

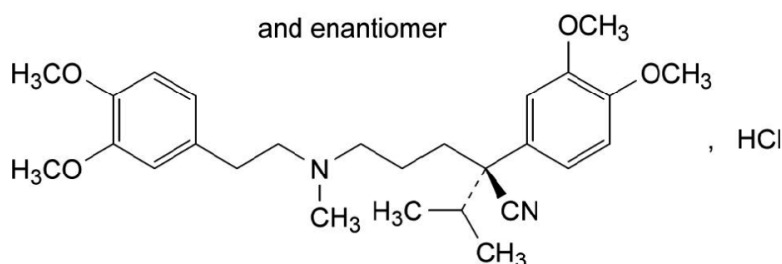
## PRODUCT INFORMATION

### NAME OF THE MEDICINE

Active ingredient: Verapamil hydrochloride

Chemical name: 5-[N-(3,4-dimethoxyphenethyl)methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride

Structural formula:



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

Molecular weight: 491.1

CAS Registry No.: 152-11-4

### DESCRIPTION

Verapamil hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist).

Verapamil hydrochloride is a white or almost white, odourless, crystalline powder. It is soluble in 20 parts of water; sparingly soluble in ethanol (96%), freely soluble in chloroform and practically insoluble in ether.

Each Anpec tablet contains verapamil hydrochloride 40 mg or 80 mg as the active ingredient. The tablets also contain the following inactive ingredients: lactose anhydrous, cellulose - microcrystalline, starch - pregelatinised maize, sodium starch glycollate, talc - purified and magnesium stearate. Anpec 40 also contains Opadry Yellow OY-LS-32814 and Anpec 80 contains Opadry Orange OY-LS-33113.

### PHARMACOLOGY

Verapamil is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) which exerts its pharmacologic effects by modulating the influx of ionic calcium ions across cell membranes of the arterial smooth muscle cell as well as in conductile and contractile myocardial cells.

#### Mechanism of Action

##### *Hypertension*

Verapamil exerts antihypertensive effects by decreasing systemic vascular resistance, usually without orthostatic

decreases in blood pressure or reflex tachycardia; bradycardia (rate less than 50 beats /min) is uncommon (1.4%). During isometric or dynamic exercise verapamil does not alter systolic cardiac function in patients with normal ventricular function.

### ***Angina Pectoris***

Verapamil dilates the main coronary arteries and coronary arterioles, both in normal and ischaemic regions, and is a potent inhibitor of coronary artery spasm, whether spontaneous or ergonovine-induced. This property increases myocardial oxygen delivery in patients with coronary artery spasm, and is responsible for the effectiveness of verapamil in vasospastic (Prinzmetal's or variant) as well as unstable angina at rest. Whether this effect plays any role in classical effort angina is not clear, but studies of exercise tolerance have not shown an increase in the maximum exercise rate-pressure product, a widely accepted measure of oxygen utilisation. This suggests that, in general, relief of spasm or dilation of coronary arteries is not an important factor in classical angina.

Verapamil regularly reduces the total systemic resistance (afterload) against which the heart works both at rest and at a given level of exercise by dilating peripheral arterioles.

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

### ***Other Pharmacological Actions***

Electrical activity through the AV node depends, to a significant degree, upon calcium influx through the slow channel. By decreasing the influx of calcium, verapamil prolongs the effective refractory period within the AV node and slows AV conduction in a rate-related manner. Normal sinus rhythm is usually not affected, but in patients with sick sinus syndrome, verapamil may interfere with sinus node impulse generation and may induce sinus arrest or sinoatrial block. Atrioventricular block can occur in patients without pre-existing conduction defects (see **PRECAUTIONS**).

Verapamil does not alter the normal atrial action potential or intraventricular conduction time, but depresses amplitude, velocity of depolarisation and conduction in depressed atrial fibres. Verapamil may shorten the antegrade effective refractory period of accessory bypass tracts. Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a co-existing accessory AV pathway following administration of verapamil (see **PRECAUTIONS**).

Verapamil has a local anaesthetic action that is 1.6 times that of procaine on an equimolar basis. It is not known whether this action is important at the doses used in humans.

