CALAN
(Verapamil hydrochloride)

I.V.

5mg/2ml

Solution for Injection or infusion

COMPOSITION

Each 2ml ampoule contains:

Verapamil Hydrochloride…. 5mg (U.S.P. Specifications)

THERAPEUTIC INDICATIONS

Tachycardias, such as paroxysmal supraventricular tachycardia, atrial fibrillation with rapid ventricular response, (except in WPW syndrome), atrial flutter with rapid conduction, extrasystoles.
For the prophylaxis and/or therapy of ectopic arrhythmias (predominantly ventricular extrasystoles) in halothane anesthesia and in the application of adrenaline in halothane anesthesia, respectively.
Acute hypertension.
Acute coronary insufficiency.

DOSAGE AND ADMINISTRATION

Adults

5 mg slowly intravenously, in tachycardias and hypertensive crises repeated, if necessary, after 5 to 10 minutes. Drip infusion to maintain the therapeutic effect: 5-10 mg/hour in physiological saline, glucose, laevulose or similar solutions, on average up to a total dose of 100 mg/day.

Special populations

Children

Calan IV must always be administered under ECG monitoring in young patients.

Age	Dose
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)

Verapamil given intravenously, depending on age and action. The injection should be made slowly under electrocardiographic control and only until onset of the effect. Intravenous infusion in hypertensive crises; initially 0.05-0.1 mg/kg/hour; if the effect proves to be insufficient, the dose is increased at 30–60-minute intervals until twice the dose or more is reached. Average total dose up to 1.5 mg/kg/day.

Method of administration

Verapamil should be given as a slow intravenous injection over at least 2 minutes under continuous ECG and blood pressure monitoring.

Intravenous injection should only be given by the physician.

CONTRAINDICATIONS

Cardiogenic shock (except for arrhythmia induced shock), complicated acute myocardial infarction (bradycardia, hypotension, left ventricular failure), second and third degree AV block, sick sinus syndrome (bradycardia-tachycardia syndrome), manifest heart failure.

In the presence of first degree AV block, sinus bradycardia and hypotension the use of Verapamil should be given critical consideration. In acute coronary insufficiency intravenous administration is only admissible with careful indication and continuous monitoring of the patient. Where heart failure is present, full compensation with cardiac glycosides must be achieved before the administration of Verapamil.

Patients with atrial flutter or atrial fibrillation and an accessory bypass tract (e.g Wolff- Parkinson-White, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil is administered.

Patients with ventricular tachycardia. Administration of intravenous verapamil to patients with wide-complex ventricular tachycardia (QRS > 0.12 sec) can result in marked hemodynamic deterioration and ventricular fibrillation. Proper diagnosis and differentiation from wide- complex supraventricular tachycardia is imperative in the emergency room setting.

Severe hypotension.

Verapamil injection should not be administered intravenously to patients on beta-blockers (except in an intensive care setting).

In patients with diminished hepatic function (parenchymal loss/reduced blood supply) the effect of Verapamil is intensified and prolonged depending on the severity of the disease due to impaired drug metabolism. In these cases, dosage should be adjusted with special care.

Concomitant administration of verapamil and ivabradine is contraindicated.

Known hypersensitivity to verapamil hydrochloride.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In atrial fibrillation and simultaneous WPW syndrome there is a risk of inducing ventricular fibrillation.

Hypotension

Severe hypotension has occasionally occurred following intravenous administration of the drug. On rare occasions this has been followed by a loss of consciousness.

Acute myocardial infarction

Use with caution in patients with acute myocardial infarction complicated by bradycardia, marked hypotension, or left ventricular dysfunction.

Ventricular fibrillation

Intravenous administration may precipitate ventricular fibrillation. Patients with atrial flutter/fibrillation producing a very rapid ventricular response after receiving intravenous verapamil. Its use in these patients is contraindicated.

Bradycardia/asystole

Verapamil slows conduction across the AV node and rarely may produce second or third degree AV block, bradycardia and in extreme cases, asystole.

Heart failure

Because of the drug's negative inotropic effect, verapamil should not be used in patients with poorly compensated congestive heart failure, unless the failure is complicated by or caused by an arrhythmia. If verapamil is used in such patients, they must be digitalized prior to treatment. Continuous monitoring is mandatory when intravenous verapamil is used in digitalized patients. It has been reported that digoxin plasma levels may increase with chronic oral administration.

Impaired hepatic or renal function

Verapamil should be used with caution in patients with hepatic impairment. Although impaired renal function has been shown to have no effect on verapamil pharmacokinetics in patients with end-stage renal failure, verapamil should be used cautiously and with close monitoring in patients with impaired renal function. Verapamil cannot be removed by hemodialysis.

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).Intravenous verapamil can precipitate respiratory muscle failure in patients with progressive muscular dystrophy and should, therefore, be used with caution.

Increased intracranial pressure

Intravenous verapamil has been seen to increase intracranial pressure in patients with supratentorial tumors at the time of an aesthesia induction.

Sick sinus syndrome

Precaution should be taken when treating any supraventricular arrhythmia on an emergency basis as it may be caused by an undiagnosed Sick Sinus Syndrome.

