SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Verapamil Hydrochloride BP Tablets 40mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 40mg tablet contains verapamil hydrochloride BP 40mg

Excipients with known effect

Each tablet contains 28mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Yellow, round, biconvex tablets plain on both the sides with an approximate diameter of 7 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Verapamil hydrochloride is useful in:

1. the treatment and prophylaxis of angina pectoris, and variant angina;
2. the treatment and prophylaxis of paroxysmal supraventricular tachycardia and atrial flutter/fibrillation (verapamil should not be used when atrial flutter/fibrillation complicates Wolff-Parkinson-White syndrome); and
3. the treatment of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

Elderly or patients with impaired liver or kidney function, or cardiac conduction problems may require a reduced dosage.

Angina:

Adults:	120mg, 3 times daily is recommended. Some patients with angina of effort may respond to 80mg, 3 times daily, but this dose is not likely to be effective in angina at rest and variant angina.

Supraventricular tachycardias:

Adults:	40mg to 120mg, 3 times daily according to the severity of the condition.

Paediatric population, 2 years and above:	40mg to 120mg, 2 to 3 times daily, according to age and effectiveness.

Hypertension:

Adults:	160mg twice daily. A small number of patients may be controlled successfully on 120mg twice daily, whereas others may require up to 480mg

	daily, given in divided doses. A further reduction in blood pressure may be obtained by combining Verapamil Tablets with other antihypertensive agents, e.g. thiazide diuretics. Verapamil hydrochloride and beta-blockers may be additive, both with respect to conduction and contraction. Verapamil hydrochloride should therefore, be given with care to those who are receiving beta-blockers.
Paediatric population:	Up to 10mg/kg/day, in divided doses, according to the severity of the condition.

Method of Administration

For oral use only

4.3 Contraindications

Hypersensitivity to the active substance or any of the other excipients listed in section 6.1.

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

Combination with beta-blockers is contraindicated in patients with poor ventricular function.

Patients with atrial flutter/fibrillation in the presence of an accessory pathway (e.g. Wolff-Parkinson-White Syndrome) may develop increased conduction across the anomalous pathway and ventricular tachycardia may be precipitated.

Concomitant ingestion of grapefruit juice is contraindicated.

Combination with ivabradine (see section 4.5)

4.4 Special warnings and precautions for use

Since verapamil is extensively metabolised in the liver, careful dose titration is required in patients with liver disease. 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.

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 in subsequent doses 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 (see section 4.8).

Hypotension
Intravenous verapamil hydrochloride often produces a decrease in blood pressure below baseline levels that is usually transient and asymptomatic but may result in dizziness.

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).

These tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 injection 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.

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.

The following are potential drug interactions due to pharmacokinetic reasons:

Acetylsalicylic acid
Concomitant use of verapamil with aspirin may increase the risk of bleeding.

Alcohol
Increase in blood alcohol has been reported.

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*. Pulmonary oedema may occur in patients with hypertrophic cardiomyopathy.

The combination of verapamil and *antiarrhythmic agents* may lead to additive cardiovascular effects (e.g. AV block, bradycardia, hypotension, heart failure).

Anticonvulsants
Verapamil may increase plasma concentrations of *carbamazepine*. This may produce side-effects such as diplopia, headache, ataxia or dizziness. Phenytoin may also decrease the plasma concentrations of verapamil.

Antidepressants

Verapamil may increase the plasma concentrations of imipramine.

Antidiabetics
Verapamil may increase the plasma concentrations of glibenclamide (glyburide). Co-administration of verapamil with metformin may reduce the efficacy of metformin.

Antihypertensives, diuretics, vasodilators

Potentiation of the hypotensive effect.

Anti-infectives

Rifampicin may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect. When verapamil and rifampicin are administered together there is no change in PK. *Erythromycin, clarithromycin* and *telithromycin* may increase the plasma concentrations of verapamil.

Antineoplastics
Verapamil may increase the plasma concentrations of doxorubicin.

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).

Intravenous beta-blockers should not be given to patients on verapamil.

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.

H2 Receptor antagonists

Cimetidine may increase the plasma concentrations of verapamil.

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*, which could lead to increased side-effects. Concentration determinations and dose adjustments of everolimus and sirolimus may be necessary.