### ***Haemodynamics and Myocardial Metabolism***

Verapamil reduces afterload and myocardial contractility. Improved left ventricular diastolic function in patients with hypertrophic cardiomyopathy (IHSS) and those with coronary heart disease has also been observed with verapamil therapy. In most patients, including those with organic cardiac disease, the negative inotropic action of verapamil is countered by reduction of afterload and cardiac index is usually not reduced. In patients with severe left ventricular dysfunction however, (e.g. pulmonary wedge pressure above 20 mmHg or ejection fraction lower than 30%), or in patients on beta-adrenergic blocking agents or other cardiodepressant drugs, deterioration of ventricular function may

occur (see **INTERACTIONS WITH OTHER MEDICINES**).

### ***Pulmonary Function***

Verapamil does not induce broncho-constriction and hence, does not impair ventilatory function.

### **Pharmacokinetics**

Anpec is rapidly and almost completely absorbed from the gastrointestinal tract. The overall oral bioavailability ranges from 22 to 35% due to a substantial hepatic first pass effect. Peak plasma concentrations are reached between one and two hours after oral administration. Chronic oral administration of 120 mg of verapamil every 6 hours resulted in plasma levels of verapamil ranging from 125 to 400 ng/mL with higher values reported occasionally. A nonlinear correlation between the verapamil dose administered and verapamil plasma levels does exist.

In early dose titration with verapamil a relationship exists between verapamil plasma concentrations and the prolongation of the PR interval. However, during chronic administration this relationship may disappear. The mean elimination half-life in single dose studies ranged from 2.8 to 7.4 hours. In these same studies, after repetitive dosing the half-life increased to a range from 4.5 to 12.0 hours (after less than ten consecutive doses given 6 hours apart). Half-life of verapamil may increase during titration.

Aging may affect the pharmacokinetics of verapamil. Elimination half-life may be prolonged in the elderly.

In healthy subjects, orally administered verapamil undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma. 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 faeces within five days. About 3% to 4% is excreted in the urine as unchanged drug. Approximately 90% is bound to plasma proteins.

In patients with hepatic insufficiency, metabolism of immediate release verapamil is delayed and elimination half-life prolonged up to 14 to 16 hours (see **Precautions**); the volume of distribution is increased and plasma clearance reduced to about 30% of normal. Verapamil clearance values suggest that patients with liver dysfunction may attain therapeutic verapamil plasma concentrations with one-third of the oral daily dose required for patients with normal liver function.

After four weeks of oral dosing (120 mg four times daily), verapamil and norverapamil levels were noted in the cerebrospinal fluid. Estimated partition coefficient of 0.06 for verapamil and 0.04 for norverapamil.

## **INDICATIONS**

- Hypertension
- Angina of effort
- Angina at rest
- Vasospastic angina (including Prinzmetal's variant angina)

- Tachyarrhythmias including paroxysmal supraventricular tachycardia
- Atrial fibrillation and atrial flutter with rapid ventricular response.

## CONTRAINDICATIONS

Verapamil HCl is contraindicated in:

- Severe left ventricular dysfunction (see **PRECAUTIONS**)
- Hypotension (systolic pressure less than 90 mmHg) or cardiogenic shock
- Sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker)
- Second- or third-degree AV block (except in patients with a functioning artificial ventricular pacemaker)
- Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g. Wolff-Parkinson-White, Lown-Ganong-Levine syndromes) (see **PRECAUTIONS**)
- Patients with known hypersensitivity to verapamil hydrochloride.

## PRECAUTIONS

### Heart Failure

Verapamil has a negative inotropic effect which, in most patients, is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. In clinical experience with 4954 patients, 87 (1.8%) developed congestive heart failure or pulmonary oedema. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30%, pulmonary wedge pressure above 20 mmHg or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker (see **INTERACTIONS WITH OTHER MEDICINES**).

Patients with milder ventricular dysfunction should, if possible, be controlled with optimum doses of digitalis and/or diuretics before verapamil treatment (see **INTERACTIONS WITH OTHER MEDICINES- Digitalis**).

