for 15-16 weeks (4 animals/group). Baboons received 2, 4, 8, 16, 32 and 64 mg/kg by mouth daily for 4 weeks (2 animals/group).

In rats, a dose related increase in heart and lung weights was found. Dogs given 25-50 mg/kg showed slight weight loss and a significant reduction in heart rate up to week 11, followed by a gradual return to normal. In one dog on 12.5 mg/kg, one on 25 mg/kg and in all animals on 50 mg/kg, there was emesis during the first two weeks of the study. SGPT was elevated for one dog on 25 mg/kg at week 9 and for two animals on 50 mg/kg at the end of the test. Macroscopic examinations at necropsy were negative and there were no drug-attributable histological changes. The baboons showed no drug related changes.

Intramuscular Studies: Beagle dogs were given 0, 2 and 10 mg/kg, 5 days/week for 30 days (4 animals/group). Injection sites in all animals became edematous and a dose-related reduction in

heart rate was observed. At 10 mg/kg, hemoglobin and hematocrit values decreased and one animal had a raised SGPT. At necropsy, edema was noted at injection sites and higher spleen weights were recorded on the 10 mg/kg dose. One dog on this dose also showed increased inflammatory cell infiltration in the liver, with some hepatic cell degenerative changes.

Intravenous Studies: Verapamil was given to Sprague-Dawley rats at 0.2, 1 and 5.0 mg/kg once daily for 4 weeks (30 animals/group) and similarly to beagle dogs at 0.1, 0.4 and 1.6 mg/kg levels (6 animals/group).

At the highest dose level, all dogs showed some restlessness, salivation and laboured breathing, along with delayed A-V conduction in one-half of the animals. In 4 of 6 animals at this highest dose (1.6 mg/kg), sporadic small focal gatherings of Kupffer cells with death of individual liver cells (necrobioses and/or necrosis of hepatocytes) were found histopathologically.

Chronic Toxicity

Oral: Rats were given verapamil at 10, 15, 25, 30, 60 and 62.5 mg/kg/day (50 animals/group) and beagle dogs at 10, 15, 25, 30, 40, 60, 62.5, 70, 81 and 85 mg/kg (6 animals/group) for 12 and 18 months. Clinical signs were observed and changes in food consumption, consistency of stools, hemograms, clinical chemistry and urinalyses performed. Blood pressure, ECG and ophthalmoscopic examinations were done on the dogs.

In one 18-month rat study, an increase in weight of the thyroid glands in females on the 62.5 mg dose was noted. In a later 12-month study, a slight reduction in weight gain was recorded.

In dogs, at doses of 60 mg and greater, toxic signs such as vomiting, salivation, reversible hyperplasia of the gums, reduced food consumption, slight weight loss and a transitory, slight to moderate elevation of SGPT were noted and three of the animals died. The 40 mg dose caused loss of coat colour and hair, and a delay in A-V conduction.

In another study, atypical lens changes (cataracts) were observed in 8 beagles receiving toxic dose levels (62.5 and 70 mg/kg). In a later study, 4 beagles were given 81 mg/kg for 18 months and none developed cataracts. It was concluded that any changes caused by verapamil in lens transparency are specific to the beagle. This is supported by the absence of similar lesions in other species studied and by the apparent lack of any impairment by verapamil of carbohydrate or energy metabolism in lenticular tissue. The water-soluble proteins of the canine lens are known to have differences from those in other species.

Mutagenicity

In vitro mutagenicity tests showed that verapamil did not have mutagenic properties in five different strains of Salmonella typhimurium, nor in studies on chromasomal aberrations and sister chromatid exchanges (SCE) in human lynphocytes, nor in the HGPRT-test with V-79 Chinese hamster cells and also not in the cell transformation assay with Syrian hamster embryo cells. Neither did verapamil show any SCE-inducing activity *in-vivo* (Chinese hamster).

Carcinogenicity

In a 24-month carcinogenicity study, verapamil hydrochloride was administered orally to 50 male and 50 female rats in the diet as actual mean doses of 9.3/9.5, 32.6/33.2, and 112.2/102.5 mg/kg/day, respectively. Two hundred animals served as controls.

Drug-related significant reductions in body weight and mortality were seen in males and females of the high dose group.

Dose-related cardiac lesions (dilatation, atrial thrombi and myocardial metaplasia, combined with hydrothorax) were seen in the high dose group. These cardiac lesions are considered to be related to a chronic, exaggerated pharmacologic effect at this high dose level.

At the end of the study, all rats were examined histopathologically with regard to tumorigenesis. All non-neoplastic and neoplastic lesions were considered to reflect the spectrum of spontaneous lesions commonly encountered in rats of this age and strain. As compared to the controls, the type and incidence of these lesions were not increased in treated rats.

Reproduction

Studies were carried out in rats and rabbits with verapamil given in food and/or by gastric tube. These studies included fertility and general reproduction performance in rats, teratogenicity studies in rats and rabbits and peri- and post-natal studies in rats. Rats were given 2.5, 12.5, 25 and 100 mg/kg body weight, by gastric tube and 1.3, 1.6, 5.2, 7.5, 13.3, 16 and 55 mg/kg body weight in food. In another teratogenicity study, rats were given 5, 10 and 20 mg/kg body weight by gavage three times daily at an interval of about 4.5 hours. Rabbits were given 5 and 15 mg/kg body weight by gastric tube.

