VERAPAMIL HYDROCHLORIDE
INJECTION USP
5MG/2ML
TAJ PHARMA

1. NAME OF THE MEDICINAL PRODUCT

Verapamil Hydrochloride Injection USP 5mg/2ml Taj Pharma

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of injection contains:
Verapamil Hydrochloride……2.5mg

3. PHARMACEUTICAL FORM

Aqueous solution for intravenous injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Verapamil HCl Injection is indicated for the treatment of paroxysmal supraventricular tachycardia and the reduction of ventricular rate in atrial flutter/fibrillation.

4.2 Posology and method of administration

For slow intravenous injection.

Adults: 5-10 mg by slow intravenous injection over a period of 2 minutes. The patient should be observed continuously, preferably under ECG and blood pressure control. If necessary, *e.g.* in paroxysmal tachycardia, a further 5 mg may be given after 5 to 10 minutes.

Children: Verapamil HCl Injection must always be administered under ECG monitoring in young patients.

0-1 year: 0.1-0.2 mg/kg bodyweight (usual single dose range: 0.75-2 mg).

1-15 years: 0.1-0.3 mg/kg bodyweight (usual single dose range: 2-5 mg).

The dose may be repeated after 30 minutes if necessary. Many cases are controlled by doses at the lower end of the range. The injection should be stopped at the onset of the desired effect.

Elderly: The dosage should be administered over 3 minutes to minimise the risk of adverse effects.

Dosage in impaired liver and renal function: Significant hepatic and renal impairment should not increase the effects of a single intravenous dose but may prolong its duration of action.

For use with beta-blocker therapy, see 'Contra-indications' and 'Special Warnings and Precautions for Use'.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Cardiogenic shock; acute myocardial infarction complicated by bradycardia, marked hypotension or left ventricular failure; second or third degree AV block (except in patients with a functioning artificial ventricular pacemaker); sino-atrial block; sick sinus syndrome (except in patients with a functioning artificial ventricular pacemaker); uncompensated heart failure; bradycardia of less than 50 beats/minute; hypotension of less than 90 mmHg systolic; simultaneous administration of intravenous beta-blockers.

Patients with atrial flutter/fibrillation in the presence of an accessory pathway (*e.g.* WPW syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.

Combination with ivabradine (see section Interactions with other medicinal products and other forms of interaction).

4.4 Special Warnings and precautions for use

Verapamil may affect impulse conduction. For this reason, Verapamil HCl Injection should be used with caution in patients with bradycardia or first degree AV block. Verapamil may affect left ventricular contractility; this effect is small and normally not important but cardiac failure may be precipitated or aggravated. In patients with poor ventricular function, therefore, Verapamil HCl Injection should only be given after cardiac failure has been controlled with appropriate therapy, *e.g.* digitalis.

Although the pharmacokinetics of verapamil in patients with renal impairment are not affected, caution should be exercised and careful patient monitoring is recommended. Verapamil is not removed during dialysis.

Caution should be exercised in treatment with HMG CoA reductase inhibitors (e.g., simvastatin, atorvastatin or lovastatin) for patients taking verapamil. These patients should be started at the lowest possible dose of verapamil and titrated upwards. If verapamil treatment is to be added to patients already taking an HMG CoA reductase inhibitor (e.g., simvastatin, atorvastatin or lovastatin), refer to advice in the respective statin product information.

Use with caution in the presence of diseases in which neuromuscular transmission is affected (myasthenia gravis, Lambert-Eaton syndrome, advanced Duchenne muscular dystrophy)

4.5 Interaction with other medicinal products and other forms of interaction

In rare instances, including when patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction were given intravenous beta-adrenergic blocking agents or disopyramide concomitantly with intravenous verapamil hydrochloride, serious adverse effects have occurred. Concomitant use of verapamil hydrochloride with agents that decrease adrenergic function may result in an exaggerated hypotensive response.

In vitro metabolic studies indicate that verapamil hydrochloride is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil has been shown to be an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for drug interactions.