### Hypotension

Occasionally, the pharmacologic action of verapamil may produce a decrease in blood pressure below normal levels, which may result in dizziness or symptomatic hypotension. The incidence of hypotension observed in 4954 patients enrolled in clinical trials was 2.5%. In hypertensive patients, decreases in blood pressure below normal are unusual. Tilt table testing (60 degrees) was not able to induce orthostatic hypotension.

### Elevated Liver Enzymes

Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported. Such elevations have sometimes been transient and may disappear even with continued verapamil treatment. Several cases of hepatocellular injury related to verapamil have been proven by rechallenge. Half of these had clinical symptoms (malaise, fever, and/or right upper quadrant pain) in addition to elevations of SGOT, SGPT

and alkaline phosphatase. Periodic monitoring of liver function in patients receiving verapamil is therefore prudent.

### **Accessory Bypass Tract (Wolff-Parkinson-White or Lown-Ganong-Levine)**

Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). 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**).

Treatment is usually DC-cardioversion. Cardioversion has been used safely and effectively after oral verapamil.

### **Atrioventricular Block**

The effect of verapamil on AV conduction and the SA node may cause asymptomatic first-degree AV block and transient bradycardia, sometimes accompanied by nodal escape rhythms. PR interval prolongation is correlated with verapamil plasma concentrations, especially during the early titration phase of therapy. Higher degrees of AV block, however, were infrequently (0.8%) observed. Marked first-degree block or progressive development to second- or third-degree AV block requires a reduction in dosage or, in rare instances, discontinuation of verapamil and institution of appropriate therapy depending upon the clinical situation.

### **Patients with Hypertrophic Cardiomyopathy (IHSS)**

In 120 patients with hypertrophic cardiomyopathy (most of them refractory or intolerant to propranolol) who received therapy with verapamil at doses up to 720 mg/day, a variety of serious adverse effects were seen. Three patients died in pulmonary oedema; all had severe left ventricular outflow obstruction and a past history of left ventricular dysfunction. Eight other patients had pulmonary oedema and/or severe hypotension; abnormally high (over 20 mmHg) capillary wedge pressure and a marked left ventricular outflow obstruction were present in most of these patients.

Concomitant administration of quinidine (see **INTERACTIONS WITH OTHER MEDICINES**) preceded the severe hypotension in 3 of the 8 patients (2 of whom developed pulmonary oedema). Sinus bradycardia occurred in 11% of the patients, second-degree AV 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 and only rarely did verapamil have to be discontinued.

### **Use in Patients with Impaired Hepatic Function**

Since verapamil is highly metabolised by the liver, it should be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction prolongs the elimination half-life of verapamil to about 14 to 16 hours; hence, approximately 30% of the dose given to patients with normal liver function should be administered to these patients. Careful monitoring for abnormal prolongation of the PR interval or other signs of excessive pharmacologic effects (see **OVERDOSAGE**) should be carried out.

### **Use in Patients with Impaired Neuromuscular Transmission**

Verapamil should be used with caution in the presence of diseases in which neuromuscular transmission is affected

(myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy).

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 Patients with Impaired Renal Function**

About 70% of an administered dose of verapamil is excreted as metabolites in the urine. Although impaired renal function has been shown to have no effect on verapamil pharmacokinetics in patients with end-stage renal failure, verapamil should be administered cautiously and with close monitoring in patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage (see **OVERDOSAGE**). Verapamil is not removed by haemodialysis.

### **Use when Driving a Vehicle or Operating Machinery**

Patients' ability to drive or operate machinery may be impaired. This may occur mainly during the initial stages of treatment or when changing over from another drug.

### **Carcinogenicity**

An 18-month toxicity study in rats, at a low multiple (6 fold) of the maximum recommended human dose, and not the maximum tolerated dose, did not suggest a tumorigenic potential. There was no evidence of a carcinogenic potential of verapamil administered in the diet of rats for two years at doses of 10, 35 and 120 mg/kg/day or approximately 1x, 3.5x and 12x, respectively, the maximum recommended human daily dose (480 mg/day or 9.6 mg/kg/day).

### **Genotoxicity**

Verapamil was not mutagenic in the Ames test in 5 test strains at 3 mg per plate, with or without metabolic activation.