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 of *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 (pharmacokinetic effect). However, there may be increased sensitivity to *lithium* causing enhanced neurotoxicity (pharmacodynamic effect). Patients receiving both drugs should be monitored carefully.

Neuromuscular blocking agents employed in anaesthesia

The effects may be potentiated.

Serotonin receptor agonists

Verapamil may increase the plasma concentrations of almotriptan.

Theophylline

Verapamil may increase the plasma concentration of theophylline.

Uricosurics

Sulfinpyrazone may reduce the plasma concentrations of verapamil which may produce a reduced blood pressure lowering effect. When verapamil and sulfinpyrazone are administrated together there is no change in PK.

Anticoagulants

When oral verapamil was co-administered with dabigatran etexilate (150mg), a P-gp substrate, the Cmax and AUC of dabigatran were increased but magnitude of this change differs depending on time between administration and the formulation of verapamil. Co-administration of verapamil 240mg extended-release at the same time as dabigatran etexilate resulted in increased dabigatran exposure (increase of Cmax by about 90% and AUC by about 70%).

Close clinical surveillance is recommended when verapamil is combined with dabigatran etexilate and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Other direct oral anticoagulants (DOACs):

Increased absorption of DOACs since they are P-gp substrates and, if applicable, also reduced elimination of DOACs which are metabolized by Cyp3A4, may increase the systemic bioavailability of DOACs. Some data suggest a possible increase of the risk of bleeding, especially in patients with further risk factors. The dose of DOAC with verapamil may need to be reduced (see DOAC label for dosing instruction).

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

There are no adequate and well-controlled study data in pregnant women. 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 considered essential for the welfare of the patient.

Verapamil hydrochloride 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. 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

Depending on individual susceptibility, the patient's ability to drive a vehicle, operate machinery or work under hazardous conditions may be impaired. This is particularly true in the initial stages of treatment, when changing over from another drug, when the dose is raised or when taken in conjunction with alcohol. Like many other common medicines, verapamil has been shown to increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

4.8 Undesirable effects

Reactions from Post marketing Surveillance or Phase IV Clinical Trials

The following adverse events reported with verapamil are listed below by system organ class.

Adverse drug reactions are ranked by frequency, using the following convention: 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).

Immune system disorders: allergic reactions (e.g. erythema, pruritus, urticaria) are very rarely seen.

Nervous system disorders: headaches, dizziness, paresthesia, tremor and

extrapyramidal syndrome (e.g. parkinsonism), dystonia.

Ear and labyrinth disorders: vertigo, tinnitus.

Cardiac disorders: bradycardic arrhythmias such as sinus bradycardia, sinus arrest with asystole, 2nd and 3rd degree AV block, bradyarrhythmia in atrial fibrillation, palpitations, tachycardia, development or aggravation of heart failure, hypotension.

Vascular disorders: flushing, peripheral oedema.

Gastrointestinal disorders: nausea, vomiting, constipation, ileus and abdominal pain/discomfort. Gingival hyperplasia may occur very rarely when the drug is administered over prolonged periods. This is fully reversible when the drug is discontinued.

Skin and subcutaneous tissue disorders: alopecia, ankle oedema, Quincke's oedema, Stevens-Johnson syndrome, erythema multiforme, erythromelalgia, purpura.

Musculoskeletal and connective tissue disorders: muscular weakness, myalgia and arthralgia.

Reproductive system and breast disorders: impotence (erectile dysfunction) has been rarely reported and isolated cases of galactorrhoea. On very rare occasions, gynaecomastia has been observed in elderly male patients under long-term verapamil treatment which was fully reversible in all cases when the drug was discontinued.

General disorders and administration site conditions: fatigue.

Investigations: On very rare occasions, a reversible impairment of liver function characterised by an increase of transaminase and/or alkaline phosphatase may occur during verapamil treatment and is most probably a hypersensitivity reaction. Rises in blood prolactin levels have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

4.9 Overdose

Symptoms

The course of symptoms in verapamil intoxication depends on the amount taken, the point in time at which detoxification measures are taken and myocardial contractility (age-related). The main symptoms are as follows: acute respiratory distress syndrome, blood pressure fall (at times to values not detectable), shock symptoms, 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, bradycardia up to high degree AV block and, sinus arrest, hyperglycaemia, stupor and metabolic acidosis. Fatalities have occurred as a result of overdose.

