**CALAN SR**
(Verapamil HCl)

240mg

Tablets

**COMPOSITION**

Each film-coated sustained release tablet contains:

Verapamil Hydrochloride ……240mg

**THERAPEUTIC INDICATIONS**

Mild to moderate hypertension and coronary heart disease, i.e. prophylaxis of myocardial ischemia, angina pectoris.

**DOSAGE AND ADMINISTRATION**

The dose of verapamil hydrochloride should be adjusted individually in accordance with the severity of disease. Long-standing clinical experience shows that the average daily dose in all indications is between 240 mg and 360 mg. The daily dose should not exceed 480 mg on a long-term basis, although a higher dose may be used for a short period. There is no limitation on the duration of use. Verapamil hydrochloride should not be discontinued abruptly after long-term use. It is recommended to taper the dosage.

Adults
Hypertension: The adult dose is one tablet (240 mg) in the morning, increasing, if necessary, after one week to 240 mg in the morning and 240 mg in the evening, with an interval of 12 hours. In elderly patients, the initial dose is half a tablet (120 mg) in the morning, increasing by 120 mg increments at weekly intervals according to patient response.
Angina pectoris: The usual dose is 120-240 mg twice daily according to patient response. It is recommended that low initial doses with upward titration are used in new patients.

Special Populations

Renal impairment
Verapamil hydrochloride should be used cautiously and with close monitoring in patients with impaired renal function.

Liver impairment
In patients with impaired liver function, metabolism of the drug is delayed to a greater or lesser extent depending on the severity of hepatic dysfunction, thus potentiating and prolonging the effects of verapamil hydrochloride. Therefore, the dosage needs to be adjusted with special caution in patients with impaired liver function and low doses should be given initially.

**Method of administration**

For oral use only.

Tablets should be taken without sucking or chewing, with sufficient liquid, preferably with or shortly after meals. Verapamil should not be taken with grapefruit juice

**CONTRAINDICATIONS**

Hypersensitivity to verapamil hydrochloride or to any of the inactive ingredients;

Cardiogenic shock:

Second-or third-degree AV block (except in patients with a functioning artificial pacemaker);

Sick sinus syndrome (except in patients with a functioning artificial pacemaker);

Heart failure with reduced ejection fraction of less than 35%, and/or pulmonary wedge pressure above 20 mm Hg (unless secondary to a supraventricular tachycardia amenable to verapamil therapy);

Atrial fibrillation/flutter, in the presence of an accessory bypass tract (e.g., Wolff-Parkinson-White syndrome, Lown-Ganong-Levine syndromes). These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil hydrochloride is administered.

Marked hypotension;

Left ventricular failure;

within 7 days of an acute MI;

Combination with ivabradine

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

Acute Myocardial infarction

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

Heart Block/ 1st Degree AV block/Bradycardia/Asystole

Verapamil hydrochloride affects the AV and SA nodes and prolongs AV conduction time. Use with caution as development of second- or third-degree AV block (contraindication) or unifascicular, bifascicular or trifascicular bundle branch block requires discontinuation reduction in subsequent doses or discontinuation of verapamil hydrochloride and institution of appropriate therapy, if needed.

Verapamil hydrochloride affects the AV and SA nodes and rarely may produce second-or third -degree AV block, bradycardia, and, in extreme cases, asystole. This is more likely to occur in patients with a sick sinus syndrome (SA nodal disease), which is more common in older patients.

Asystole in patients other than those with sick sinus syndrome is usually of short duration (few seconds or less), with spontaneous return to AV nodal or normal sinus rhythm. If this does not occur promptly, appropriate treatment should be initiated immediately.

When treating hypertension, the patient's blood pressure should be monitored at regular intervals.