### **Effects on Fertility**

Studies in female rats at daily dietary doses up to 5.5 times (55 mg/kg/day) the maximum recommended human dose did not show impaired fertility. Effects on male fertility have not been determined.

### **Use in Pregnancy (Category C)**

Calcium channel blockers carry the potential to produce fetal hypoxia associated with maternal hypotension.

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. In the rat, however, this multiple of the human dose was embryocidal and retarded foetal growth and development, probably because of adverse maternal effects reflected in the reduced weight gains of the dams. This oral dose has also been shown to cause hypotension in rats. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy

only if clearly needed. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery.

*Australian categorisation of Category C.* Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

*Labour and Delivery.* It is not known whether the use of verapamil during labour or delivery has immediate or delayed adverse effects on the foetus or whether it prolongs the duration of labour or increases the need for forceps delivery or other obstetric intervention. Such adverse experiences have not been reported in the literature, despite a long history of use of verapamil in Europe in the treatment of cardiac side effects of beta-adrenergic agonist agents used to treat premature labour.

### **Use in Lactation**

Verapamil is excreted in human milk. Limited human data from oral administration have shown that the estimated infant dose is low (0.01 – 1% of the mother's oral dose). Because of the potential for adverse reactions in breastfed infants, verapamil should only be used during lactation if it is essential for the welfare of the mother.

### **Animal pharmacology and/or animal toxicology**

In chronic animal toxicology studies verapamil caused lenticular and/or suture line changes at 30 mg/kg/day or greater and frank cataracts at 62.5 mg/kg/day or greater in the beagle dog but not the rat.

Development of cataracts due to verapamil has not been reported in humans.

## **INTERACTIONS WITH OTHER MEDICINES**

### ***Beta-Blockers***

Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility.

Asymptomatic bradycardia (36 beats/min) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil.

Atenolol, metoprolol and propranolol plasma levels may be increased by concomitant administration of verapamil.

### ***Digitalis***

Clinical use of verapamil in digitalised patients has shown the combination to be well tolerated if digoxin doses are properly adjusted. Chronic verapamil treatment can increase serum digoxin levels by 50 to 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 digoxin by 27% and 29%, respectively. Maintenance digitalis doses should be reduced when verapamil is administered, and the patient should be carefully monitored to avoid over- or underdigitalisation. Whenever overdigitalisation is suspected, the daily dose of digitalis should be reduced or temporarily discontinued. Upon discontinuation of Anpec, the patient should be reassessed to avoid underdigitalisation. In clinical trials related to the control of ventricular

response in digitalised patients who had atrial fibrillation or atrial flutter, ventricular rates below 50/min at rest occurred in 15% of patients and asymptomatic hypotension occurred in 5% of patients.

### ***Antihypertensive Agents***

Verapamil administered concomitantly with oral antihypertensive agents (e.g. vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta-blockers) will usually have an additive effect on lowering blood pressure. Patients receiving these combinations should be appropriately monitored. Concomitant use of agents that attenuate alpha-adrenergic function with verapamil may result in a reduction in blood pressure that is excessive in some patients. Such an effect was observed in one study following the concomitant administration of verapamil and prazosin.

### ***Antiarrhythmic Agents***

When combined with antiarrhythmic drugs (e.g. disopyramide, flecainide, mexiletine, amiodarone) additive (depressant) effects on myocardial contractility and AV conduction may occur.

In a small number of patients with hypertrophic cardiomyopathy (IHSS), 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 electrophysiological effects of quinidine and verapamil on AV conduction were studied in 8 patients. Verapamil significantly counteracted the effects of quinidine on AV conduction. There has been a report of increased quinidine levels during verapamil therapy.

### ***Nitrates***

Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. The pharmacologic profile of both drugs and clinical experience suggest beneficial interactions.

### ***Cimetidine***

The interaction between cimetidine and chronically administered verapamil has not been studied. Variable results on clearance have been obtained in acute studies of healthy volunteers; clearance of verapamil was either reduced or unchanged.

### ***Lithium***

Increased sensitivity to the effects of lithium (neurotoxicity) 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.