Management

The therapeutic measures to be taken depend on the point in time at which verapamil was taken and the type and severity of intoxication symptoms. In intoxications with large amounts of slow-release preparations, it should be noted that the release of the active drug and the absorption in the intestine may take more than 48 hours. Verapamil hydrochloride cannot be removed by haemodialysis. Depending on the time of ingestion, it should be taken into account that there may be some lumps of incompletely dissolved tablets along the entire length of the gastrointestinal tract, which function as active drug depots.

General measures to be taken: Gastric lavage with the usual precautions, even later than 12 hours after ingestion, if no gastrointestinal motility (peristaltic sounds) is detectable. Where intoxication by a modified release preparation is suspected, extensive elimination measures are indicated, such as induced vomiting, removal of the contents of the stomach and the small intestine under endoscopy, intestinal lavage, laxative, high enemas. The usual intensive resuscitation measures apply, such as extrathoracic heart massage, respiration, defibrillation and/or pacemaker therapy.

Specific measures to be taken: Elimination of cardiodepressive effects, hypotension or bradycardia. The specific antidote is calcium, e.g. 10 20 ml of a 10% calcium gluconate solution administered intravenously (2.25 - 4.5 mmol), repeated if necessary or given as a continuous drip infusion (e.g. 5 mmol/hour).

The following measures may also be necessary: In case of 2nd or 3rd degree AV block, sinus bradycardia, asystole - atropine, isoprenaline, orciprenaline or pacemaker therapy. In case of hypotension - dopamine, dobutamine, noradrenaline (norepinephrine). If there are signs of continuing myocardial failure - dopamine, dobutamine, if necessary repeated calcium injections.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective calcium channel blockers with direct cardiac effects, phenylalkylamine derivatives.
ATC code: CO8 DA01

Mechanism of action

Verapamil, a phenylalkylamine calcium antagonist, has a balanced profile of cardiac and peripheral effects. It lowers heart rate, increases myocardial perfusion and reduces coronary spasm. In a clinical study in patients after myocardial infarction, verapamil reduced total mortality, sudden cardiac death and reinfarction rate.

Verapamil reduces total peripheral resistance and lowers high blood pressure by vasodilation, without reflex tachycardia. Because of its use-dependent action on the voltage-operated calcium channel, the effects of verapamil are more pronounced on high than on normal blood pressure.

As early as day one of treatment, blood pressure falls; the effect is found to persist also in long-term therapy.

Verapamil is suitable for the treatment of all types of hypertension: for monotherapy in mild to moderate hypertension; combined with other antihypertensives (in particular with diuretics and, according to more recent findings, with ACE inhibitors) in more severe types of hypertension. In hypertensive diabetic patients with nephropathy, verapamil in combination with ACE inhibitors led to a marked reduction of albuminuria and to an improvement of creatinine clearance.

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 metabolised. 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.

Absorption

Greater than 90% of verapamil is rapidly absorbed from the small intestine after oral administration. Mean systemic availability of the unchanged compound after

a single dose of SR verapamil is approximately 33%, owing to an extensive hepatic first-pass metabolism. Bioavailability is about two times higher with repeated administration. Peak verapamil plasma levels are reached four to five hours after SR administration. The peak plasma concentration of norverapamil is attained approximately five hours after SR administration. The presence of food has no effect on the bioavailability of verapamil.

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%.

Biotransformation

Verapamil is extensively metabolised. In vitro metabolic studies indicate that verapamil is metabolised 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 oral administration, the elimination half-life is three to seven hours. Approximately 50% of an administered dose is eliminated renally within 24 hours, 70% within five days. Up to 16% of a dose is excreted in the faeces. About 3% to 4% of renally excreted drug is excreted as unchanged drug. The total clearance of verapamil is nearly as high as the hepatic blood flow, approximately 1 L/h/kg (range 0.7-1.3 L/h/kg).

Special Populations

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 haemodialysis.

Hepatic insufficiency

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

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, maize starch, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose (E464), quinoline yellow (E104) and titanium dioxide (E171).

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place.

6.5 Nature and contents of container

Blisters of 250µm Opaque PVC and Aluminium Foil.
Pack sizes: 28, 30, 56, 60, 84, 90, 100, 112 and 120 tablets.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0145

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10 DATE OF REVISION OF THE TEXT

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