Care should be taken in patients with: Broad complex ventricular tachycardia, Bradycardia less than 50 beats/minute, Systolic blood pressure less than 90 mmHg, Atrial fibrillation/flutter, Simultaneous pre-excitation syndrome, e.g. Wolff-Parkinson-White syndrome (risk of inducing ventricular tachycardia). Intravenous beta-blockers should not be co-administered to patients on sustained release verapamil (except in ICU settings).

If acute cardiovascular side effects arise, treat as for overdose.

Antiarrhythmics, Beta-blockers

Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension). Asymptomatic bradycardia (36 beats/minute) with a wandering atrial pacemaker has been observed in a patient receiving concomitant timolol (a beta-adrenergic blocker) eye drops and oral verapamil hydrochloride.

Colchicine

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 CYP3A4 and P-gp inhibition by verapamil. Combined use of verapamil and colchicine is not recommended.

Digoxin

If verapamil is administered concomitantly with digoxin, reduce digoxin dosage.

Heart Failure

Heart failure patients with ejection fraction higher than 35% should be compensated before starting verapamil treatment and should be adequately treated throughout.

HMG-CoA Reductase Inhibitors ("Statins") – Describe in drug interactions

Neuromuscular transmission disorders

Verapamil hydrochloride 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).

Respiratory standstill has been reported for one patient with progressive muscular dystrophy following administration of Calan.

Renal impairment

Although impaired renal function has been shown in robust comparator studies to have no effect on verapamil pharmacokinetics in patients with end-stage renal failure, several case reports suggest that verapamil should be used cautiously and with close monitoring in patients with impaired renal function.

Verapamil cannot be removed by hemodialysis.

Liver impairment

Use with caution in patients with severely impaired liver function

**DRUG INTERACTIONS**

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. Coadministration of verapamil and a drug primarily metabolized by CYP3A4 or being a P-gp substrate may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

**Antiarrhythmics, 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. The combination of sustained release verapamil and beta-adrenergic blocking agents has not been studied. However, there have been reports of excessive bradycardia and AV block, including complete heart block, when the combination has been used for the treatment of hypertension. For hypertensive patients, the risks of combined therapy may outweigh the potential benefits. The combination should be used only with caution and close monitoring.

Mutual potentiation of cardiovascular effects (higher-grade AV block, higher-grade lowering of heart rate, induction of heart failure and potentiated hypotension). 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.

Metoprolol and propranolol plasma levels may be increased by concomitant administration of verapamil.

**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

**Digitalis**

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. 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 verapamil, the patient should be reassessed to avoid underdigitalisation.

**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 the clinical experience suggest beneficial interactions.

**Other**

**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 hydrochloride-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**

Phenobarbital therapy may increase verapamil clearance.

**Ciclosporin**

Verapamil therapy may increase serum levels of ciclosporin.

**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**

Phenytoin may decrease verapamil plasma levels.

**Alcohol**

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

**Inhalation anaesthetic**

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

**Neuromuscular blocking agents**

Clinical data and animal studies suggest that verapamil hydrochloride may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing). It may be necessary to decrease the dose of verapamil hydrochloride 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 VERAPAMIL.

**HMG-CoA reductase inhibitors**

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 statin dose and retitrate against serum cholesterol concentrations.

Verapamil hydrochloride may increase the serum levels of HMG CoA reductase inhibitors primarily metabolized by CYP3A enzymes (e.g., atorvastatin and simvastatin). Similarly, verapamil AUC may increase by approximately 42.8% 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.

**Sulfinpyrazone**

Blood pressure lowering effect may be reduced.

**Aspirin**

Increased tendency to bleed.

**Anticoagulants**

Use of dabigatran with verapamil may increase dabigatran plasma concentrations. Verapamil immediate release: ↑dabigatran (Cmax up to 180% and AUC up to 150%). Verapamil sustained release: ↑dabigatran (Cmax up to 90% and AUC up to 70%).

The risk of bleeding may increase. When co-administered with oral verapamil, the dose of dabigatran may need to be reduced (refer to dabigatran data sheet for dabigatran dosing instructions).