### ***Prazosin, Terazosin***

Additive hypotensive effect.

### ***HIV antiviral agents***

Due to the metabolic inhibitory potential of some of the HIV antiviral agents, such as ritonavir, plasma concentrations of verapamil may increase. Caution should be used or the dose of verapamil may be decreased.



***Carbamazepine***

Verapamil therapy may increase carbamazepine concentrations during combined therapy. This may produce carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

***Erythromycin, clarithromycin and telithromycin***

Erythromycin, clarithromycin and telithromycin therapy may increase serum levels of verapamil.

***Rifampicin***

Blood pressure lowering effect may be reduced.

***Phenobarbital***

Phenobarbitone therapy may increase verapamil clearance.

***Cyclosporin***

Verapamil therapy may increase serum levels of cyclosporin.

***Everolimus, sirolimus and tacrolimus***

Verapamil therapy may increase serum levels of everolimus, sirolimus and tacrolimus.

***Buspirone***

Verapamil therapy may increase plasma levels of buspirone.

***Midazolam***

Verapamil therapy may increase plasma levels of midazolam.

***Theophylline***

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

***Phenytoin***

Verapamil therapy may alter plasma levels of phenytoin.

***Alcohol***

Verapamil therapy may inhibit metabolism of alcohol increasing its CNS depressant effects.

***Inhalation Anaesthetics***

Animal experiments have shown that inhalation anaesthetics depress cardiovascular activity by decreasing the inward movement of calcium ions. When used concomitantly, inhalation anaesthetics and calcium antagonists, such as verapamil, should each be titrated carefully to avoid excessive cardiovascular depression.

***Neuromuscular Blocking Agents***

Clinical data and animal studies suggest that verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarising). 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.

***Grapefruit Juice***

Grapefruit juice has been shown to increase the plasma levels of verapamil and therefore grapefruit and its juice should not be taken with Anpec.

***HMG CoA Reductase Inhibitors***

Treatment with HMG CoA reductase inhibitors (e.g. simvastatin or atorvastatin) in a patient taking verapamil should be started at the lowest possible dose and titrated upwards. If verapamil treatment is to be added to patients already taking a HMG CoA reductase inhibitor (e.g. simvastatin or atorvastatin), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.

Verapamil hydrochloride may increase the serum levels of HMG CoA reductase inhibitors primarily metabolised by CYP3A enzymes (e.g. atorvastatin and simvastatin). An interaction in healthy subjects demonstrated a 43% increase in verapamil AUC in combination with atorvastatin. Consider using caution when these HMG CoA reductase inhibitors and verapamil are concomitantly administered.

Fluvastatin, pravastatin and rosuvastatin are not metabolised by CYP3A4 and are less likely to interact with verapamil.

***Sulfinpyrazone***

Blood pressure lowering effect may be reduced.

***Aspirin***

Increased tendency to bleed.

***Doxorubicin***

Caution should be used when oral verapamil is administered in combination with doxorubicin due to the potential for increased doxorubicin levels.

***Colchicine***

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (P-gp). Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicines are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to colchicine. Combined use is not recommended.

***Imipramine***

Verapamil therapy may increase serum levels of imipramine.

***Glibenclamide***

Verapamil therapy may increase serum levels of glibenclamide.

## ADVERSE EFFECTS

Verapamil is usually well tolerated.

Serious adverse reactions are uncommon when verapamil therapy is initiated with upward dose titration within the recommended single and total daily dose. See **PRECAUTIONS** for discussion of heart failure, hypotension, elevated liver enzymes, AV block and rapid ventricular response.

The following reactions to orally administered verapamil occurred at rates greater than 1.0% or occurred at lower rates but appeared clearly drug-related in clinical trials in 4,954 patients.

Constipation	7.3%			Fatigue	1.7%
Dizziness	3.3%			Dyspnoea	1.4%
Nausea	2.7%			Bradycardia (HR<50 /min)	1.4%
Hypotension	2.5%			AV block - total 1°, 2°, 3°	1.2%
Headache	2.2%			AV block - 2° and 3°	0.8%
Oedema	1.9%			Rash	1.2%
CHF, Pulmonary oedema	1.8%			Flushing	0.6%
Elevated liver enzymes (see <b>PRECAUTIONS</b> )					

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

The following reactions, reported in 1% or less of patients, occurred under verapamil HCl administration in general (all formulations) and most of them under conditions (open trials, marketing experience) where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship.

