PACKAGE INSERT

SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml injection.

COMPOSITION:

Each 2 ml contains 5 mg verapamil hydrochloride.

Excipients: hydrochloric acid, nitrogen, sodium chloride, water for injections.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.4 Vasodilators - coronary and other medicines used in angina pectoris.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Verapamil is a calcium channel blocker. Increased concentrations of cytosolic Ca2+ cause increased contractions of the myocardium and vascular smooth muscle.

The entry of extracellular Ca2+ is more important in initiating the contraction of myocardial cells, while the release of Ca2+ from intracellular storage sites also participates in vascular smooth muscle, particularly in some vascular beds. In addition, the entry of extracellular Ca2+ can trigger the release of additional Ca2+ from intracellular stores.

Verapamil not only reduces the magnitude of Ca2+ current through the slow channel, but also decreases the rate of recovery of the channel. In addition, channel blockade caused by verapamil

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is enhanced as the frequency of stimulation increases. Verapamil depresses the rate of the sinus node pacemaker and slow atrio ventricular conduction, the latter effect is the basis for its use in the treatment of supraventricular tachyarrhythmias.

INDICATIONS:

Intravenous verapamil is indicated in those cases where oral therapy is not feasible. **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** is used in the control of supraventricular tachyarrhythmias, and in the management of classical and variant angina pectoris. It is also used in the treatment of hypertension.

CONTRAINDICATIONS:

Hypersensitivity to verapamil or to any of the other ingredients of **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml**. **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** is contraindicated in hypotension associated with carciogenic shock, in marked bradycardia, in partial or complete atrioventricular block, and in uncompensated heart failure.

It is also contraindicated in the sick-sinus syndrome unless a pacemaker is fitted. [~~Verapamil~~] **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** may precipitate or worsen existing heart failure. **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** is contraindicated in patients with atrial flutter or fibrillation and an accessory pathway with anterograde conduction for example Wolff-Parkinson-White syndrome. In these instances **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** may induce severe ventricular tachycardia. Safety in pregnancy has not been established. Do not use during lactation. Verapamil is excreted in breastmilk. **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** is contraindicated in digitalis toxicity.

WARNINGS and SPECIAL PRECAUTIONS:

Severe toxicity has followed the concomitant use of verapamil and beta-adrenoceptor blocking agents, particularly by the intravenous route. Verapamil can also cause increases in the plasma concentration of digoxin.

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. Verapamil should be avoided in patients with severe left ventricular dysfunction (e.g. ejection fraction less than 30 %, pulmonary wedge pressure above 20 mm Hg, or severe symptoms of heart failure) and in patients with any degree of ventricular dysfunction if they are receiving a beta-adrenergic blocker. Patients with milder ventricular dysfunction should, if possible, be controlled with optimal doses of digitalis and/or diuretics before verapamil treatment.

Hypotension: Verapamil may produce symptomatic hypotension in normotensive patients.

Elevated liver enzymes: Elevation of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported.

Accessory bypass tract (Wolff-Parkinson-White or Lown-Ganonq-Levine): Some patients with paroxysmal and/or chronic atrial fibrillation or atrial flutter and a coexisting accessory AV pathway have developed an increased anterograde conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving intravenous verapamil (or digitalis). Patients receiving oral verapamil may be at risk.

Atrioventricular block: The effect of verapamil on AV conduction and the SA node may lead to 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 phases of therapy. Marked first-degree or progressive development to second- or third-degree AV block, requires a reduction in dosage or, less

frequently discontinuation of the medicine.

Patients with hypertrophic cardiomyopathy (HSS): A variety of serious adverse effects can occur in patients with hypertrophic cardiomyopathy - pulmonary oedema and/or severe hypotension, sinus bradycardia, AV block and sinus arrest.

Special Precautions:

Reduced dosage may be required in patients with impaired liver function owing to the risk of reduced metabolism. Severe liver dysfunction prolongs the elimination half-life of immediate-release verapamil to about 15 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 pharmacological effects should be carried out.