Verapamil therapy increases absorption of other direct oral anticoagulants (DOACs) and may also reduce elimination leading to increased systemic bioavailability of DOACs. The dose of DOACs with verapamil may need to be reduced as risk of bleeding may increase.

**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.

**Almotriptan**

Verapamil therapy may increase serum levels of almotriptan.

**St John's Wort**

St John's Wort may decrease serum levels of verapamil.

**FERTILITY, PREGNANCY AND LACTATION**

**Pregnancy**

There are no or limited amount of data from the use of verapamil in pregnant women. Studies in animals have shown reproductive toxicity.

Because animal reproduction studies are not always predictive of human response, during pregnancy (especially in the first trimester) verapamil should only be used if considered essential by the physician.

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

**Lactation**

Verapamil hydrochloride/metabolites are 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.

A risk to the newborns/infants cannot be excluded. 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.

**EFFECTS ON ABILITY TO DRIVE**

Due to its antihypertensive effect, depending on the individual response, verapamil hydrochloride may affect the ability to react to the point of impairing the ability to drive a vehicle, operate machinery or work under hazardous conditions. This applies all the more at the start of treatment, when the dose is raised, when switching from another drug and in conjunction with alcohol. Verapamil may increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

**ADVERSE DRUG REACTIONS**

*The following adverse events reactions have been reported with verapamil from clinical studies, post marketing surveillance or Phase IV clinical trials and are listed below by system organ class.*

Frequencies are defined as:

very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

The most commonly reported ADRs were: headache, dizziness, gastrointestinal disorders: nausea, constipation and abdominal pain, bradycardia, tachycardia, palpitations, hypotension, flushing, oedema peripheral, fatigue.

**Adverse reactions reported from clinical studies with verapamil and post-marketing surveillance activities**

| **MedDRA System Organ Class** | **Common** | **Uncommon** | **Rare** | **Unknown** |
|---|---|---|---|---|
| **Immune** system disorders | | | | Hypersensitivity |
| **Metabolism** and nutrition disorders | | | | Glucose tolerance impaired, Hyperkalaemia |
| **Nervous** system disorders | Dizziness, Headache | | Paresthesia, Tremor | Extrapyramidal disorder, Hypoesthesia, Neuropathy peripheral, paralysis (tetraparesis)[1] , Seizures. |
| **Psychiatric** disorders | | | Somnolence | Nervousness |
| **Ear** and labyrinth disorders | | | Tinnitus | Vertigo |
| **Cardiac** disorders | Bradycardia | Palpitations, Tachycardia | | Atrioventricular block (1°, 2°, 3°), Cardiac failure, Sinus arrest, cardiac arrest, Bradyarrythmia, Sinus bradycardia; asystole |
| **Vascular** disorders | Flushing, Hypotension | | | |
| **Respiratory**, thoracic and mediastinal disorders | | | | Bronchospasm, Dyspnea |
| **Gastrointestinal** disorders | Constipation, Nausea | Abdominal pain | Vomiting | Abdominal discomfort, Gingival hyperplasia, Ileus, abdominal distension |
| **Skin** and subcutaneous tissue disorders | | | Hyperhidrosis | Angioedema, Stevens-Johnson syndrome, Erythema multiforme, Alopecia, Itching, Pruritus, Purpura, Rash maculopapular, Urticaria, Photosensitivity reaction, Erythema, Rash |
| **Musculoskeletal and connective tissue disorders** | | | | Arthralgia, Muscular weakness, Myalgia |
| **Renal and urinary disorders** | | | | Renal failure |
| **Reproductive system and breast disorders** | | | | Erectile dysfunction, Galactorrhea, Gynecomastia |
| **General disorders and administration site conditions** | Oedema peripheral | Fatigue | | |

| | | | | |
|---|---|---|---|---|
| **Investigations** | | | | Blood prolactin increased<br>Hepatic enzymes increased |
| **Injury, poisoning and procedural complications** | | | | Elevated pacing threshold * |

[1]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 CYP3A4 and P-gp inhibition by verapamil.