There was no evidence of teratogenicity in either species and no embryotoxic effects observed in the rats dosed via food, or with doses up to 12.5 mg/kg body weight given by gastric tube, or with doses up to 10 mg/kg t.i.d. The single daily dose of 25 mg/kg body weight or more, caused a higher resorption rate in the rat. The dose of 20 mg/kg t.i.d was embryocidal and retarded fetal

growth and development, probably because of adverse maternal effects reflected in reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There was no difference in resorption rates observed in the rabbit and no effect on peri- and post-natal development or fertility in the rat.

BIBLIOGRAPHY

1. Anavekar SN, Christophidis N, Louis WJ, Doyle AE. Verapamil in the treatment of hypertension. J Cardiovase Phann 1981; 3: 287-92.

2. Bauer LA, et al. Verapamil inhibits ethanol elimination and prolongs the perception of intoxication. Clin Pharmacol Ther 1992;52(l): 6-10.

3. Bonow RO, Lcon MB, Rosing DR, et al. Effects of verapamil and propranolol on left ventricular systolic function and diastolic filling in patients with coronary artery disease: Radionuclide angiographic studies at rest and during exercise. Circulation 1981; 65: 1337-50.

4. Cubeddu LX, Aranda J, Singh B, et al. A comparison of verapamil and propranolol for the initial treatment of hypertension - racial differences in response. J Am Med Assoc 1986; 256: 2214-21.

5. Ferlinz J, Easthope JL. Effects of verapamil on myocardial performance in coronary disease. Circulation 1979; 59: 313-9.

6. Ferlinz J, Turbow ME, Aronow WS. Myocardial metabolism and anginal threshold in coronary disease after verapamil administration. Clin Invest Med 1980; 3: 101-9.

7. Follath F, Fromer M, Meier P, Vozeh S. Pharmacodynamic comparison of oral and intravenous verapamil in atrial fibrillation. Clin Invest Med 1980; 3: 49-52.

8. Frishman YM, Klein NA, Klein P, et al. Comparison of oral propranolol and verapamil for combined systemic hypertension and angina pectoris. A placebo-controlled double-blind randomized crossover trial. Amer J Cardiol 1982; 50: 1164-1172.

9. Frishman WH, Klein NA, Strom JA, et al. Superiority of verapamil to propranolol in stable angina pectoris: A double-blind, randomized crossover trial. Circulation 1982; 65(suppl.l): 151-9.

10. Gould BA, Mann S, Kieso H, Balasubramanian V, Raftery EB. The role of a slow channel inhibitor, verapamil, in the management of hypertension. Clin Exp Pharmacol Physiol 1982; Suppl 6: 113-121

11. Johnson SM, Mauritson DR, Corbett JR, Woodward W, Willerson JT, Hillis LD. Double-blind, randomized, placebo-controlled comparison of propranolol and verapamil in the treatment of patients with stable angina pectoris. Am J Med 1981; 71: 443-5 1.

12. Johnson SM, Mauritson DR, Willerson JT, Hillis LD. A controlled trial of verapamil for Prinzmetal's variant angina. New Eng J Med 1981; 304: 862-6.

13. Kaltenbach M, Hopf R, Kober G, Bussrnann WD, Keller M, Petersen Y. Treatment of hypertrophic obstructive cardiomyopathy by verapamil. Br Heart J 1979; 42: 35-42.

14. Klein HO, Lang R, Weiss E, et al. The influence of verapamil in scrum digoxin concentrations. Circulation 1982; 65: 998-1003.

15. Miller MR, Withers R, Bhamra R, Holt DW. Verapamil and breast-feeding. Eur J Clin Pharmacol, 1986; 30: 125-6.

16. Nayler WG. Cardioprotective effects of calcium ion antagonists in myocardial ischemia. Clin Invest Med 1980; 3: 91-9.

17. Packer M, Meller J, Medina N, et al. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. Circulation 1982; 65: 660-8.

18. Perez-Reyes M, et al. Interaction between ethanol and calcium channel blockers in humans. Alcohol Clin Exp Res 1992; 16(4): 769-775.

19. Pozenel H. Plasma concentration and blood pressure effect of a sustained release verapamil preparation. In Calcium Antagonists & Hypertension. Current Status, Excerpta Medica, Amsterdam, 1986, pp 56-65.

20. Rinkenberger RL, Prystowsky EN, Heger JJ, Troup PJ, Jackman WM, Zipes DP. Effects of intravenous and chronic oral verapamil administration in patients with supraventricular tachyarrhythmias. Circulation 1980; 62: 996-1010.

21. Rosing DR, Condit JR, Maron BJ, et al. Verapamil therapy: A new approach to the pharmacologic treatment of hypertrophic cardiomyopathy: III. Effects of long term administration. Am J Cardiol 1981; 48: 545-53.

22. Schwartz JB, Keefe DL, Kirsten E, Kates RE, Harrison DC. Prolongation of verapamil elimination kinetics during chronic oral administration. Am Heart J 1982; 104: 198-203.

23. Subramanian VB, Bowles MJ, Khunni NS, Davies AB, Raferty EB. Randomized double-blind comparison of verapamil and nifedipine in chronic stable angina. Am J Cardiol 1982; 50: 696-703.

24. Vohra J, Ross D, Cole P, Hunt D, Sloman G. The effect of orally administered verapamil on atrioventriculam nodal conduction and refractoriness. I.R.C.S., Med Sci 1980; 8: 45.

25. Zachariah PK, Sheps SG, Schirger A, Spiekennan RE, O'Brien PC, Simpson KK. Verapamil & 24-hour ambulatory blood pressure monitoring in essential hypertension. Am J Cardiol 1986; 57: 74D-79D.

26. Zacny JP, Yajnik S. Effects of calcium channel inhibitors on ethanol effects and pharmacokinetics in healthy volunteers. Alcohol 1993; 10(6): 505-509.