**Cardiovascular.** Angina pectoris, atrioventricular dissociations, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope.

**Digestive System.** Diarrhoea, dry mouth, gastrointestinal distress, abdominal discomfort/pain, gingival hyperplasia.

**Haemic and Lymphatic.** Ecchymosis or bruising.

**Nervous System.** Cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paraesthesia, psychotic symptoms, shakiness, somnolence.

**Skin.** Arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme.

**Special Senses.** Blurred vision.

**Ear and Labyrinth Disorders.** Vertigo, tinnitus.

***Urogenital.***

Gynaecomastia, increased urination, spotty menstruation, impotence.

**Treatment of Acute Cardiovascular Adverse Reactions**

The frequency of cardiovascular adverse reactions which require therapy is rare; hence, experience with their treatment is limited. Whenever severe hypotension or complete AV block occur following oral administration of verapamil, the appropriate emergency measures should be applied immediately, e.g. intravenously administered isoprenolol, noradrenaline, atropine (all in the usual doses), or calcium gluconate (10% solution). In patients with hypertrophic cardiomyopathy (IHSS), alpha-adrenergic agents (phenylephrine, metaraminol bitartrate or methoxamine) should be used to maintain blood pressure, and isoprenolol and noradrenaline should be avoided. If further support is necessary, inotropic agents (dopamine or dobutamine) may be administered.

Actual treatment and dosage should depend on the severity and the clinical situation and the judgement and experience of the treating physician.

**Adverse Effects from Post-marketing Surveillance**

There has been a single post marketing report of paralysis (tetraparesis) associated with the combined use of verapamil and colchicine. This may have been caused by colchicine crossing the blood-brain barrier due to CYP3A and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended.

Other adverse effects reported from post-marketing surveillance include myalgia, vomiting, tachycardia, ileus, galactorrhoea, increased blood prolactin and extrapyramidal syndrome.

**DOSAGE AND ADMINISTRATION**

The individual dose and frequency of dosing should be determined in accordance with the indication and individual patient response.

***Adults***

The usual starting dose is one 80 mg tablet two or three times daily. The maintenance dose may be adjusted to two 80 mg tablets two or three times daily.

Usual maintenance dose: 160 mg twice daily.

***Children***

Dose range 40 to 360 mg per day in two or three divided daily doses according to age and response.

***Elderly, Impaired Renal Function***

The recommended daily dosage is usually well tolerated.

***Impaired Hepatic Function***

Caution should be exercised when initiating therapy since the pharmacological action of Anpec may be increased or prolonged by hepatic insufficiency.

## OVERDOSAGE

### Symptoms

Bradycardia, cardiac arrest, second and third degree AV block, hypotension and myocardial insufficiency.

**Fatalities have occurred as a result of overdose.**

### Treatment

Treatment of overdose should be supportive. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase calcium ion flux across the slow channel, and have been used effectively in treatment of deliberate overdose with verapamil. Verapamil cannot be removed by haemodialysis. Clinically significant hypotensive reactions or fixed high degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Asystole should be handled by the usual measures including cardiopulmonary resuscitation.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of overdose.

## PRESENTATION AND STORAGE CONDITIONS

*Anpec 40*, 40 mg tablet: pale yellow, film coated, marked “VL/40” on one side, “G” on the other; available in blister packs of 100’s and bottles\* of 30’s, 90’s and 100's\*.

*Anpec 80*, 80 mg tablet: orange/yellow, film coated, marked “VL/80” on one side, “G” on the other; available in blister packs of 100’s bottles\* of 30’s, 90’s and 100's\*.

Store below 30°C.

\* Marketed in Australia.

## NAME AND ADDRESS OF THE SPONSOR

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## POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF  
THERAPEUTIC GOODS (THE ARTG)**

26/10/2001

**DATE OF MOST RECENT AMENDMENT**

23/10/2012