Use in patients with attenuated 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 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. Verapamil is not removed by haemodialysis. Until further data are available, it should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for abnormal prolongation of the PR interval or other signs of overdosage.

Effects on the ability to drive and use machines:

Patients should be advised not to drive or use machines until they know how they are affected by the administration of **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml**.

INTERACTIONS:

Beta-blockers: Concomitant therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, AV conduction, and/or cardiac contractility. The combination should be used only with caution and close monitoring.

Digitalis: Chronic verapamil treatment can increase serum digoxin levels by 50 to 70 % during the first week of therapy, and this can result in digitalis toxicity. Whenever over digitalisation is suspected, the daily dose of digitalis should be reduced or temporarily discontinued.

Antihypertensive agents: Verapamil may intensify the blood pressure lowering effect of concomitantly administered antihypertensives, and this often makes it possible to reduce the dose of the antihypertensives, particularly in patients on long-term treatment with verapamil.

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: It has been reported that concomitant administration of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarisation. Concomitant therapy with flecainide and verapamil may result in additive negative inotropic effect and prolongation of AV conduction.

Quinidine: In a small number of patients with hypertrophic cardiomyopathy (HSS), 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. There has been a report of increased quinidine levels during verapamil therapy.

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

Lithium: Pharmacokinetic and pharmacodynamic interactions between oral verapamil and lithium have been reported. The former may result in lowering of serum lithium levels in patients receiving chronic stable oral lithium therapy. The latter may result in an increased sensitivity to the effects of lithium. Patients receiving both agents must be monitored carefully.

Carbamazepine: Verapamil therapy may increase carbamazepine concentrations during combined therapy.

Rifampicin: Therapy with rifampicin may markedly reduce oral verapamil bioavailability.

Phenobarbitone: Phenobarbitone therapy may increase verapamil clearance.

Ciclosporin: Verapamil may increase serum levels of ciclosporin.

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 should 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 depolarizing). It may be necessary to decrease the dose of verapamil and/or the dose of the neuromuscular blocking agent, when the medicines are used concomitantly.

PREGNANCY AND LACTATION:

The safety of **PHARMA-Q VERAPAMIL INJECTION 5 mg/2 ml** during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE:

Intravenous injections should be given under continuous ECG monitoring particularly in infancy.

ADULTS:

An intravenous dose of 5 to l0mg is injected over a period of 30 seconds, followed by a further 5mg, if necessary, after 5 to 10 minutes interval.

CHILDREN:

Suggested intravenous doses for children are:

Neonates: 0,75 to 1mg.

Infants: 0,75 to 2mg.

Children aged 1 to 5 years: 2 to 3 mg.

Children aged 6 to 15 years: 2,5 to 5 mg.

Smaller doses may be adequate and the injection must be stopped when a response has been obtained.

SIDE EFFECTS

Nervous system disorders:

Frequent: Dizziness, flushing, and headaches.

Cardiac disorders:

Frequent: Bradycardia.

Less frequent: Depression of atrioventricular or sinoatrial nodal function, atrioventricular block, worsening heart failure, and transient asystol.

Vascular disorders:

Frequent: Hypotension.

Gastrointestinal disorders:

Frequent: Constipation.

Less frequent: Nausea.

Hepato-biliary disorders:

Less frequent: Abnormal liver function.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See **SIDE EFFECTS** for symptoms.

Treatment of cardiovascular effects is supportive and symptomatic.

IDENTIFICATION:

A clear, colourless or almost colourless solution in 2 ml amber ampoules.

PRESENTATION:

Containers containing 100 or 10 x 2 ml ampoules.

STORAGE INSTRUCTIONS:

Store at or below 25 ˚C.

Protect from light.

Keep out of reach of children.

REGISTRATION NUMBER:

29/7.1.4/0666

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

PHARMA-Q HOLDINGS (PTY) LTD.

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