The following are potential drug interactions associated with verapamil:

Acetylsalicylic acid

Concomitant use of verapamil with aspirin may increase the risk of bleeding

Alpha blockers

Verapamil may increase the plasma concentrations of *prazosin* and *terazosin* which may have an additive hypotensive effect.

Antiarrhythmics

Verapamil may slightly decrease the plasma clearance of *flecainide* whereas *flecainide* has no effect on the verapamil plasma clearance.

Verapamil may increase the plasma concentrations of *quinidine*.

The combination of verapamil and *antiarrhythmic agents* may lead to

additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure). Care must be exercised if Verapamil HCl Injection is combined with anti-arrhythmic agents by any route.

Anticonvulsants

Verapamil may increase the plasma concentrations of *carbamazepine*. This may produce side effects such as diplopia, headache, ataxia or dizziness. Verapamil may also increase the plasma concentrations of *phenytoin*.

Antidepressants

Verapamil may increase the plasma concentrations of *imipramine*.

Antidiabetics

Verapamil may increase the plasma concentrations of *glibenclamide (glyburide).*

Anti-infectives

Rifampicin may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect. *Erythromycin, clarithromycin* and *telithromycin* may increase the plasma concentrations of verapamil.

Antineoplastics

There is no significant difference between the pharmacokinetic parameters of *doxorubicin* with intravenous verapamil administration.

Barbiturates

Phenobarbital may reduce the plasma concentrations of verapamil.

Benzodiazepines and other anxiolytics

Verapamil may increase the plasma concentrations of *buspirone* and *midazolam*.

Beta blockers

Verapamil may increase the plasma concentrations of *metoprolol* and *propranolol* which may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Verapamil HCl Injection should not be given in combination with intravenous *beta-blocker* therapy and care must be exercised if Verapamil HCl Injection is combined with oral *beta-blocker* therapy.

Cardiac glycosides

Verapamil may increase the plasma concentrations of *digitoxin* and *digoxin.* Verapamil has been shown to increase the serum concentration of *digoxin* and caution should be exercised with regard to digitalis toxicity. The digitalis level should be determined and the glycoside dose reduced, if required.

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 *colchicine* are administered together, inhibition of P-gp and/or CYP3A by verapamil may lead to increased exposure to *colchicine*. Combined use is not recommended.

H_2 Receptor antagonists

Cimetidine may increase the plasma concentrations of verapamil following intravenous verapamil administration.

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 dose of verapamil may be decreased.

Immunosuppressants

Verapamil may increase the plasma concentrations of *ciclosporin, everolimus, sirolimus* and *tacrolimus*.

Inhaled anaesthetics

When used concomitantly, *inhalation anaesthetics* and calcium antagonists, such as verapamil hydrochloride, should each be titrated carefully to avoid additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Lipid lowering agents

Verapamil may increase the plasma concentrations *atorvastatin, lovastatin* and *simvastatin.*

Treatment with *HMG CoA reductase inhibitors* (e.g., *simvastatin, atorvastatin* or *lovastatin*) 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 an *HMG CoA reductase inhibitor* (e.g., *simvastatin, atorvastatin* or *lovastatin*), consider a reduction in the statin dose and retitrate against serum cholesterol concentrations.

Atorvastatin has been shown to increase verapamil levels. Although there is no direct in vivo clinical evidence, there is strong potential for verapamil to significantly affect *atorvastatin* pharmacokinetics in a similar manner to *simvastatin* or *lovastatin*. Consider using caution when *atorvastatin* and verapamil are concomitantly administered.

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

Lithium

Serum levels of *lithium* may be reduced. However there may be increased sensitivity to *lithium* causing enhanced neurotoxicity.

Neuromuscular blocking agents employed in anaesthesia

The effects may be potentiated.

Protein-bound drugs

As verapamil hydrochloride is highly bound to plasma proteins, it should be administered with caution to patients receiving other highly *protein-bound drugs*.