* This has been reported in patients with pacemakers while on verapamil hydrochloride treatment.

**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**

**Symptoms**

Hypotension, shock, loss of consciousness, 1st and 2nd degree AV block (frequently as Wenckebach's phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, sinus bradycardia, sinus arrest, hyperglycemia, metabolic acidosis. Fatalities have occurred as a result of overdose.

**Treatment**

Treatment of overdose depends upon the type and severity of symptoms. Verapamil hydrochloride cannot be removed by hemodialysis. 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/hr). Gastric lavage, taking the usual precautionary measures, may be appropriate. The usual emergency measures for acute cardiovascular collapse should be applied, and followed by intensive care.

Similarly, in the case of 2nd and 3rd degree AV block, atropine, isoprenaline, orciprenaline and, if required, pacemaker therapy should be considered. Asystole should be handled by the usual measures including beta adrenergic stimulation (e.g., isoproterenol hydrochloride).

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**

ATC Code: C08DA01

The calcium antagonist verapamil inhibits the transmembrane influx of calcium ions into the heart and vascular smooth muscle cells.

The antihypertensive effect of Verapamil SR 240 mg Prolonged Release Tablets results from a decrease in peripheral vascular resistance, without an increase in heart rate as a reflex response. As early as day one of treatment, blood pressure falls and the effect persists in long-term therapy. Verapamil is suitable for the treatment of all types of hypertension: for monotherapy in mild to moderate hypertension and combined with other antihypertensives (in particular with diuretics and according to more recent findings, with ACE inhibitors) in more severe types of hypertension. Due to its calcium antagonistic effect in the smooth muscle of the coronaries, Verapamil enhances myocardial blood flow, even in post-stenotic areas, and relieves coronary spasm. Verapamil has an additional anti-arrhythmic effect, particularly in supraventricular arrhythmias. It delays impulse conduction in the AV node. Owing to this, sinus rhythm is restored and/or ventricular rate is normalized, depending on the type of arrhythmia.

**Pharmacokinetic properties**

About 92% of verapamil is absorbed rapidly from the small intestine. Mean systemic availability of the unchanged compound after a single dose is 22% owing to an extensive hepatic first pass metabolism. Bioavailability is about 2 times higher with the repeated administration.

Peak verapamil hydrochloride plasma levels are reached one to two hours after IR administration. The elimination half-life is 3 to 7 hours. Verapamil hydrochloride in plasma is approximately 90% protein bound. The drug is extensively metabolized. A number of metabolites are generated in humans (twelve have been identified). 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.

Verapamil hydrochloride and its metabolites are primarily eliminated by the renal route. Only 3 to 4% of the renally excreted drug is eliminated as the unchanged drug. About 50% of the dose is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in feces. Impaired renal function has no effect on verapamil hydrochloride pharmacokinetics, as shown by comparative studies in patients with end-stage renal failure and subjects

with healthy kidneys. The half-life of verapamil is prolonged in patients with impaired liver function owing to lower oral clearance and a higher volume of distribution.

**PRECLINICAL SAFETY DATA**

Reproduction studies have been performed in rabbits and rats at oral verapamil doses up to 0.6 (180 mg/m$^2$/day) and 1.2 times (360 mg/m$^2$/day) respectively the equivalent maximum recommended human oral daily dose (300 mg/m$^2$/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 reduced weight gain of dams). This oral dose has also been shown to cause hypotension in rats.

**PRESENTATION**

Calan SR tablets are available in blister pack of Alu-PVC 10's.

**INSTRUCTIONS**

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

- Protect from sunlight, moisture and heat.

- Store below 30°C.

- Keep all medicines out of sight & reach of children.

**REGISTRATION NUMBER**

Calan SR 240 mg: 009773

Manufacturing License No: 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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