Heart block

Development of second- or third-degree AV block or unifascicular, bifascicular or trifascicular bundle branch block requires reduction in subsequent doses or discontinuation of verapamil and institution of appropriate therapy, if needed.

DRUG INTERACTIONS

During the simultaneous administration of Verapamil and drugs with cardiodepressive action and/or inhibitory effect on AV conduction watch should be kept for additive effects. Above all Verapamil should not be administered intravenously without compelling reason if the patient is on-adrenergic blockers.

The concomitant administration of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

The additional hypotensive effect of Verapamil should be borne in mind particularly in patients on antihypertensive drugs.

Diuretics, vasodilators

Potentiation of the antihypertensive effect.

Digoxin

Elevation of digoxin plasma levels because of diminished renal excretion. However since both drugs slow AV conduction, patients should be monitored for AV block or excessive bradycardia.

Quinidine

Enhanced blood pressure lowering is possible. Pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy. Elevation of quinidine plasma level.

Flecainide

May result in an additive negative inotropic effect and prolongation of atrioventricular conduction.

Disopyramide

Possible additive effects and impairment of left ventricular function. Pending further accumulation of data, disopyramide should be discontinued 48 hours prior to initiating verapamil therapy and should not be reinstituted until 24 hours after verapamil has been discontinued.

Ivabradine

Concomitant administration of verapamil and ivabradine is contraindicated. Ivabradine use in combination with verapamil is associated with increased plasma concentrations of ivabradine and additional heart rate lowering effects.

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 an 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 verpamil 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 metabolized by CYP3A4 and are less likely to interact with verapamil.

Inhalation anaesthetics

Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure, enhanced blood pressure lowering).

Carbamazepine

Potentiation of carbamazepine effect, enhanced neurotoxicity.

Cimetidine

Cimetidine reduces verapamil clearance following intravenous verapamil administration.

Lithium

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

Phenytoin, phenobarbital (phenobarbitone)

Lowering of the plasma level and attenuation of the effects of verapamil.

Erythromycin, clarithromycin and telithromycin

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

Rifampicin

Blood pressure lowering effect may be reduced.

Sulfinpyrazone

Blood pressure lowering effect may be reduced.

Theophylline

Elevation of theophylline plasma levels.

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.

Ciclosporin

Elevation of ciclosporin plasma levels.

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

Elevation of midazolam.

Muscle relaxants

Possible potentiation by verapamil.

Protein bound drugs

As verapamil is highly protein bound, it should be administered with caution to patients receiving other highly protein bound drugs.

Dantrolene

Animal studies suggest that concomitant use of IV verapamil and IV dantrolene may result in cardiovascular collapse.

Aspirin

Increased tendency to bleed.

Ethanol (alcohol)

Delayed ethanol breakdown and elevation of ethanol plasma levels, resulting in enhancement of the alcoholic effect through verapamil.

Grapefruit juice

Increase in verapamil serum level has been reported. Therefore grapefruit and its juice should not be taken with verapamil.

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 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.

Imipramine

Verapamil therapy may increase serum levels of imipramine.

Glibenclamide

Verapamil therapy may increase serum levels of glibenclamide.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category C

Verapamil carries the potential to produce fetal hypoxia associated with maternal hypotension. Verapamil should not be administered intravenously during the first six months of pregnancy. There are no data on use in the first and second trimester. Verapamil should not be used in the final trimester unless the benefits clearly outweigh the risks.

Breast feeding

Verapamil hydrochloride is excreted in human breast milk. There are currently no reports of verapamil injection or infusion use during breast feeding. Due to the potential for serious adverse reactions in nursing infants, intravenous verapamil is not recommended during breast feeding.

Fertility

No data available.

EFFECTS ON ABILITY TO DRIVE

The antihypertensive effect of verapamil may affect the ability to drive a vehicle or operate machinery. Special caution should be taken at the start of treatment, during dose titration and when switching from another medicine.

ADVERSE DRUG REACTIONS

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 Post marketing 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, gynecomastia 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

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, hyperglycemia, 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 hemodialysis. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

ATC-Code: C08DA01

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.

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 pediatric 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.

PRECLINICAL SAFETY DATA

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 0.6 (180mg/m2/day) and 1.2 times (360 mg/m2/day) respectively the equivalent maximum recommended human oral daily dose of 300mg/m2/day) and have revealed no evidence of teratogenicity. In the rat, the highest dose was embryocidal and retarded foetal growth and development. These effects occurred in the presence of maternal toxicity (reflected by reduced food consumption and weight gain of dams). This oral dose has also been shown to cause hypotension in rats.

PRESENTATION

Calan Injection 5mg/2ml is available in a pack of 5 Ampoules x 2ml.

INSTRUCTIONS

- Injection should not be used if container is leaking, solution is cloudy or it contains un-dissolved particle(s).

- To be sold on prescription of a registered medical practitioner only.

- Store below 25^{o}C.

- Keep out of sight and reach of children.

- Protect from sunlight, moisture and heat.

REGISTRATION NUMBER

Calan 5mg/2ml Injection : 091256

Manufacturing license Number: 000016

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Manufactured by:

The Searle Company Limited,

F-319, S.I.T.E., Karachi-Pakistan

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