Serotonin receptor agonists

Verapamil may increase the plasma concentrations of *almotriptan.*

Theophylline

Verapamil may increase the plasma concentrations of *theophylline.*

Uricosurics

Sulfinpyrazone may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect.

Anticoagulants

Dabigatran ↑ dabigatran (C_{max} up to 180%) and AUC (up to 150%)

The Risk of bleeding may increase. The Dose of dabigatran with oral verapamil may need to be reduced. (See dabigatran label for dosing instructions).

Other Cardiac therapy

Concomitant use with *ivabradine* is contraindicated due to the additional heart rate lowering effect of verapamil to *ivabradine* (see section 4.3).

Other

St. John's Wort may reduce the plasma concentrations of verapamil,

whereas *grapefruit juice* may increase the plasma concentrations of verapamil.

4.6 Fertility, Pregnancy and lactation

Although animal studies have not shown any teratogenic effects, verapamil should not be given during the first trimester of pregnancy unless, in the clinician's judgement, it is essential for the welfare of the patient. Verapamil crosses the placental barrier and can be detected in umbilical vein blood at delivery. Also, verapamil is excreted in human breast milk. Limited human data from oral administration has shown that the infant relative dose of verapamil is low (0.1-1% of the mother's oral dose) and that verapamil use may be compatible with breastfeeding. However, there are currently no reports of verapamil injection or infusion use during breastfeeding. Due to the potential for serious adverse reactions in nursing infants, verapamil should only be used during lactation if it is essential for the welfare of the mother.

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable Effects

Adverse events observed in clinical trials are depicted in the following table. Within each system organ class, the adverse drug reactions are ranked under headings of frequency, using the following convention: common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.

System Organ Class	Frequency	Undesirable Effects
Nervous system disorders		
	common	- dizziness - headache
Cardiac disorders/vascular disorders		
	common	- bradycardia - hypotension
	uncommon	- tachycardia
Gastrointestinal disorders		
	uncommon	- nausea -abdominal pain

Cases of seizures during verapamil hydrochloride injection have been reported.

In rare cases of hypersensitivity, bronchospasm accompanied by pruritis and urticaria has been reported.

Other Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

Other adverse events reported with verapamil are listed below by system organ class:

Psychiatric disorders: on rare occasions, nervousness has been reported.

Nervous system disorders: somnolence and extrapyramidal syndrome.

Ear and labyrinth disorders: vertigo.

Cardiac disorders/vascular disorders: decreased myocardial contractility has been reported. On rare occasions, 2nd and 3rd block may occur and in extreme cases, this may lead to asystole. The asystole is usually of short duration and cardiac action returns spontaneously after a few seconds, usually in the form of sinus rhythm. If necessary, the procedures for the treatment of overdosage should be followed as described below. On rare occasions, flushing has been reported.

Gastrointestinal disorders: gingival hyperplasia may occur very rarely when the drug is administered over prolonged periods, and is fully reversible when the drug is discontinued. On rare occasions, vomiting has also been reported.

Skin and subcutaneous tissue disorders: Steven-Johnson syndrome, erythema and hyperhidrosis.

Reproductive system and breast disorders: On very rare occasions, gynaecomastia has been observed in elderly

male patients under long-term verapamil treatment; this was fully reversible in all cases when the drug was discontinued.

Investigations: A reversible impairment of liver function characterized by an increase of transaminase and/or alkaline phosphatase may occur on very rare occasions during verapamil treatment and is most probably a hypersensitivity reaction.

4.9 Overdose

The symptoms of overdosage include hypotension, shock, loss of consciousness, first and second degree AV block (frequently as Wenckebach's phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, bradycardia up to high degree AV block and, sinus arrest, hyperglycaemia, stupor and metabolic acidosis. Fatalities have occurred as a result of overdose.

Treatment of overdosage depends on the type and severity of symptoms. The specific antidote is calcium, *e.g.* 10-20 ml of 10% calcium gluconate solution i.v. (2.25-4.5 mmol) if necessary by repeated injection or continuous infusion (*e.g.* 5 mmol/hour). The usual emergency measures for acute cardiovascular collapse should be applied and followed by intensive care. Verapamil hydrochloride cannot be removed by haemodialysis. Similarly, in the case of second or third degree AV block, atropine, orciprenaline, isoprenaline and if required, pacemaker therapy should be considered. If there are signs of myocardial insufficiency, dopamine, dobutamine, cardiac glycosides or calcium gluconate (10-20 ml of a 10% solution) can be administered.

In the case of hypotension, after appropriately positioning the patient, dopamine, dobutamine or noradrenaline may be given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives.

Verapamil is a calcium antagonist which blocks the inward movement of calcium ions in cardiac muscle cells, in smooth muscle cells of the coronary and systemic arteries and in cells of the intracardiac conduction system. Because of its effect on the movement of calcium in the intracardiac conduction system, verapamil reduces automaticity, decreases conduction velocity and increases the refractory period.

5.2 Pharmacokinetic properties

Verapamil hydrochloride is a racemic mixture consisting of equal portions of the R-enantiomer and the S-enantiomer. Verapamil is extensively metabolized. Norverapamil is one of 12 metabolites identified in urine, has 10 to 20% of the pharmacologic activity of verapamil and accounts for 6% of excreted drug. The steady-state plasma concentrations of norverapamil and verapamil are similar.

Steady state after multiple once daily dosing is reached after three to four days.

Distribution

Verapamil is widely distributed throughout the body tissues, the volume of distribution ranging from 1.8–6.8 L/kg in healthy subjects. Plasma protein binding of verapamil is approximately 90%.

Metabolism

Verapamil is extensively metabolized. *In vitro* metabolic studies indicate that verapamil is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8,

CYP2C9 and CYP2C18. In healthy men, orally administered verapamil hydrochloride undergoes extensive metabolism in the liver, with 12 metabolites having been identified, most in only trace amounts. The major metabolites have been identified as various N and O-dealkylated products of verapamil. Of these metabolites, only norverapamil has any appreciable pharmacological effect (approximately 20% that of the parent compound), which was observed in a study with dogs.

Elimination

Following intravenous infusion, verapamil is eliminated bi-exponentially, with a rapid early distribution phase (half-life about four minutes) and a slower terminal elimination phase (half-life two to five hours).

Special Populations

Pediatric:

Limited information on the pharmacokinetics in the paediatric population is available. After intravenous dosing, the mean half-life of verapamil was 9.17 hours and the mean clearance was 30 L/h, whereas it is around 70 L/h for a 70-kg adult.

Geriatric:

Aging may affect the pharmacokinetics of verapamil given to hypertensive patients. Elimination half-life may be prolonged in the elderly. The antihypertensive effect of verapamil was found not to be age-related.

Renal insufficiency:

Impaired renal function has no effect on verapamil pharmacokinetics, as shown by comparative studies in patients with end-stage renal failure and subjects with healthy kidneys. Verapamil and norverapamil are not significantly removed by hemodialysis.

Hepatic insufficiency:

Verapamil hydrochloride, administered intravenously, has been shown to be rapidly metabolized.

5.3 Preclinical safety data

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 0.6 and 1.2 times respectively the maximum recommended human oral daily dose based on a body surface area comparison (mg/m^2) and have revealed no evidence of teratogenicity. In the rat, however, a dose similar to the clinical dose was embryocidal and retarded fetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and reduced weight gain of dams). This oral dose has also been shown to cause hypotension in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections, sodium chloride (8.5 mg/ml), hydrochloric acid 10% as pH adjuster.

6.2 Incompatibilities

Verapamil HCl Injection is incompatible with alkaline solutions.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

2 ml glass ampoule (hydrolytic type 1) containing 5 mg verapamil. Pack size: 5 × 2 ml ampoules.

6.6 Special precautions for disposal and other handling

None.

7. MANUFACTURED IN INDIA BY:

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